



US012391749B2

(12) **United States Patent**
Cady et al.

(10) **Patent No.:** US 12,391,749 B2
(45) **Date of Patent:** *Aug. 19, 2025

(54) **ACUTE TREATMENT AND RAPID
TREATMENT OF HEADACHE USING
ANTI-CGRP ANTIBODIES**

(71) Applicant: **H. LUNDBECK A/S**, Valby (DK)

(72) Inventors: **Roger K. Cady**, Bothell, WA (US);
Jeffrey T. L. Smith, Dublin (IE);
Joseph Hirman, Bothell, WA (US);
Barbara Schaeffler, Bothell, WA (US);
Lahar Mehta, Valby (DK)

(73) Assignee: **H. Lundbeck A/S**, Valby (DK)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/173,116**

(22) Filed: **Feb. 23, 2023**

(65) **Prior Publication Data**

US 2024/0076359 A1 Mar. 7, 2024

Related U.S. Application Data

(62) Division of application No. 16/736,925, filed on Jan. 8, 2020, now Pat. No. 11,639,380.

(60) Provisional application No. 62/789,828, filed on Jan. 8, 2019, provisional application No. 62/872,989, filed on Jul. 11, 2019, provisional application No. 62/842,162, filed on May 2, 2019.

(51) **Int. Cl.**

C07K 16/18 (2006.01)
A61K 9/00 (2006.01)
A61K 31/4172 (2006.01)
A61K 39/00 (2006.01)
A61K 39/395 (2006.01)
A61K 45/06 (2006.01)
A61K 47/26 (2006.01)
A61P 25/06 (2006.01)
A61K 38/00 (2006.01)

(52) **U.S. Cl.**

CPC *C07K 16/18* (2013.01); *A61K 9/0019* (2013.01); *A61K 31/4172* (2013.01); *A61K 39/3955* (2013.01); *A61K 45/06* (2013.01); *A61K 47/26* (2013.01); *A61P 25/06* (2018.01); *A61K 38/00* (2013.01); *A61K 2039/505* (2013.01); *A61K 2039/545* (2013.01); *C07K 2317/24* (2013.01)

(58) **Field of Classification Search**

CPC .. *C07K 16/18; C07K 2317/24; A61K 9/0019; A61K 31/4172; A61K 39/3955; A61K 45/06; A61K 47/26; A61K 38/00; A61K 2039/505; A61K 2039/545; A61P 25/06*

See application file for complete search history.

(56)

References Cited

U.S. PATENT DOCUMENTS

5,116,964 A	5/1992	Capon et al.
5,266,561 A	11/1993	Cooper et al.
5,364,841 A	11/1994	Cooper et al.
5,585,089 A	12/1996	Queen et al.
5,624,821 A	4/1997	Winter et al.
5,648,260 A	7/1997	Winter et al.
5,942,227 A	8/1999	Cooper et al.
6,180,370 B1	1/2001	Queen et al.
6,313,097 B1	11/2001	Eberlein et al.
6,509,014 B1	1/2003	De Lacharrière et al.
6,521,609 B1	2/2003	Doods et al.
6,737,056 B1	5/2004	Presta
6,956,107 B2	10/2005	Fung et al.
7,279,471 B2	10/2007	Mueller et al.
7,479,488 B2	1/2009	Mueller et al.
7,696,209 B2	4/2010	Mueller et al.
7,700,735 B2	4/2010	Young et al.
7,879,991 B2	2/2011	Vater et al.
7,927,863 B2	4/2011	Clegg et al.
7,935,340 B2	5/2011	Garcia-Martinez et al.
8,007,794 B2	8/2011	Zeller et al.
8,293,239 B2	10/2012	Poulsen et al.
8,298,536 B2	10/2012	Corradini et al.
8,586,045 B2	11/2013	Zeller et al.
8,597,649 B2	12/2013	Zeller et al.
8,623,366 B2	1/2014	Pios et al.
8,734,802 B1	5/2014	Zeller et al.
9,073,991 B2	7/2015	Allan et al.
9,708,393 B2	7/2017	Russo et al.
9,745,373 B2	8/2017	Kovacevich et al.
9,855,332 B2	1/2018	Russo et al.

(Continued)

FOREIGN PATENT DOCUMENTS

AU	2006313434	5/2007
CA	2611433	12/2006

(Continued)

OTHER PUBLICATIONS

Alstadhaug, Karl B et al. "Preventing and treating medication overuse headache." Pain reports vol. 2,4 e612. Jul. 26, 2017, doi:10.1097/PR9.0000000000000612.

(Continued)

Primary Examiner — Olga N Chernyshev

(74) Attorney, Agent, or Firm — Robin L. Teskin; Baker, Donelson, Bearman, Caldwell & Berkowitz PC

(57) **ABSTRACT**

Methods for rapid treatment of chronic migraine are provided. Exemplary methods provide relief from migraine within 24 hours of administration. Also provided are methods for acute treatment of migraine. Exemplary methods comprise administration of an anti-CGRP antagonist antibody to a patient in need thereof.

22 Claims, 63 Drawing Sheets

Specification includes a Sequence Listing.

(56)	References Cited		KR	10-1250049	4/2013
	U.S. PATENT DOCUMENTS		RU	2329062	7/2008
10,066,009 B2	9/2018	Kovacevich et al.	WO	WO 1996/0004928	2/1996
10,179,809 B2	1/2019	Kovacevich et al.	WO	WO 97/09046	3/1997
10,189,895 B2	1/2019	Kovacevich et al.	WO	WO 98/09630	3/1998
10,208,112 B2	2/2019	Kovacevich et al.	WO	WO 98/11128	3/1998
10,214,582 B2	2/2019	Kovacevich et al.	WO	WO 98/56779	12/1998
10,266,587 B2	4/2019	Russo et al.	WO	WO 00/18764	4/2000
10,533,048 B2	1/2020	Kovacevich et al.	WO	WO 2001/022972	4/2001
11,639,380 B2 *	5/2023	Cady	A61K 9/0019	WO 2003/045424	6/2003
			424/130.1	WO 2003/093472	11/2003
11,639,381 B2 *	5/2023	Cady	A61K 47/26	WO 03/104236	12/2003
			424/133.1	WO 2004/003019	1/2004
2001/0036647 A1	11/2001	Choudary et al.	WO	WO 2004/014351	2/2004
2002/0162125 A1	10/2002	Salmon et al.	WO	WO 2004/050683	6/2004
2002/0164707 A1	11/2002	Adamou et al.	WO	WO 2004058184	7/2004
2003/0027213 A1	2/2003	Zhu et al.	WO	WO 2004/082602	9/2004
2003/0181462 A1	9/2003	Doods et al.	WO	WO 2004/082605	9/2004
2003/0194404 A1	10/2003	Greenfeder et al.	WO	WO 2004/082678	9/2004
2004/0110170 A1	6/2004	Pisegna et al.	WO	WO 2004/083187	9/2004
2004/0132824 A1	7/2004	Gil et al.	WO	WO 2004/087649	10/2004
2005/0234054 A1	10/2005	Mueller et al.	WO	WO 2004/091514	10/2004
2006/0183700 A1	8/2006	Vater et al.	WO	WO 2004/092166	10/2004
2006/0270045 A1	11/2006	Cregg et al.	WO	WO 2004/092168	10/2004
2009/0023644 A1	1/2009	Southard et al.	WO	WO 2004096122	11/2004
2009/0028784 A1	1/2009	Garcia-Martinez et al.	WO	WO 2004097421	11/2004
2009/0220489 A1	9/2009	Zeller et al.	WO	WO 2005/009962	2/2005
2010/0152171 A1	6/2010	Rudolf et al.	WO	WO 2005/040395	5/2005
2011/0054150 A1	3/2011	Poulsen et al.	WO	WO 2005/040397	5/2005
2011/0257371 A1	10/2011	Poulsen et al.	WO	WO 2005/041757	5/2005
2011/0305711 A1	12/2011	Allan et al.	WO	WO 2005070444	8/2005
2012/0000192 A1	1/2012	Zeller et al.	WO	WO 2005/100360	10/2005
2012/0114741 A1	5/2012	Aung-Din	WO	WO 2006/077212	7/2006
2012/0225075 A1	9/2012	Pios et al.	WO	WO 2007/025212	3/2007
2012/0294797 A1	11/2012	Kovacevich et al.	WO	WO 2007/048026	4/2007
2012/0294802 A1	11/2012	Russo et al.	WO	WO 2007/141285	12/2007
2012/0294822 A1	11/2012	Russo et al.	WO	WO 2008/011190	1/2008
2013/0216535 A1	8/2013	Zeller et al.	WO	2008144757	11/2008
2013/0295087 A1	11/2013	Poulsen et al.	WO	WO 2009/109908	9/2009
2013/0295088 A1	11/2013	Poulsen et al.	WO	WO 2009/109911	9/2009
2015/0266948 A1	9/2015	Bigal et al.	WO	WO 2010075238	7/2010
2017/0088612 A1	3/2017	Bigal	WO	WO 2011/024113	3/2011
2017/0174754 A1	6/2017	Kovacevich et al.	WO	WO 2011/156324	12/2011
2018/0127490 A1	5/2018	Bigal et al.	WO	2012162243	11/2012
2018/0142029 A1	5/2018	Boone et al.	WO	2015143409	9/2015
2018/0161434 A1	6/2018	Russo et al.	WO	2015173539	11/2015
2019/0211085 A1	7/2019	Kovacevich et al.	WO	2016171742	10/2016
2019/0240331 A1	8/2019	Russo et al.	WO	2016205037	12/2016
2019/0367590 A1	12/2019	Russo et al.	WO	2017186928	11/2017
2020/0010537 A1	1/2020	Baker et al.	WO	2018/055574	3/2018
2020/0216524 A1	7/2020	Cady et al.	WO	2020146527	7/2020
2020/0216525 A1	7/2020	Cady et al.			

FOREIGN PATENT DOCUMENTS

CA	2626120	12/2012
CN	101309704	11/2008
CN	101979650	2/2011
CN	103421114	12/2013
EA	015526	10/2008
EP	0212432	3/1987
EP	1031350	8/2000
EP	1770091	4/2007
EP	1556020	2/2009
EP	1957106	10/2013
JP	Hei6-87890	3/1994
JP	08-268874	10/1996
JP	2005523418	8/2005
JP	2007517911	7/2007
JP	2009-515942	4/2009
JP	2011046710	3/2011
JP	2011513386	4/2011
JP	2011513387	4/2011
JP	5123197	1/2013
JP	2014-517699	7/2014
JP	2017-515579	6/2017

OTHER PUBLICATIONS

[No Author Attributed] Clinical Trial No. LY2951742, started Mar. 2015, "A Study of LY2951742 in Participants With Episodic Cluster Headache," from ClinicalTrials.gov [database online], Retrieved from the Internet: <<https://clinicaltrials.gov/ct2/show/study/NCT02397473?term=LY2951742&rank=9>>, retrieved Sep. 3, 2016. 6 pages.

[No Author Attributed] [machine translated from website] "Dysfunction of the temporomandibular joint," as published on the Colgate-Palmolive Company website [online], Retrieved from the Internet: <<http://www.colgate.ru/ru/ru/oc/oral-health/conditions/temporomandibular-disorder>> 2017; 7 pages.

Androulakis, X Michelle et al. "Central Executive and Default Mode Network Intranet work Functional Connectivity Patterns in Chronic Migraine." Journal of neurological disorders vol. 6,5 (2018): 393. doi:10.4172/2329-6895.1000393.

Carlsen, Louise Ninett, et al. "Complete detoxification is the most effective treatment of medication-overuse headache: a randomized controlled open-label trial." Cephalalgia 38.2 (2018): 225-236.

(56)

References Cited**OTHER PUBLICATIONS**

- Cevoli, Sabina, et al. "Family history for chronic headache and drug overuse as a risk factor for headache chronicification." *Headache: The Journal of Head and Face Pain* 49.3 (2009): 412-418.
- Chen, Zhiye, et al. "Altered functional connectivity architecture of the brain in medication overuse headache using resting state fMRI." *The Journal of Headache and Pain* 18.1 (2017): 1-9.
- Ferrari, Anna, et al. "Need for analgesics/drugs of abuse: a comparison between headache patients and addicts by the Leeds Dependence Questionnaire (LDQ)." *Cephalalgia* 26.2 (2006): 187-193.
- Ferraro, Stefania, et al. "In medication overuse headache, fMRI shows long-lasting dysfunction in midbrain areas." *Headache* vol. 52,10 (2012): 1520-34. doi: 10.1111/j.1526-4610.2012.02276.x.
- Find, Ninette Louise, et al. "Medication overuse headache in Europe and Latin America: general demographic and clinical characteristics, referral pathways and national distribution of painkillers in a descriptive, multinational, multicenter study." *The journal of headache and pain* 17.1 (2016): 1-12.
- Fuh, Jong-Ling, et al. "Does medication overuse headache represent a behavior of dependence?" *Pain* vol. 119,1-3 (2005): 49-55. doi:10.1016/j.pain.2005.09.034.
- Fumal, Arnaud, et al. "Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine." *Brain* 129.2 (2006): 543-550.
- "Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition." *Cephalalgia : an international journal of headache* vol. 38,1 (2018): 1-211. doi:10.1177/033102417738202.
- Grande, Ragnhild Berling, et al. "The Severity of Dependence Scale detects people with medication overuse: the Akershus study of chronic headache." *Journal of Neurology, Neurosurgery & Psychiatry* 80.7 (2009): 784-789.
- Lai, Tzu-Hsien, et al. "Gray matter changes related to medication overuse in patients with chronic migraine." *Cephalgia* 36.14 (2016): 1324-1333.
- Lundqvist, C., et al. "An adapted Severity of Dependence Scale is valid for the detection of medication overuse: the Akershus study of chronic headache." *European Journal of Neurology* 18.3 (2011):512-518.
- Newman-Norlund, Roger D., et al. "Cortical and subcortical changes following sphenopalatine ganglion blocks in chronic migraine with medication overuse headache: a preliminary longitudinal study." *Women's midlife health* 6.1 (2020): 1-8.
- Riederer, Franz, et al. "Decrease of gray matter volume in the midbrain is associated with treatment response in medication-overuse headache: possible influence of orbitofrontal cortex." *Journal of Neuroscience* 33.39 (2013): 15343-15349.
- Riederer, Franz, et al. "Grey matter changes associated with medication-overuse headache: correlations with disease related disability and anxiety." *The world journal of biological psychiatry* 13.7 (2012): 517-525.
- Torta, D. M., et al. "Nucleus accumbens functional connectivity discriminates medication-overuse headache." *NeuroImage: Clinical* 11 (2016): 686-693.
- Lundqvist, Christofer, et al. "The severity of dependence score correlates with medication overuse in persons with secondary chronic headaches. The Akershus study of chronic headache." *PAIN®* 148.3 (2010): 487-491.
- Scuteri, et al. "New trends in migraine pharmacology: targeting calcitonin gene-related peptide (CGRP) with monoclonal antibodies." *Frontiers in pharmacology*. Apr. 9, 2019;10:363.
- Winner, et al. "Effects of Intravenous Eptinezumab vs Placebo on Headache Pain and Most Bothersome Symptom When Initiated During a Migraine Attack: A Randomized Clinical Trial." *JAMA*. Jun. 15, 2021;325(23):2348-56.
- Goadsby, et al. Pathophysiology of Migraine: A Disorder of Sensory Processing. *Physiological reviews*. Apr;97 (2):553-622, 1997.
- Messlinger, et al. "The Big CGRP Flood-sources, Sinks and Signalling Sites in the Trigeminovascular System." *The Journal of Headache and Pain*. Dec. 2018;19(1):1-7.
- Kumar, et al. "Protective role of α -calcitonin gene-related peptide in cardiovascular diseases." *Frontiers in physiology*. Jul. 2, 2019;10:821.
- Van Dongen, et al. "Migraine biomarkers in cerebrospinal fluid: A systematic review and meta-analysis." *Cephalalgia*. Jan. 2017;37(1):49-63.
- Christensen, et al. "Migraine induction with calcitonin gene-related peptide in patients from erenumab trials." *The Journal of Headache and Pain*. Dec. 2018;19(1):1-9.
- Covasala, et al. "Calcitonin gene-related peptide receptors in rat trigeminal ganglion do not control spinal trigeminal activity." *Journal of neurophysiology*. Jul. 15, 2012;108(2):431-40.
- Storer, et al. "Calcitonin gene-related peptide (CGRP) modulates nociceptive trigeminovascular transmission in the cat." *British journal of pharmacology*. Aug. 2004;142(7):1171-81.
- Burstein, et al. "The neurobiology of photophobia." *Journal of neuro-ophthalmology: the official journal of the North American Neuro-Ophthalmology Society*. Mar. 2019;39(1):94.
- Wang, et al. "Monoclonal antibody exposure in rat and cynomolgus monkey cerebrospinal fluid following systemic administration." *Fluids and Barriers of the CNS*. Dec. 2018;15(1):1-0.
- Kelman, L. "Pain characteristics of the acute migraine attack." *Headache: The Journal of Head and Face Pain*. Jun. 2006;46(6):942-53.
- Kopruszinski, et al. "Prevention of stress-or nitric oxide donor-induced medication overuse headache by a calcitonin gene-related peptide antibody in rodents." *Cephalalgia*. May 2017;37(6):560-70.
- Iranian Office Action dated Apr. 15, 2022, for Pat. Appl. No. 140050140003002468, filed Jun. 15, 2021 entitled "Treatment of Medication Overuse Headache Using Anticgrp or Anti-CGRP-R Antibodies".
- Iranian Office Action dated Feb. 7, 2022, for Pat. Appl. No. 140050140003002305, filed Jun. 9, 2021 entitled "Acute Treatment and Rapid Treatment of Headache Using Anti-CGRP Antibodies." "Cluster Headache," Wolff's Headache 1974, p. 348.
- "Highlights of Prescribing Information" BLA STN 103000/5215—FDA Approved Labeling Text, Botox Package Insert, Oct. 2010, 25 pages.
- "Teva to Acquire Labrys Biologics, Inc.: Novel Migraine Prophylaxis Treatment Adds Significant New Dimension to Teva's Growing Pain Care Franchise" "Business Wire" Jun. 3, 2014." 4 pages.
- "TMJ Disorders," National Institute of Dental and Craniofacial Research, NIH Publication No. 15-3487, Apr. 2015. 20 pages.
- Abdiche, YN, et al. "Probing the binding mechanism and affinity of tanazumab, a recombinant humanized anti-NGF monoclonal antibody, using a repertoire of biosensors," *Protein Sci.* Aug. 2008; 17(8):1326-35.
- Adwanikar H, et al. Spinal CGRP1 receptors contribute to supraspinally organized pain behavior and pain-related sensitization of amygdala neurons. *Pain*. Nov. 2007;132(1-2):53-66. Epub Mar. 1, 2007.
- Akerman S, et al. "Nitric oxide synthase inhibitors can antagonize neurogenic and calcitonin gene-related peptide induced dilation of dural meningeal vessels," *Br J Pharmacol*. Sep. 2002;137(1):62-8.
- Akerman, S., et al. "Pearls and pitfalls in experimental in vivo models of migraine: dural trigeminovascular nociception," *Cephalgia*. Jun. 2013;33(8):577-92.
- Alder Biopharmaceuticals Inc., "Alder Presents Positive ALD403 Clinical Data at European Headache and Migraine Trust International Congress," Press Release, Sep. 15, 2016.
- Alder Biopharmaceuticals Inc., "Alder Presents Positive Clinical Data for ALD403 at the 17th Congress of the International Headache Society" Press Release, May 15, 2015. (3 pages).
- Alder Biopharmaceuticals Inc., "Alder Reports Phase 2b Trial of ALD403 Meets Primary and Secondary Endpoints Demonstrating Migraine Prevention in Patients with Chronic Migraine," Press Release, Mar. 28, 2016. (4 pages).
- Alder Biopharmaceuticals Inc., "Alder Reports Positive Top-Line 24-Week Data Demonstrating Persistent Migraine Prevention in Phase 2b Study of ALD403 in Patients with Chronic Migraine" Press Release, Jul. 25, 2016. (3 pages).
- Alder Biopharmaceuticals Inc., "Data From Proof-of-Concept Clinical Trial of ALD403, a Monoclonal Antibody Against CGRP for the

(56)

References Cited**OTHER PUBLICATIONS**

- Prevention of Migraine, to be Presented at 56th Annual Scientific Meeting of the American Headache Society." Press Release, Jun. 26, 2014. 2 pages.
- Almagro JC et al. "Chapter 13 Antibody Engineering: Humanization, Affinity Maturation, and Selection Techniques." Therapeutic Monoclonal Antibodies: From Bench to Clinic (Zhiqiang An (Editor) Oct. 2009: 311-34.
- Amara SG, et al. "Expression in brain of a messenger RNA encoding a novel neuropeptide homologous to calcitonin gene-related peptide." *Science*. Sep. 13, 1985;229(4718):1094-7.
- Ambalavanar R., et al. "Deep tissue inflammation upregulates neuropeptides and evokes nociceptive behaviors which are modulated by a neuropeptide antagonist." *Pain*. Jan. 2006;120(1-2):53-68. Epub Dec. 13, 2005.
- Amrutkar DV. "Calcitonin gene-related peptide (CGRP) uptake and release in rat dura mater, trigeminal ganglion and trigeminal nucleus caudalis," PhD thesis, Faculty of Health and Medical Sciences University of Copenhagen, Academic advisor: Inger Jansen-Olesen and Jes Olesen, Submitted: Feb. 20, 2013.
- An Z. "Therapeutic Monoclonal Antibodies: From Bench to Clinic." Wiley & Sons, Inc., 2009 Chapter 31, 711-62.
- Andersen DC, et al. "Production technologies for monoclonal antibodies and their fragments," *Carr Opin Biotechnol*. Oct. 2004;15(5):456-62.
- Andrew DP, et al. "Monoclonal antibodies distinguishing alpha and beta forms of calcitonin gene-related peptide." *J Immunol Methods*. Nov. 6, 1990;134(1):87-94.
- Antibody Structure and Function, Chapter 4 of Elgert's Immunology: Understanding the Immune System, pp. 58-78. Wiley 1998.
- Aoki KR. "Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A," *Neurotoxicology*. Oct. 2005;26(5):785-93.
- Aoki-Nagase T, et al. "Attenuation of antigen-induced airway hyperresponsiveness in CGRP-deficient mice," *Am J Physiol Lung Cell Mol Physiol*. Nov. 2002;283(5):L963-70.
- Armour KL, et al. "Recombinant human IgG molecules lacking Fc gamma receptor I binding and monocyte triggering activities," *Eur J Immunol*. Aug. 1999;29(8):2613-24.
- Arulmani U et al. "Calcitonin gene-related peptide and its role in migraine pathophysiology." *Eur J Pharmacol*. Oct. 1, 2004;500(1-3):315-30.
- Arulmani U, et al. "Experimental migraine models and their relevance in migraine therapy," *Cephalgia*. Jun. 2006;26(6):642-59.
- Arulmozhai DK, et al., "Migraine: current concepts and emerging therapies," *Vascul Pharmacol*. Sep. 2005;43(3):176-87.
- Asghar, MS, et al. "Evidence for a vascular factor in migraine," *Ann Neurol*. Apr. 2011;69(4):635-45.
- Ashina M. "Vascular changes have a primary role in migraine," *Cephalgia*. Apr. 2012;32(5):428-30.
- Ashina M, et al. "Evidence for increased plasma levels of calcitonin gene-related peptide in migraine outside of attacks." *Pain*. May 2000;86(1-2):133-8.
- Ashina M, et al. "Pearls and pitfalls in human pharmacological models of migraine: 30 years' experience," *Cephalgia*. Jun. 2013;33(8):540-53.
- Ashina M, et al. "Plasma levels of calcitonin gene-related peptide in chronic tension-type headache," *Neurology*. Nov. 14, 2000;55(9):1335-40.
- Ashina M. "Calcitonin gene-related peptide in tension-type headache," *ScientificWorldJournal*. Jun. 7, 2002;2:1527-31.
- Aziz Q., "Visceral hypersensitivity: fact or fiction." *Gastroenterology*. Aug. 2006;131(2):661-4.
- Bagdy, G, et al. "Headache-type adverse effects of NO donors: vasodilation and beyond," *Br J Pharmacol*. May 2010;160(1):20-35.
- Balint RF, et al. "Antibody engineering by parsimonious mutagenesis." *Gene*. Dec. 27, 1993;137(1):109-18.
- Barker JN, et al. "Progress in psoriasis. Psoriasis: from gene to clinic. London, UK, Dec. 5-7, 1996," *Mol Med Today*. May 1997;3(5):193-4.
- Batra SK, et al. "Pharmacokinetics and biodistribution of genetically engineered antibodies," *Curr Opin Biotechnol*. Dec. 2002;13(6):603-8.
- Baxter LT, et al. "Biodistribution of monoclonal antibodies: scale-up from mouse to human using a physiologically based pharmacokinetic model," *Cancer Res*. Oct. 15, 1995;55(20):4611-22.
- Bell RD, et al. "Breaching the blood-brain barrier for drug delivery." *Neuron*. Jan. 8, 2014;81(1):1-3.
- Benarroch EE. "CGRP: sensory neuropeptide with multiple neurologic implications." *Neurology*. Jul. 19, 2011;77(3):281-7.
- Benemei S, et al. "CGRP receptors in the control of pain and inflammation," *Curr Opin Pharmacol*. Feb. 2009;9(1):9-14.
- Benemei S, et al. "Migraine," *Handb Exp Pharmacol*. 2009;(194):75-89.
- Benemei S, et al. "Pain pharmacology in migraine: focus on CGRP and CGRP receptors," *Neurol Sci*. May 2007;28 Suppl 2:S89-93.
- Benincosa LJ, et al. "Pharmacokinetics and Pharmacodynamics of a Humanized Monoclonal Antibody to Factor IX in Cynomolgus Monkeys," *J Pharmacol Exp Ther*. Feb. 2000;292(2):810-6.
- Bennett AD, et al. "Alleviation of mechanical and thermal allodynia by CGRP(8-37) in a rodent model of chronic central pain." *Pain*. May 2000;86(1-2):163-75.
- Benschop U.S. Appl. No. 60/753,044, filed Dec. 22, 2005. File History, 48 pages.
- Biacore 3000 Instrument Handbook, Mar. 1999. 201 pages.
- Bigal and Krymchantowski, "Emerging drugs for migraine prophylaxis and treatment," *Med. Gen. Med.* 2006;8(2):31.
- Bigal M. "Clinical Trials Update—2012: Year in Review—A Comment" *Headache*. Jun. 2013;53(6):1003-4.
- Bigal ME, et al. "Emerging drugs for migraine prophylaxis and treatment," *MedGenMed*. May 4, 2006;8(2):31.
- Bigal ME, et al. "Ergotamine and dihydroergotamine: a review," *Curr Pain Headache Rep*. Feb. 2003;7(1):55-62.
- Bigal ME, et al. "Headache prevention outcome and body mass index," *Cephalgia*. Apr. 2006;26(4):445-50.
- Bigal ME, et al. "Migraine in the Triptan Era: Lessons From Epidemiology, Pathophysiology, and Clinical Science," *Headache*. Feb. 2009;49 Suppl 1:S21-33.
- Bigal ME, et al. "Migraine in the triptan era: progresses achieved, lessons learned and future developments," *Arq Neuropsiquiatr*. Jun. 2009;67(2B):559-69.
- Bigal ME, et al. "Modifiable risk factors for migraine progression," *Headache*. Oct. 2006;46(9):1334-43.
- Bigal ME, et al. "Monoclonal Antibodies for Migraine: Preventing Calcitonin Gene-Related Peptide Activity," *CNS Drugs*. May 2014;28(5):389-99.
- Bigal ME, et al. "New developments in migraine prophylaxis," *Expert Opin Pharmacother*. Apr. 2003;4(4):433-43.
- Bigal ME, et al. "New migraine preventive options: an update with pathophysiological considerations," *Rev Hosp Clin Fac Med Sao Paulo*. Nov.-Dec. 2002;57(6):293-8.
- Bigal ME, et al. "Obesity and migraine: a population study," *Neurology*. Feb. 28, 2006;66(4):545-50.
- Bigal ME, et al. "Obesity is a risk factor for transformed migraine but not chronic tension-type headache," *Neurology*. Jul. 25, 2006;67(2):252-7.
- Bigal ME, et al. "Prophylactic migraine therapy: emerging treatment options," *Curr Pain Headache Rep*. Jun. 2004;8(3):178-84.
- Bigal ME, et al. "Safety and tolerability of LBR-101, a humanized monoclonal antibody that blocks the binding of CGRP to its receptor: Results of the Phase 1 program," *Cephalgia*. Dec. 23, 2013;34(7):483-492.
- Bigal ME, et al. "Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study," *Lancet Neurol*. Nov. 2015;14(11):1081-90.
- Bigal ME, et al. "The preventive treatment of migraine," *Neurologist*, Jul. 2006;12(4):204-13.
- Bigal ME, et al. "The triptans," *Expert Rev Neurother*. May 2009;9(5):649-59.
- Bigal, ME "Glutamate Receptor Antagonists," *Headache Currents*, 1:20-21. Jul. 2004.

(56)

References Cited**OTHER PUBLICATIONS**

- Birder L, et al. "Neural control of the lower urinary tract: peripheral and spinal mechanisms," *Neurorol Urodyn.* 2010;29(1):128-39.
- Boeckh M, et al. "Phase 1 Evaluation of the Respiratory Syncytial Virus-Specific Monoclonal Antibody Palivizumab in Recipients of Hematopoietic Stem Cell Transplants," *J Infect Dis.* Aug. 1, 2001;184(3):350-4.
- Bolay H, et al. "Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model," *Nat Med.* Feb. 2002;8(2):136-42.
- Brain SD, et al. "CGRP receptors: a headache to study, but will antagonists prove therapeutic in migraine?" *Trends Pharmacol Sci.* Feb. 2002;23(2):51-3.
- Brain SD, et al. "Vascular actions of calcitonin gene-related peptide and adrenomedullin." *Physiol Rev.* Jul. 2004;84(3):903-34.
- Brekke OH, et al. "Therapeutic Antibodies For Human Diseases At The Dawn Of The Twenty-First Century," *Nat Rev Drug Discov.* Jan. 2003;2(1):52-62.
- Borson K, et al. "Mutational analysis of avidity and fine specificity of anti-levan antibodies." *J Immunol.* Dec. 1, 1999;163(12):6694-701.
- Brüggemann M, et al. "The Immunogenicity Of Chimeric Antibodies," *J Exp Med.* Dec. 1, 1989;170(6):2153-7.
- Brummell DA, et al. "Probing the combining site of an anti-carbohydrate antibody by saturation-mutagenesis: role of the heavy-chain CDR3 residues." *Biochemistry.* Feb. 2, 1993;32(4):1180-7.
- Buckley TL, et al. "The partial inhibition of inflammatory responses induced by capsaicin using the Fab fragment of a selective calcitonin gene-related peptide antiserum in rabbit skin." *Neuroscience.* Jun. 1992;48(4):963-8.
- Burke EA, "In vitro scanning saturation mutagenesis of an antibody binding pocket." *Proc Natl Acad Sci U S A.* Jan. 2, 1997;94(2):412-7.
- Buzzi MG, et al. "The antimigraine drug, sumatriptan (GR43175), selectively blocks neurogenic plasma extravasation from blood vessels in dura mater," *Br J Pharmacol.* Jan. 1990;99(1):202-6.
- Carter PJ. "Potent antibody therapeutics by design," *Nat Rev Immunol.* May 2006;6(5):343~ 57.
- Casset F, et al. "A peptide mimetic of an anti-CD4 monoclonal antibody by rational design." *Biochem Biophys Res Commun.* Jul. 1, 2003;307(1):198-205.
- Castaño A, et al. "Headache in symptomatic intracranial hypertension secondary to leptospirosis: a case report," *Cephalgia.* Apr. 2005;25(4):309-11.
- Cernuda-Morollón E, et al. "CGRP and VIP levels as predictors of efficacy of Onabotulinumtoxin type A in chronic migraine," *Headache.* Jun. 2014;54(6):987-95.
- Chancellor MB, et al. "Neurophysiology of stress urinary incontinence," *Rev Urol.* 2004;6 Suppl 3:619-28.
- Charbit, A et al. "Dopamine: what's new in migraine?" *Curr Opin Neurol.* Jun. 2010;23(3):275-81.
- Charles A, "Migraine is not primarily a vascular disorder," *Cephalgia.* Apr. 2012;32(5):431-2.
- Chauhan M, et al. "Studies on the effects of the N-terminal domain antibodies of calcitonin receptor-like receptor and receptor activity-modifying protein 1 on calcitonin gene-related peptide-induced vasorelaxation in rat uterine artery," *Biol Reprod.* Jun. 2004;70(6):1658-63.
- Chen JT, et al. "Menopausal flushes and calcitonin-gene-related peptide," *Lancet.* Jul. 3, 1993;342(8862):49.
- Chen Y, et al. "Selection and analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen." *J Mol Biol.* Nov. 5, 1999;293(4):865-81.
- Cheung B et al. "Adrenomedullin: Its Role in the Cardiovascular System," *Semin Vasc Med.* May 2004;4(2):129-34.
- Chowdhury PS, et al. "Tailor-made antibody therapeutics," *Methods.* May 2005;36(1):11-24.
- Chuang YC, et al. "Intraprostatic botulinum toxin a injection inhibits cyclooxygenase-2 expression and suppresses prostatic pain on capsaicin induced prostatitis model in rat," *J Urol.* Aug. 2008;180(2):742-8.
- Chuang YC, et al. "Urodynamic and immunohistochemical evaluation of intravesical botulinum toxin A delivery using liposomes," *J Urol.* Aug. 2009;182(2):786-92.
- Clanchetti C. "The role of the neurovascular scalp structures in migraine," *Cephalgia.* Jul. 2012;32(10):778-84.
- Colcher D, et al. "Pharmacokinetics and biodistribution of genetically-engineered antibodies," *Q J Nucl Med.* Dec. 1998;42(4):225-41.
- Colman PM. "Effects of amino acid sequence changes on antibody-antigen interactions." *Res Immunol.* Jan. 1994;145(1):33-6.
- Conner AC, et al. "Interaction of calcitonin-gene-related peptide with its receptors." *Biochem Soc Trans.* Aug. 2002;30(4):451-5.
- Conner AC, et al. "Ligand binding and activation of the CGRP receptor," *Biochem Soc Trans.* Aug. 2007;35(Pt 4):729-32.
- Connor K M et al: "Randomized, controlled trial of telcageptan for the acute treatment of migraine.", *Neurology* Sep. 22, 2009, vol. 73, No. 12, Sep. 22, 2009 (Sep. 22, 2009), pp. 970-977, XP002732737, ISSN: 1526-632X.
- Correia IR. "Stability of IgG isotypes in serum," *MAbs.* May-Jun. 2010;2(3):221-32.
- Cottrell GS, et al. "Localization of calcitonin receptor-like receptor (CLR) and receptor activity-modifying protein 1 (RAMP1) in human gastrointestinal tract," *Peptides.* Jun. 2012;35(2):202-11.
- Covell DG, et al. "Pharmacokinetics of monoclonal immunoglobulin G1, F(ab')2, and Fab' in mice." *Cancer Res.* Aug. 1986;46(8):3969-78.
- Cutrer F. "Pathophysiology of Migraine," *Semin Neurol.* Apr. 2006;26(2):171-80.
- Cutrer F. "Pathophysiology of Migraine," *Semin Neurol.* Apr. 2010;30(2):120-30.
- Dakhama A, et al. "Calcitonin gene-related peptide: role in airway homeostasis," *Curr Opin Pharmacol.* Jun. 2004;4(3):215-20.
- Davies J, et al. "Affinity improvement of single antibody VH domains: residues in all three hypervariable regions affect antigen binding." *Immunotechnology.* Sep. 1996;2(3):169-79.
- Davis CD et al. "The Tortuous Road to an Ideal CGRP Function Blocker for the Treatment of Migraine," *Curr Top Med Chem.* 2008;8(16):1468-79.
- Davietov B, et al. "Beyond BOTOX: advantages and limitations of individual botulinum neurotoxins," *Trends Neurosci.* Aug. 2005;28(8):446-52.
- De Pascalis R, et al. "Grafting of "abbreviated" complementarity-determining regions containing specificity-determining residues essential for ligand contact to engineer a less immunogenic humanized monoclonal antibody." *J Immunol.* Sep. 15, 2002;169(6):3076-84.
- Delafoy L, et al. "Interactive involvement of brain derived neurotrophic factor, nerve growth factor, and calcitonin gene related peptide in colonic hypersensitivity in the rat." *Gut.* Jul. 2006;55(7):940-5. Epub Jan. 9, 2006.
- Denekas T, et al. "Inhibition of stimulated meningeal blood flow by a calcitonin gene-related peptide binding mirror-image RNA oligonucleotide," *Br J Pharmacol.* Jun. 2006;148(4):536-43.
- Deng R et al. "Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data," *MAbs.* Jan.-Feb. 2011;3(1):61-6.
- Derosa G, et al. "Optimizing combination treatment in the management of type 2 diabetes," *Vasc Health Risk Manag.* 2007;3(5):665-71.
- Diamond S, et al. "Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study," *Headache.* Mar. 2007;47(3):355-63.
- Diener HC, et al. "Utility of topiramate for the treatment of patients with chronic migraine in the presence or absence of acute medication overuse," *Cephalgia.* Oct. 2009;29(10):1021-7.
- Dockray et al., "Immunoneutralization studies with calcitonin gene-related peptide," *Ann. NY Acad Sci.* 1992;657:258-67.
- Dodick D, et al. "Cluster Headache: Diagnosis, Management and Treatment," *Wolff's Headache* 2001, p. 283.
- Dodick DW, et al. "Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent

(56)

References Cited**OTHER PUBLICATIONS**

- episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial," *Lancet Neurol.* Nov. 2014;13(11):1100-7.
- Doggett S. "Migraine and beyond: cardiovascular therapeutic potential for CGRP modulators," *Expert Opin Investig Drugs.* Jun. 2001;10(6):1131-8.
- Dolgin E. "Antibody drugs set to revive flagging migraine target," *Nat Rev Drug Discov.* Apr. 2013;12(4):249-50.
- Doods H, et al. "Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist." *Br J Pharmacol.* Feb. 2000;129(3):420-3.
- Doods, H et al. "CGRP antagonists: unravelling the role of CGRP in migraine," *Trends Pharmacol Sci.* Nov. 2007;28(11):580-7.
- Dooley JS, et al. "Antibiotics in the treatment of biliary infection," *Gut.* Sep. 1984;25(9):988-98.
- Drake AW, et al. "Characterizing high-affinity antigen/antibody complexes by kinetic- and equilibrium-based methods," *Anal Biochem.* May 1, 2004;328(1):35-43.
- Dressler and Saberi, "Botulinum toxin: mechanisms of action," *Eur. Neurol.* 2005;53:3-9.
- Dressler D, et al. "Botulinum toxin: mechanisms of action," *Arq Neuropsiquiatr.* Mar. 2005;63(1):180-5.
- Dufner P, et al. "Hamming phage and ribosome display for antibody optimisation." *Trends Biotechnol.* Nov. 2006;24(11):523-9. Epub Sep. 26, 2006.
- Durham P. "CGRP-receptor antagonists—a fresh approach to migraine therapy?" *N Engl J Med.* Mar. 11, 2004;350(11):1073-5.
- Durham Paul L et al: "Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists in the Treatment of Migraine", *CNS Drugs*, vol. 24, No. 7, 2010, pp. 539-548.
- Durham PL et al. "New insights into the molecular actions of serotonergic antimigraine drugs," *Pharmacol Ther.* Apr.-May 2002;94(1-2):77-92.
- Durham PL, et al. "Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy," *Headache.* Jan. 2004;44(1):35-42; discussion 42-3.
- Durham PL. "Calcitonin Gene-Related Peptide (CGRP) and Migraine," *Headache.* Jun. 2006;46 Suppl 1:S3~8.
- Durham PL. "Inhibition of calcitonin gene-related peptide function: a promising strategy for treating migraine," *Headache.* Sep. 2008;48(8):1269-75.
- Edvinsson L et al. "Blockade of CGRP receptors in the intracranial vasculature: a new target in the treatment of headache," *Cephalgia.* Aug. 2004;24(8):611-22.
- Edvinsson L et al. "CGRP Receptor Antagonism and Migraine," *Neurotherapeutics.* Apr. 2010;7(2):164-75.
- Edvinsson L et al. "Extracerebral manifestations in migraine. A peptidergic involvement?" *J Intern Med.* Oct. 1990;228(4):299-304.
- Edvinsson L et al. "Neurobiology in primary headaches," *Brain Res Brain Res Rev.* Jun. 2005;48(3):438-56.
- Edvinsson L et al. "Perivascular neuropeptides (NPY, VIP, CGRP and SP) in human brain vessels after subarachnoid haemorrhage," *Acta Neurol Scand.* Nov. 1994;90(5):324-30.
- Edvinsson L et al. "The blood-brain barrier in migraine treatment," *Cephalgia.* Dec. 2008;28(12):1245-58.
- Edvinsson L et al: "New drugs in migraine treatment and prophylaxis: telcagepant and topiramate", *The Lancet*, the Lancet Publishing Group, GB, vol. 376, No. 9741, Aug. 21, 2010 (Aug. 21, 2010), pp. 645-655.
- Edvinsson L, et al. "Calcitonin gene-related peptide and cerebral blood vessels: distribution and vasomotor effects," *J Cereb Blood Flow Metab.* Dec. 1987;7(6):720-8.
- Edvinsson L, et al. "Inhibitory effect of BIBN4096BS, CGRP(8-37), a CGRP antibody and an RNA-Spiegelmer on CGRP induced vasodilatation in the perfused and non-perfused rat middle cerebral artery." *Br J Pharmacol.* Mar. 2007;150(5):633-40. Epub Jan. 22, 2007.
- Edvinsson L, et al. "Innervation of the human middle meningeal artery; immunohistochemistry, ultrastructure, and role of endothelium for vasomotility," *Peptides.* 1998;19(7):1213-25.
- Edvinsson L, et al. "Neuropeptides in migraine and cluster headache," *Cephalgia.* Oct. 1994;14(5):320-7.
- Edvinsson L. "Aspects on the Pathophysiology of Migraine and Cluster Headache," *Pharmacol Toxicol.* Aug. 2001;89(2):65-73.
- Edvinsson L. "Calcitonin Gene-Related Peptide (CGRP) and the Pathophysiology of Headache Therapeutic Implications," *CNS Drugs.* 2001;15(10):745-53.
- Edvinsson L. "Cgrp blockers in migraine therapy: where do they act?" *Br J Pharmacol.* Dec. 2008;155(7):967-9.
- Edvinsson L. "CGRP-receptor antagonism in migraine treatment." *Lancet.* Dec. 20, 2008;372(9656):2089-90.
- Edvinsson L. "Clinical Data on the CGRP Antagonist BIBN4096BS for Treatment of Migraine Attacks," *CNS Drug Rev.* 2005 Spring;11(1):69-76.
- Edvinsson L. "Innervation and effects of dilatory neuropeptides on cerebral vessels. New aspects," *Blood Vessels.* 1991;28(1-3):35-45.
- Edvinsson L. "Neuronal Signal Substances as Biomarkers of Migraine," *Headache.* Jul.-Aug. 2006;46(7):1088-94.
- Edvinsson L. "New therapeutic target in primary headaches—blocking the CGRP receptor," *Expert Opin Ther Targets.* Jun. 2003;7(3):377-83.
- Edvinsson L. "Novel migraine therapy with calcitonin gene-regulated peptide receptor antagonists," *Expert Opin Ther Targets.* Sep. 2007;11(9):1179-88.
- Edvinsson L: "CGRP blockers in migraine therapy: where do they act?", *British Journal of Pharmacology*, vol. 155, No. 7, Dec. 2008 (Dec. 20, 2008), pp. 967-969.
- Edvinsson Lars: "CGRP-receptor antagonism in migraine treatment.", *LANCET* Dec. 20, 2008, vol. 372, No. 9656, Dec. 20, 2008 (Dec. 20, 2008), pp. 2089-2090.
- Eftekhari S et al. "Differentiation of Nerve Fibers Storing CGRP and CGRP Receptors in the Peripheral Trigeminovascular System," *J Pain.* Nov. 2013;14(11):1289-303.
- Elshourbagy NA, et al. "Molecular cloning and characterization of the porcine calcitonin gene-related peptide receptor." *Endocrinology.* Apr. 1998;139(4):1678-83.
- Emerick GT. "Migraines in the Presence of Glaucoma, Recent advances in diagnosis and management," *Glaucoma Today.* Sep./ Oct. 2008, 21-23.
- Escott et al., "Effect of a calcitonin gene-related peptide antagonist (CGRP8-37) on skin vasodilatation and oedema induced by stimulation of the rat saphenous nerve," *Br. J. Pharmacol.* 1993;110:772-6.
- Escott KJ, et al. "Trigeminal ganglion stimulation increases facial skin blood flow in the rat: a major role for calcitonin gene-related peptide." *Brain Res.* Jan. 9, 1995;669(1):93-9.
- Esfandyari T. "The Role Of Calcitonin Gene-Related Peptide (CGRP) In Colonic Inflammation, And Secretion In The Rat Distal Colon," Thesis, University of Calagary, Department of Neuroscience and Gastrointestinal Sciences. 1999. 145 pages.
- Evans BN, et al. "CGRP-RCP, a novel protein required for signal transduction at calcitonin gene-related peptide and adrenomedullin receptors," *J Biol Chem.* Oct. 6, 2000;275(40):31438-43.
- Evans RW, et al. "Target doses and titration schedules for migraine preventive medications," *Headache.* Jan. 2006;46(1):160-4.
- Evans RW. "Exploding head syndrome followed by sleep paralysis: a rare migraine aura," *Headache.* Apr. 2006;46(4):682-3.
- Everitt DE et al. "The Pharmacokinetics, Antigenicity, and Fusion-Inhibition Activity of RSHZ19, a Humanized Monoclonal Antibody to Respiratory Syncytial Virus, in Healthy Volunteers," *J Infect Dis.* Sep. 1996;174(3):463-9.
- Faraci FM, et al. "Vascular responses of dura mater," *Am J Physiol.* Jul. 1989;257(1 Pt 2):H157-61.
- Farinelli, I et al. "Future drugs for migraine," *Intern Emerg Med.* Oct. 2009;4(5):367-73.
- Feuerstein G et al. "Clinical perspectives of calcitonin gene related peptide pharmacology," *Can J Physiol Pharmacol.* Jul. 1995;73(7):1070-4.

(56)

References Cited**OTHER PUBLICATIONS**

- File History U.S. Appl. No. 60/736,623, filed Nov. 14, 2005, Zeller, et al. Antagonist Antibodies Directed Against Calcitonin Gene-Related Peptide and Methods Using Same. 110 pages.
- Fischer MJ et al. "The Nonpeptide Calcitonin Gene-Related Peptide Receptor Antagonist BIBN4096BS Lowers the Activity of Neurons with Meningeal Input in the Rat Spinal Trigeminal Nucleus," *J Neurosci*. Jun. 22, 2005;25(25):5877-83.
- Fischer MJ. "Calcitonin gene-related peptide receptor antagonists for migraine," *Expert Opin Investig Drugs*. Jul. 2010;19(7):815-23.
- Forssman B, et al. "Atenolol for migraine prophylaxis," *Headache*, Jul. 1983;23(4):188-90.
- Forster ER, et al. "The role of calcitonin gene-related peptide in gastric mucosal protection in the rat," *Exp Physiol*. Jul. 1991;76(4):623-6.
- Friend PJ, et al. "Phase I study of an engineered aglycosylated humanized CD3 antibody in renal transplant rejection," *Transplantation*. Dec. 15, 1999;68(11):1632-7.
- Frobert Y, et al. "A sensitive sandwich enzyme immunoassay for calcitonin gene-related peptide (CGRP): characterization and application," *Peptides*. 1999;20(2):275-84.
- Galitsky BA, et al. "Predicting amino acid sequences of the antibody human VH chains from its first several residues," *Proc Natl Acad Sci U S A*. Apr. 28, 1998;95(9):5193-8.
- Gallai V, et al. "Vasoactive peptide levels in the plasma of young migraine patients with and without aura assessed both interictally and ictally," *Cephalgia*. Oct. 1995;15(5):384-90.
- Gangula PR, et al. "Increased blood pressure in alpha-calcitonin gene-related peptide/calcitonin gene knockout mice," *Hypertension*. Jan. 2000;35(1 Pt 2):470-5.
- Gearing D, et al. "A fully caninised anti-NGF monoclonal antibody for pain relief in dogs," *BMC Vet Res*. Nov. 9, 2013;9:226.
- Geppetti P et al. "Antidromic vasodilatation and the migraine mechanism," *J Headache Pain*. Mar. 2012;13(2):103-11.
- Geppetti P et al., "CGRP and migraine: neurogenic inflammation revisited," *J Headache Pain*. Apr. 2005;6(2):61-70.
- Geppetti P et al. "Novel therapeutic targets," *Neurol Sci*. May 2006;27 Suppl 2:S111-4.
- Giamberardino MA, et al. "Emerging drugs for migraine treatment," *Expert Opin Emerg Drugs*. Mar. 2015;20(1):137-47.
- Gillies S et al. "Improving the efficacy of antibody-interleukin 2 fusion proteins by reducing their interaction with Fc receptors," *Cancer Res*. May 1, 1999;59(9):2159-66.
- Giniatullin R et al. "Molecular Mechanisms of Sensitization of Pain-transducing P2X3 Receptors by the Migraine Mediators CGRP and NGF," *Mol Neurobiol*, Feb. 2008;37(1):83-90.
- Glennie MJ, et al. "Clinical trials of antibody therapy," *Immunol Today*. Aug. 2000;21(8):403-10.
- Glover V, et al. "Can the vascular and neurogenic theories of migraine finally be reconciled?" *Trends Pharmacol Sci*. Jan. 1989;10(1):1-3.
- Goadsby PJ et al. "Release of vasoactive peptides in the extracerebral circulation of humans and the cat during activation of the trigeminovascular system," *Ann Neurol*. Feb. 1988;23(2):193-6.
- Goadsby PJ, et al. "Migraine—current understanding and treatment," *N Engl J Med*. Jan. 24, 2002;346(4):257-70.
- Goadsby PJ, et al. "Vasoactive peptide release in the extracerebral circulation of humans during migraine headache," *Ann Neurol*. Aug. 1990;28(2):183-7.
- Goadsby PJ. "Advances in the understanding of headache," *Br Med Bull*. Oct. 5, 2005;73-74:83-92. Print 2005.
- Goadsby PJ. "Calcitonin gene-related peptide antagonists as treatments of migraine and other primary headaches," *Drugs*. 2005;65(18):2557-67.
- Goadsby PJ. "Can we develop neurally acting drugs for the treatment of migraine?" *Nat Rev Drug Discov*. Sep. 2005;4(9):741-50.
- Goadsby PJ. "Headache: a good year for research," *Lancet Neurol*. Jan. 2006;5(1):5-6.
- Goadsby PJ. "Migraine Pathophysiology," *Headache*. Apr. 2005;45 Suppl 1:S14-24.
- Goadsby PJ. "New targets in the acute treatment of headache," *Curr Opin Neurol*. Jun. 2005;18(3):283-8.
- Goadsby PJ. "The vascular theory of migraine—a great story wrecked by the facts," *Brain*. Jan. 2009;132(Pt 1):6-7.
- Goadsby, PJ, et al. "Randomized, double-blind, placebo-controlled trial of ALD403, an anti-CGRP antibody in the prevention of frequent episodic migraine." 56th Annual Scientific Meeting of the American Headache Society, Jun. 2014. 4 pages.
- Gómez-Foix AM, et al., "Anti-insulin effects of amylin and calcitonin-gene-related peptide on hepatic glycogen metabolism," *Biochem J*. Jun. 15, 1991;276 (Pt 3):607-10.
- Green LL, et al. "Antigen-specific human monoclonal antibodies from mice engineered with human Ig heavy and light chain YACs," *Nat Genet*. May 1994;7(1):13-21.
- Grunenberger F. "[Calcitonin gene-related peptide (CGRP): a vaso-dilator neuropeptide with many potential applications]" *Pathol Biol (Paris)*. Dec. 1993;41(10):936-42.
- Gupta S et al. "Evidence for CGRP re-uptake in rat dura mater encephali," *Br J Pharmacol*. Dec. 2010;161(8):1885-98.
- Gupta S et al. "Intravital microscopy on a closed cranial window in mice: a model to study trigeminovascular mechanisms involved in migraine," *Cephalgia*. Nov. 2006;26(11):1294-303.
- Gupta S et al. "Potential role of female sex hormones in the pathophysiology of migraine," *Pharmacol Ther*. Feb. 2007;113(2):321-40.
- Gupta S et al. "The relevance of preclinical research models for the development of antimigraine drugs: focus on 5-HT(1B/1D) and CGRP receptors," *Pharmacol Ther*. Oct. 2010;128(1):170-90.
- Hakala JM, et al. "Modelling constrained calcitonin gene-related peptide analogues," *Protein Eng*. Feb. 1996;9(2):143-8.
- Halimi S, et al. "Combination treatment in the management of type 2 diabetes: focus on vildagliptin and metformin as a single tablet," *Vasc Health Risk Manag*. 2008;4(3):481-92.
- Hanes J et al. "Picomolar affinity antibodies from a fully synthetic naive library selected and evolved by ribosome display," *Nat Biotechnol*. Dec. 2000;18(12):1287-92.
- Hansen JM, et al. "Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura," *Cephalgia*. Oct. 2010;30(10):1179-86.
- Hargreaves R. "New Migraine and Pain Research," *Headache*. Apr. 2007;47 Suppl 1:S26-43.
- Hatcher JP, et al. "Biologics: the next-generation therapeutics for analgesia?" *Expert Rev Neurother*. Nov. 2011;11(11):1653-8.
- Hay D et al. "A comparison of the actions of BIBN4096BS and CGRP(8-37) on CGRP and adrenomedullin receptors expressed on SK-N-MC, L6, Col 29 and Rat 2 cells," *Br J Pharmacol*. Sep. 2002;137(1):80-6.
- Hay D et al. "International Union of Pharmacology. LXIX. Status of the Calcitonin Gene-Related Peptide Subtype 2 Receptor," *Pharmacol Rev*. Jun. 2008;60(2):143-5.
- Hay D et al. "The pharmacology of CGRP-responsive receptors in cultured and transfected cells," *Peptides*. Nov. 2004;25(11):2019-26.
- Hay D et al. "The Preclinical Pharmacology of BIBN4096BS, a CGRP Antagonist," *Cardiovasc Drug Rev*. 2005 Spring;23(1):31-42.
- Hay D. "What Makes a CGRP2 Receptor?" *Clin Exp Pharmacol Physiol*. Oct. 2007;34(10):963-71.
- Hay DL, et al. "CL/RAMP2 and CL/RAMP3 produce pharmacologically distinct adrenomedullin receptors: a comparison of effects of adrenomedullin22-52, CGRP8-37 and BIBN4096BS," *Br J Pharmacol*. Oct. 2003;140(3):477-86. Epub Aug. 26, 2003.
- Hershey JC, et al. "Investigation of the species selectivity of a nonpeptide CGRP receptor antagonist using a novel pharmacodynamic assay," *Regul Pept*. Apr. 15, 2005;127(1-3):71-7.
- Hill RG et al. "Neuropeptide and Kinin Antagonists," *Handb Exp Pharmacol*. 2007;(177):181-216.
- Hillmen P, et al. "Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria," *N Engl J Med*. Feb. 5, 2004;350(6):552-9.
- Hinton PR, et al. "Engineered human IgG antibodies with longer serum half-lives in primates," *J Biol Chem*. Feb. 20, 2004;279(8):6213-6.

(56)

References Cited**OTHER PUBLICATIONS**

- Hirsch S et al. "The CGRP receptor antagonist BIBN4096BS peripherally alleviates inflammatory pain in rats," *Pain*. May 2013;154(5):700-7.
- Ho TW et al. "CGRP and its receptors provide new insights into migraine pathophysiology," *Nat Rev Neurol*. Oct. 2010;6(10):573-82.
- Ho TW, et al. "Impact of recent prior opioid use on rizatriptan efficacy. A post hoc pooled analysis," *Headache*. Mar. 2009;49(3):395-403.
- Ho TW, et al. "Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention," *Neurology*. Sep. 9, 2014;83(11):958-66.
- Ho TW, et al. "Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial," *Lancet*. Dec. 20, 2008;372(9656):2115-23.
- Hoff AO et al. "Increased bone mass is an unexpected phenotype associated with deletion of the calcitonin gene," *J Clin Invest*. Dec. 2002;110(12):1849-57.
- Hoffmann J, et al. "New Agents for Acute Treatment of Migraine: CGRP Receptor Antagonists, iNOS Inhibitors," *Curr Treat Options Neurol*. Feb. 2012;14(1):50-9.
- Holland J et al. "Calcitonin Gene-Related Peptide Reduces Brain Injury in a Rat Model of Focal Cerebral Ischemia," *Stroke*. Oct. 1994;25(10):2055-8; discussion 2058-9.
- Holliger P, et al. "Engineered antibody fragments and the rise of single domains," *Nat Biotechnol*. Sep. 2005;23(9):1126-36.
- Holm P, et al. "Functional mapping and single chain construction of the anti-cytokeratin 8 monoclonal antibody TS1," *Mol Immunol*. Feb. 2007;44(6):1075-84. Epub Sep. 20, 2006.
- Holman JJ, et al. "Human alpha- and beta-CGRP and rat alpha-CGRP are coronary vasodilators in the rat," *Peptides*. Mar.-Apr. 1986;7(2):231-5.
- Holt LJ, et al. "Domain antibodies: proteins for therapy," *Trends Biotechnol*. Nov. 2003;21(11):484-90.
- Holzer P et al. "Afferent Nerve-Mediated Protection Against Deep Mucosal Damage in the Rat Stomach," *Gastroenterology*. Apr. 1990;98(4):838-48.
- Holzer P et al. "Sensory neurons mediate protective vasodilation in rat gastric mucosa," *Am J Physiol*. Mar. 1991;260(3 Pt 1):G363-70.
- Holzer P et al. "Stimulation Of Afferent Nerve Endings By Intragastric Capsaicin Protects Against Ethanol-Induced Damage Of Gastric Mucosa," *Neuroscience*. Dec. 1988;27(3):981-7.
- Holzer P. "Implications of tachykinins and calcitonin gene-related peptide in inflammatory bowel disease," *Digestion*. Jul.-Aug. 1998;59(4):269-83.
- Holzer P. "Capsaicin: Cellular Targets, Mechanisms of Action, and Selectivity for Thin Sensory Neurons," *Pharmacol Rev*. Jun. 1991;43(2):143-201.
- Hong KW, et al. "Effect of omega-conotoxin GVIA and omega-agatoxin IVA on the capsaicin-sensitive calcitonin gene-related peptide release and autoregulatory vasodilation in rat pial arteries," *J Cereb Blood Flow Metab*. Jan. 1999;19(1):53-60.
- Hong KW, et al. "Pharmacological coupling and functional role for CGRP receptors in the vasodilation of rat pial arterioles," *Am J Physiol*. Jan. 1996;270(1 Pt 2):H317-23.
- Hong KW, et al. "Pharmacological evidence that calcitonin gene-related peptide is implicated in cerebral autoregulation," *Am J Physiol*. Jan. 1994;266(1 Pt 2):H11-6.
- Hoogenboom HR, et al. "Multi-subunit proteins on the surface of filamentous phage: methodologies for displaying antibody (Fab) heavy and light chains," *Nucleic Acids Res*. Aug. 11, 1991;19(15):4133-7.
- Hoogenboom HR. "Selecting and screening recombinant antibody libraries," *Nat Biotechnol*. Sep. 2005;23(9):1105-16.
- Hopkins, CR. "ACS Chemical Neuroscience Molecule Spotlight on Telcagepant (MK-0974)," *ACS Chem Neurosci*. Jul. 20, 2011;2(7):334-5.
- Hu H, et al. "Acute migraine treatment with rizatriptan in real world settings—focusing on treatment strategy, effectiveness, and behavior," *Headache*. Feb. 2009;49 Suppl 1:S34-42.
- Hubbard JA, et al. "Identification of the epitopes of calcitonin gene-related peptide (CGRP) for two anti CGRP monoclonal antibodies by 2D NMR," *Protein Sci*. Sep. 1997;6(9):1945-52.
- Hudson PJ, et al. "Engineered antibodies," *Nat Med*. Jan. 2003;9(1):129-34.
- Hughes SR et al. "A calcitonin gene-related peptide (CGRP) antagonist (CGRP8-37) inhibits microvascular responses induced by CGRP and capsaicin in skin," *Br J Pharmacol*. Nov. 1991;104(3):738-42.
- Hurley D. "Cgrp Drug Improves Wellness on Headache-Free Days, Study Finds," *Neurology Today*, p. 31, Jul. 2016.
- Hwang WY, et al. "Immunogenicity of engineered antibodies," *Methods*. May 2005;36(1):3-10.
- Ibrahimi K, et al. "Development of an experimental model to study trigeminal nerve-mediated vasodilation on the human forehead," *Cephalgia*. Jan. 3, 2014;34(7):514-522.
- Idusogie EE, et al. "Mapping of the C1q Binding Site on Rituxan, a Chimeric Antibody with a Human IgG1 Fc," *J Immunol*. Apr. 15, 2000;164(8):4178-84.
- Tovino M, et al. "Safety, tolerability and pharmacokinetics of BIBN 4096 BS, the first selective small molecule calcitonin gene-related peptide receptor antagonist, following single intravenous administration in healthy volunteers," *Cephalgia*. Aug. 2004;24(8):645-56.
- Janeway CA et al. "Immuno Biology: The Immune System in Health and Disease," Current Biology Ltd./Garland Publishing Inc. 1994 Glossary p. G:2.
- Jang YJ, et al. "The structural basis for DNA binding by an anti-DNA autoantibody," *Mol Immunol*. Dec. 1998;35(18):1207-17.
- Jansen-Olesen I, et al. "In-depth characterization of CGRP receptors in human intracranial arteries," *Eur J Pharmacol*. Nov. 28, 2003;481(2-3):207-16.
- Jones PT, et al. "Replacing the complementarity-determining regions in a human antibody with those from a mouse," *Nature*. May 29-Jun. 4, 1986;321(6069):522-5.
- Juaneda C, et al. "The molecular pharmacology of CGRP and related peptide receptor subtypes," *Trends Pharmacol Sci*. Nov. 2000;21(11):432-8.
- Juhasz G, et al. "NO-induced migraine attack: strong increase in plasma calcitonin gene-related peptide (CGRP) concentration and negative correlation with platelet serotonin release," *Pain*. Dec. 2003;106(3):461-70.
- Juhl L, et al. "Effect of two novel CGRP-binding compounds in a closed cranial window rat model," *Eur J Pharmacol*. Jul. 12, 2007;567(1-2):117-24.
- Julia V, et al. "Tachykininergic mediation of viscerosensitive responses to acute inflammation in rats: role of CGRP," *Am J Physiol*. Jan. 1997;272(1 Pt 1):G141-6.
- Jung ST, et al. "Bypassing glycosylation: engineering aglycosylated full-length IgG antibodies for human therapy," *Curr Opin Biotechnol*. Dec. 2011;22(6):858-67.
- Kaiser EA, et al. "CGRP and migraine: could PACAP play a role too?" *Neuropeptides*. Dec. 2013;47(6):451-61.
- Kapoor K, et al. "Effects of BIBN4096BS on cardiac output distribution and on CGRP-induced carotid haemodynamic responses in the pig," *Eur J Pharmacol*. Aug. 15, 2003;475(1-3):69-77.
- Kapoor K, et al. "Effects of the CGRP receptor antagonist BIBN4096BS on capsaicin-induced carotid haemodynamic changes in anaesthetised pigs," *Br J Pharmacol*. Sep. 2003;140(2):329-38.
- Kapoor, K. "Novel Potential Antimigraine Compounds: Carotid and Systemic Haemodynamic Effects in a Porcine Model of Migraine," Thesis, Erasmus University, Rotterdam. With summary in Dutch. 2003. 157 pages.
- Karasek C., et al. "Characterization of the intrinsic binding features of three anti-CGRP therapeutic antibodies effective in preventing migraine: a comparative pre-clinical case study of ALD403, LY-2951742,

(56)

References Cited**OTHER PUBLICATIONS**

- TEV-48125." 5th European Headache and Migraine Trust International Congress, Sep. 2016. 4 pages.
- Kato K, et al. "CGRP antagonists enhance gastric acid secretion in 2-h pylorus-ligated rats," *Peptides*. 1995;16(7):1257-62.
- Kawamura M, et al. "Antinociceptive effect of intrathecally administered antiserum against calcitonin gene-related peptide on thermal and mechanical noxious stimuli in experimental hyperalgesic rats." *Brain Res.* Sep. 11, 1989;497(1):199-203.
- Kaymakcalan Z, et al. "Comparisons of affinities, avidities, and complement activation of adalimumab, infliximab, and etanercept in binding to soluble and membrane tumor necrosis factor," *Clin Immunol.* May 2009;131(2):306-16.
- Keates AC, et al. "CGRP upregulation in dorsal root ganglia and ileal mucosa during *Clostridium difficile* toxin A-induced enteritis," *Am J Physiol.* Jan. 1998;274(1 Pt 1):G196-202.
- Kennel SJ, et al. "Direct Binding of Radioiodinated Monoclonal Antibody to Tumor Cells: Significance of Antibody Purity and Affinity for Drug Targeting or Tumor Imaging," *Hybridoma*. 1983;2(3):297-310.
- Kim SJ, et al. "Antibody Engineering for the Development of Therapeutic Antibodies," *Mol Cells*. Aug. 31, 2005;20(1):17-29.
- Kipriyanov S, et al. "Generation and Production of Engineered Antibodies," *Mol Biotechnol.* Jan. 2004;26(1):39-60.
- Kipriyanov S. "Generation of Antibody Molecules Through Antibody Engineering" from *Methods in Molecular Biology*, vol. 207: Recombinant Antibodies for Cancer Therapy Methods and Protocols, 2003 pp. 3-25.
- Knotkova H, et al. "Imaging intracranial plasma extravasation in a migraine patient: a case report," *Pain Med.* May-Jun. 2007;8(4):383-7.
- Kobayashi D, et al. "Calcitonin Gene-Related Peptide Mediated Neurogenic Vasorelaxation in the Isolated Canine Lingual Artery," *Jpn J Pharmacol.* Apr. 1995;67(4):329-39.
- Kobayashi H, et al. "Tryptophan H33 plays an important role in pyrimidine (6-4) pyrimidone photoproduct binding by a high-affinity antibody." *Protein Eng.* Oct. 1999;12(10):879-84.
- Krymchantowski AV, et al. "New and emerging prophylactic agents for migraine," *CNS Drugs*. 2002;16(9):611-34.
- Krymchantowski AV, et al. "Rizatriptan in migraine," *Expert Rev Neurother.* Sep. 2005;5(5):597-603.
- Krymchantowski AV, et al. "Rizatriptan vs. rizatriptan plus trimebutine for the acute treatment of migraine: a double-blind, randomized, cross-over, placebo-controlled study," *Cephalgia*, Jul. 2006;26(7):871-4.
- Krymchantowski AV, et al. "Topiramate plus nortriptyline in the preventive treatment of migraine: a controlled study for nonresponders," *J Headache Pain.* Jan. 2012;13(1):53-9.
- Kumar S, et al. "Molecular cloning and expression of the Fabs of human autoantibodies in *Escherichia coli*. Determination of the heavy or light chain contribution to the anti-DNA-cardiolipin activity of the Fab." *J Biol Chem.* Nov. 10, 2000;275(45):35129-36.
- Kunkel RS, et al. "Surgical treatment of chronic migraineous neuralgia," *Cleve Clin Q.* 1974 Winter;41(4):189-92.
- Kuraishi Y, et al. "Antinociception induced in rats by intrathecal administration of antiserum against calcitonin gene-related peptide." *Neurosci Lett.* Oct. 17, 1988;92(3):325-9.
- Kurosawa M, et al. "Increase of meningeal blood flow after electrical stimulation of rat dura mater encephali: mediation by calcitonin gene-related peptide," *Br J Pharmacol.* Apr. 1995;114(7):1397-402.
- Kuus-Reichel K, et al. "Will Immunogenicity Limit the Use, Efficacy, and Future Development of Therapeutic Monoclonal Antibodies?" *Clin Diagn Lab Immunol.* Jul. 1994;1(4):365-72.
- Lambrecht N, et al. "Role of calcitonin gene-related peptide and nitric oxide in the gastroprotective effect of capsaicin in the rat," *Gastroenterology*. May 1993;104(5):1371-80.
- Lance J. "Migraine Pain Originates from Blood Vessels." *Headache Pathogenesis: Monoamines, Neuropeptides, Purines, and Nitric Oxide*, edited by J. Olesen and L. Edvinsson, Lippincott-Raven Publishers, Philadelphia, 1997. Chapter 1, pp. 3-9.
- Lassen LH, et al. "CGRP may play a causative role in migraine." *Cephalgia*. Feb. 2002;22(1):54-61.
- Lassen LH, et al. "Involvement of calcitonin gene-related peptide in migraine: regional cerebral blood flow and blood flow velocity in migraine patients," *J Headache Pain.* Jun. 2008;9(3):151-7.
- Lazzeria M, et al. "The Challenge of the Overactive Bladder: From Laboratory to New Drugs," European Association of Urology, vol. 5, Issue 6, Dec. 2007, pp. 250-258.
- Lee CV, et al. "High-affinity human antibodies from phage-displayed synthetic Fab libraries with a single framework scaffold," *J Mol Biol.* Jul. 23, 2004;340(5):1073-93.
- Leighton B, et al. "Pancreatic amylin and calcitonin gene-related peptide cause resistance to insulin in skeletal muscle in vitro," *Nature*. Oct. 13, 1988;335(6191):632-5.
- Levèque D, et al. "Pharmacokinetics of therapeutic monoclonal antibodies used in oncology," *Anticancer Res.* May-Jun. 2005;25(3c):2327-43.
- Levy D, et al. "A critical view on the role of migraine triggers in the genesis of migraine pain," *Headache*. Jun. 2009;49(6):953-7.
- Levy D, et al. "Calcitonin gene-related peptide does not excite or sensitize meningeal nociceptors: implications for the pathophysiology of migraine," *Ann Neurol.* Nov. 2005;58(5):698-705.
- Levy D, et al. "Migraine pain and nociceptor activation—where do we stand?" *Headache*. May 2010;50(5):909-16.
- Levy D, et al. "The vascular theory of migraine: leave it or love it?" *Ann Neurol.* Apr. 2011;69(4):800-1.
- Li DS, et al. "Role of calcitonin gene-related peptide in gastric hyperemic response to intragastric capsaicin," *Am J Physiol.* Oct. 1991;261(4 Pt 1):G657-61.
- Lin HC, et al. "Immuneutralization of Calcitonin Gene-Related Peptide (CGRP) During Inhibition of Intestinal Transit by Fat," *Gastroenterology* vol. 114, No. 4, 1998. 1 page, Abstract No. G3253.
- Lin YS, et al. "Preclinical pharmacokinetics, interspecies scaling, and tissue distribution of a humanized monoclonal antibody against vascular endothelial growth factor," *J Pharmacol Exp Ther.* Jan. 1999;288(1):371-8.
- Link AS, et al. "Treatment of migraine attacks based on the interaction with the trigemino-cerebrovascular system," *J Headache Pain.* Feb. 2008;9(1):5-12.
- Lipton RB, et al. "CGRP antagonists in the acute treatment of migraine," *Lancet Neurol.* Jun. 2004;3(6):332.
- Lipton RB, et al. "Headache: triumphs in translational research," *Lancet Neurol.* Jan. 2005;4(1):11-2.
- Lipton RB, et al. "Moving forward—essential questions for the next 10 years," *Headache*. Feb. 2009;49 Suppl 1:S43-6.
- Little M, et al. "Of mice and men: hybridoma and recombinant antibodies." *Immunol Today*. Aug. 2000;21(8):364-70.
- Lonberg N, et al. "Antigen-specific human antibodies from mice comprising four distinct genetic modifications," *Nature*, Apr. 28, 1994;368(6474):856-9.
- Lonberg N, et al. "Human antibodies from transgenic animals," *Nat Biotechnol.* Sep. 2005;23(9):1117-25.
- Longoni M, et al. "Inflammation and excitotoxicity: role in migraine pathogenesis," *Neurol Sci.* May 2006;27 Suppl 2:S107-10.
- Louis SM, et al. "Antibodies to calcitonin-gene related peptide reduce inflammation induced by topical mustard oil but not that due to carrageenin in the rat." *Neurosci Lett.* Jul. 31, 1989;102(2-3):257-60.
- Louis SM, et al. "Immunization with calcitonin gene-related peptide reduces the inflammatory response to adjuvant arthritis in the rat," *Neuroscience*. 1990;39(3):727-31.
- Louis SM, et al. "The role of substance P and calcitonin gene-related peptide in neurogenic plasma extravasation and vasodilatation in the rat." *Neuroscience*. 1989;32(3):581-6.
- MacCallum RM, et al. "Antibody-antigen interactions: contact analysis and binding site topography." *J Mol Biol.* Oct. 11, 1996;262(5):732-45.
- MacGregor EA, "Migraine in pregnancy and lactation; a clinical review," *J Fam Plann Reprod Health Care.* Apr. 2007;33(2):83-93.
- Majima, M, et al. "Roles of calcitonin gene-related peptide in channelling of angiogenesis," *Inflammation and Regeneration* vol. 31 No. 2 Mar. 2011, 146-150.

(56)

References Cited**OTHER PUBLICATIONS**

- Mallee JJ, et al. "Receptor activity-modifying protein 1 determines the species selectivity of non-peptide CGRP receptor antagonists." *J Biol Chem.* Apr. 19, 2002;277(16):14294-8.
- Marcelo E. Bigal et al: "Calcitonin Gene-Related Peptide (CGRP) and Migraine Current Understanding and State of Development", *Headache*, vol. 53, No. 8, Sep. 12, 2013 (Sep. 12, 2013), pp. 1230-1244.
- Mareska M, et al. "Lambert-Eaton myasthenic syndrome," *Semin Neurol.* Jun. 2004;24(2):149-53.
- Marquez de Prado B and Russo AF, "CGRP receptor antagonists: A new frontier of anti-migraine medications," *Drug Discov Today Ther Strateg.* 2006 Winter;3(4):593-597.
- Marshall I, et al. "Human and rat alpha-CGRP but not calcitonin cause mesenteric vasodilatation in rats." *Eur J Pharmacol.* Apr. 16, 1986;123(2):217-22.
- Martinez-Sáenz A, et al., "Role of calcitonin gene-related peptide in inhibitory neurotransmission to the pig bladder neck," *J Urol.* Aug. 2011;186(2):728-35.
- Maynard JA, et al. "Protection against anthrax toxin by recombinant antibody fragments correlates with antigen affinity," *Nat Biotechnol.* Jun. 2002;20(6):597-601.
- McCafferty J, et al. "Phage antibodies: filamentous phage displaying antibody variable domains," *Nature.* Dec. 6, 1990;348(6301):552-4.
- McCulloch J, et al. "Calcitonin gene-related peptide: functional role in cerebrovascular regulation," *Proc Natl Acad Sci U S A.* Aug. 1986;83(15):5731-5.
- McLatchie LM, et al. "RAMPs regulate the transport and ligand specificity of the calcitonin-receptor-like receptor," *Nature.* May 28, 1998;393(6683):333-9.
- Mehrotra S, et al. "Current and prospective pharmacological targets in relation to antimigraine action," *Naunyn Schmiedebergs Arch Pharmacol.* Oct. 2008;378(4):371-94.
- Mense S. "Pathophysiology of low back pain and the transition to the chronic state—experimental data and new concepts." *Schmerz.* Dec. 2001;15(6):413-7.
- Messlinger K, et al. "Neuropeptide effects in the trigeminal system: pathophysiology and clinical relevance in migraine," *Keio J Med.* 2011;60(3):82-9.
- Messlinger K. "Migraine: where and how does the pain originate?" *Exp Brain Res.* Jun. 2009; 196(1):179-93.
- Messlinger, et al. "Inhibition of neurogenic blood flow increases in the rat cranial dura matter by a CGRP-binding Spiegelmer," *Cephalgia*, No. F022 2004.
- Middlemiss DN. "Direct evidence for an interaction of beta-adrenergic blockers with the 5-HT receptor," *Nature.* May 19, 1977;267(5608):289-90.
- Middlemiss DN. "Stereoselective blockade at [3H]5-HT binding sites and at the 5-HT autoreceptor by propranolol," *Eur J Pharmacol.* Jun. 1, 1984;101(3-4):289-93.
- Mirick GR, et al. "A review of human anti-globulin antibody (HAGA, HAMA, HACA, HAHA) responses to monoclonal antibodies. Not four letter words," *Q J Nucl Med Mol Imaging.* Dec. 2004;48(4):251-7.
- Molina JM, et al. "Induction of insulin resistance in vivo by amylin and calcitonin gene-related peptide," *Diabetes.* Feb. 1990;39(2):260-5.
- Moore CK, et al. "Urological Applications of Botulinum Toxin," *Female Urology: A Practical Clinical Guide.* 2007 Chapter 14:213-217.
- Moore EL, et al. "Targeting a family B GPCR/RAMP receptor complex: CGRP receptor antagonists and migraine," *Br J Pharmacol.* May 2012;166(1):66-78.
- Morara S, et al. "Monoclonal antibodies reveal expression of the CGRP receptor in Purkinje cells, interneurons and astrocytes of rat cerebellar cortex," *Neuroreport.* Nov. 16, 1998;9(16):3755-9.
- Morell A, et al. "Metabolic properties of IgG subclasses in man." *J Clin Invest.* Apr. 1970;49(4):673-80.
- Morrison SL, et al. "Chimeric human antibody molecules: mouse antigen-binding domains with human constant region domains," *Proc Natl Acad Sci U S A.* Nov. 1984;81(21):6851-5.
- Moskowitz MA, "Neurogenic inflammation in the pathophysiology and treatment of migraine," *Neurology.* Jun. 1993;43(6 Suppl 3):S16-20.
- Moskowitz MA, et al. "CGRP: blood flow and more?" *Cephalgia.* Aug. 1996;16(5):287.
- Moskowitz MA. "Pathophysiology of headache—past and present," *Headache.* Apr. 2007;47 Suppl 1:S58-63.
- Mould DR, et al. "A population pharmacokinetic-pharmacodynamic analysis of single doses of clenoliximab in patients with rheumatoid arthritis," *Clin Pharmacol Ther.* Sep. 1999;66(3):246-57.
- Mountain A, et al. "Engineering antibodies for therapy," *Biotechnol Genet Eng Rev.* 1992;10:1-142.
- Muff R, et al. "Calcitonin, calcitonin gene-related peptide, adrenomedullin and amylin: homologous peptides, separate receptors and overlapping biological actions," *Eur J Endocrinol.* Jul. 1995;133(1):17-20.
- Mulderry PK, et al. "Differential expression of alpha-CGRP and beta-CGRP by primary sensory neurons and enteric autonomic neurons of the rat," *Neuroscience.* Apr. 1988;25(1):195-205.
- Mullins MW, et al. "Characterization of a calcitonin gene-related peptide (CGRP) receptor on mouse bone marrow cells," *Regul Pept.* Nov. 19, 1993;49(1):65-72.
- Nakamura-Craig M, et al. "Effect of neurokinin A, substance P and calcitonin gene related peptide in peripheral hyperalgesia in the rat paw," *Neurosci Lett.* Mar. 11, 1991;124(1):49-51.
- Naot D, et al. "The role of peptides and receptors of the calcitonin family in the regulation of bone metabolism," *Bone.* Nov. 2008;43(5):813-8.
- Negro A, et al. "CGRP receptor antagonists: an expanding drug class for acute migraine?" *Expert Opin Investig Drugs.* Jun. 2012;21(6):807-18.
- Newman R, et al. "Modification of the Fc region of a primatized IgG antibody to human CD4 retains its ability to modulate CD4 receptors but does not deplete CD4(+) T cells in chimpanzees," *Clin Immunol.* Feb. 2001;98(2):164-74.
- Ng-Mak DS, et al. "Migraine treatment with rizatriptan and almotriptan: a crossover study," *Headache.* May 2009;49(5):655-62.
- Nippon Rinsho, "Recent Development of Calcitonin Gene-related Peptide (CGRP) receptor antagonist," 2005, vol. 63, Suppl.10, pp. 263-266 [Original With English Translation].
- Nishimoto N, et al. "Anti-interleukin-6 receptor antibody therapy in rheumatic diseases," *Endocr Metab Immune Disord Drug Targets.* Dec. 2006;6(4):373-81.
- Oates PJ, et al. "Studies on the mechanism of ethanol-induced gastric damage in rats," *Gastroenterology.* Jan. 1988;94(1):10-21.
- Ober RJ, et al. "Visualizing the site and dynamics of IgG salvage by the MHC class I-related receptor, FeRn," *J Immunol.* Feb. 15, 2004;172(4):2021-9.
- O'Connell JP, et al. "On the role of the C-terminus of alpha-calcitonin-gene-related peptide (alpha CGRP). The structure of des-phenylalaninamide37-alpha CGRP and its interaction with the CGRP receptor," *Biochem J.* Apr. 1, 1993;291 (Pt 1):205-10.
- Oh-hashi Y, et al. "Elevated sympathetic nervous activity in mice deficient in alphaCGRP," *Circ Res.* Nov. 23, 2001;89(11):983-90.
- Olesen J, et al. "Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine," *N Engl J Med.* Mar. 11, 2004;350(11):1104-10.
- Olesen J, et al. "Chapter 16: Calcitonin Gene-Related Peptide and Other Peptides." *The Headaches Third Edition.* Lippincott Williams & Wilkins 2006 159-164.
- Olesen J, et al. "Chapter 31: CGRP Involvement in Migraines." *The Headaches Third Edition.* Lippincott Williams & Wilkins 2006 289-99.
- Olesen J, et al. "Emerging migraine treatments and drug targets," *Trends Pharmacol Sci.* Jun. 2011;32(6):352-9.
- Olesen J, et al. "Finding new drug targets for the treatment of migraine attacks," *Cephalgia.* Sep. 2009;29(9):909-20.
- Olesen J, et al. "Migraine: a research field matured for the basic neurosciences," *Trends Neurosci.* Jan. 1991;14(1):3-5.

(56)

References Cited**OTHER PUBLICATIONS**

- Olesen J, et al. "Origin of pain in migraine: evidence for peripheral sensitisation," *Lancet Neurol.* Jul. 2009;8(7):679-90.
- Olesen J. "Migraine: A neural pathway for photophobia in migraine," *Nat Rev Neurol.* May 2010;6(5):241-2.
- Ondo WG, et al. "Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study," *Cephalgia.* Jan. 2004;24(1):60-5.
- O'Sullivan J, et al. "Migraine development, treatments, research advances, and anesthesia implications," *Anaesthesia.* Feb. 2006;74(1):61-9.
- Ottosson A, et al. "Release of histamine from dural mast cells by substance P and calcitonin gene-related peptide," *Cephalgia.* May 1997;17(3):166-74.
- Pabst MA, et al. "Ablation of capsaicin sensitive afferent nerves impairs defence but not rapid repair of rat gastric mucosa," *Gut.* Jul. 1993;34(7):897-903.
- Panconesi A, et al. "Migraine pain: reflections against vasodilation," *J Headache Pain.* Oct. 2009;10(5):317-25.
- Panka DJ, et al. "Defining the structural correlates responsible for loss of arsonate affinity in an IDCR antibody isolated from an autoimmune mouse," *Mol Immunol.* Aug. 1993;30(11):1013-20.
- Paone DV, et al. "Calcitonin gene-related peptide receptor antagonists for the treatment of migraine: a patent review," *Expert Opin Ther Pat.* Dec. 2009;19(12):1675-713.
- Papadopoulos N, et al. "Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab," *Angiogenesis.* Jun. 2012;15(2):171-85.
- Papp K, et al. "The treatment of moderate to severe psoriasis with a new anti-CD11a monoclonal antibody," *J Am Acad Dermatol.* Nov. 2001;45(5):665-74.
- Pavlou AK, et al. "Recombinant protein therapeutics—success rates, market trends and values to 2010," *Nat Biotechnol.* Dec. 2004;22(12):1513-9.
- Peroutka SJ, et al. "Neurogenic inflammation and migraine: implications for the therapeutics," *Mol Interv.* Oct. 2005;5(5):304-11.
- Peskar BM, et al. "A monoclonal antibody to calcitonin gene-related peptide abolishes capsaicin-induced gastroprotection," *Eur J Pharmacol.* Nov. 30, 1993;250(1):201-3.
- Petersen KA, et al. "BIBN4096BS antagonizes human alpha-calcitonin gene related peptide-induced headache and extracerebral artery dilatation," *Clin Pharmacol Ther.* Mar. 2005;77(3):202-13.
- Petersen KA, et al. "Effect of hypotension and carbon dioxide changes in an improved genuine closed cranial window rat model," *Cephalgia.* Jan. 2005;25(1):23-9.
- Petersen KA, et al. "Inhibitory effect of BIBN4096BS on cephalic vasodilatation induced by CGRP or transcranial electrical stimulation in the rat," *Br J Pharmacol.* Nov. 2004;143(6):697-704.
- Petersen KA, et al. "Presence and function of the calcitonin gene-related peptide receptor on rat pial arteries investigated in vitro and in vivo," *Cephalgia.* Jun. 2005;25(6):424-32.
- Petersen KA, et al. "The effect of nonpeptide CGRP-antagonist, BIBN4096BS on human-alphaCGRP induced headache and hemodynamics in healthy volunteers," *Cephalgia.* vol. 23, extract from Abstracts of the XI Congress of the International Headache Society, p. 725, 2003.
- Petkova SB, et al. "Enhanced half-life of genetically engineered human IgG1 antibodies in a humanized FcRn mouse model: potential application in humorally mediated autoimmune disease," *Int Immunol.* Dec. 2006;18(12):1759-69.
- Pietrobon D, et al. "Pathophysiology of migraine," *Annu Rev Physiol.* 2013;75:365-91.
- Plessas IN, et al. "Migraine-like episodic pain behavior in a dog: can dogs suffer from migraines?" *J Vet Intern Med.* Sep.-Oct. 2013;27(5):1034-40.
- Plourde V, et al. "CGRP antagonists and capsaicin on celiac ganglia partly prevent postoperative gastric ileus," *Peptides.* Nov.-Dec. 1993;14(6):1225-9.
- Poyner DR, et al. "International Union of Pharmacology. XXXII. The mammalian calcitonin gene-related peptides, adrenomedullin, amylin, and calcitonin receptors," *Pharmacol Rev.* Jun. 2002;54(2):233-46.
- Presta L. "Antibody engineering for therapeutics," *Curr Opin Struct Biol.* Aug. 2003;13(4):519-25.
- Presta LG, et al. "Engineering therapeutic antibodies for improved function," *Biochem Soc Trans.* Aug. 2002;30(4):487-90.
- Prewett M, et al. "The biologic effects of C225, a chimeric monoclonal antibody to the EGFR, on human prostate carcinoma," *J Immunother Emphasis Tumor Immunol.* Nov. 1996;19(6):419-27.
- Qing-Hui Niu, et al. "Expression of mast cell and calcitonin gene related peptides in the mucosa of irritable bowel syndrome," *World Chinese Journal of Digestology.* Jan. 18, 2009 p. 213-217; ISSN 1099-3079.
- Raddatt AC, et al. "Calcitonin gene-related peptide in migraine: intersection of peripheral inflammation and central modulation," *Expert Rev Mol Med.* Nov. 29, 2011;13:e36.
- Ramadan NM, et al. "New and future migraine therapy," *Pharmacol Ther.* Oct. 2006;112(1):199-212.
- Ramadan NM. "Acute treatments: future developments," *Curr Med Res Opin.* 2001;17 Suppl 1:s81-6.
- Ramos ML, et al. "AMG 334 CGRP antibody for migraine: time to celebrate?" *Lancet Neurol.* Apr. 2016;15(4):347-9.
- Rapoport AM, Bigal ME, et al. "Naratriptan in the preventive treatment of refractory chronic migraine." In Olsen J, Silberstein SD, Tfelt-Hansen P, eds. *Preventive Pharmacotherapy of Headache Disorders.* Copenhagen: Oxford University Press, 2004, Chapter 31.
- Rapoport AM, et al. "Intranasal medications for the treatment of migraine and cluster headache," *CNS Drugs.* 2004;18(10):671-85.
- Rapoport AM, et al. "Levetiracetam in the preventive treatment of transformed migraine: A prospective, open-label, pilot study," *Curr Ther Res Clin Exp.* May 2005;66(3):212-21.
- Rapoport AM, et al. "Migraine preventive therapy: current and emerging treatment options," *Neurol Sci.* May 2005;26 Suppl 2:s111-20.
- Rapoport AM, et al. "Preventive migraine therapy: what is new," *Neurol Sci.* Oct. 2004;25 Suppl 3:S177-85.
- Raybould HE, et al. "Selective ablation of spinal afferent neurons containing CGRP attenuates gastric hyperemic response to acid," *Peptides.* Mar.-Apr. 1992;13(2):249-54.
- Reasbeck PG, et al. "Calcitonin gene-related peptide: enteric and cardiovascular effects in the dog," *Gastroenterology.* Oct. 1988;95(4):966-71.
- Recober A, et al. "Calcitonin gene-related peptide: A molecular link between obesity and migraine?" *Drug News Perspect.* Mar. 2010;23(2):112-7.
- Recober A, et al. "Calcitonin gene-related peptide: an update on the biology," *Curr Opin Neurol.* Jun. 2009;22(3):241-6.
- Recober A, et al. "Olcegeptan, a non-peptide CGRP1 antagonist for migraine treatment," *IDrugs.* Aug. 2007;10(8):566-74.
- Recober A, et al., "Role of calcitonin gene-related peptide in light-aversive behavior: implications for migraine," *J Neurosci.* Jul. 8, 2009;29(27):8798-804.
- Reddy MP, et al. "Elimination of Fc receptor-dependent effector functions of a modified IgG4 monoclonal antibody to human CD4," *J Immunol.* Feb. 15, 2000;164(4):1925-33.
- Reff ME, et al. "A review of modifications to recombinant antibodies: attempt to increase efficacy in oncology applications," *Crit Rev Oncol Hematol.* Oct. 2001;40(1):25-35.
- Reff ME, et al. "Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20," *Blood.* Jan. 15, 1994;83(2):435-45.
- Reichert JM, et al. "Monoclonal antibody successes in the clinic," *Nat Biotechnol.* Sep. 2005;23(9):1073-8.
- Reinshagen M, et al. "Calcitonin gene-related peptide mediates the protective effect of sensory nerves in a model of colonic injury," *J Pharmacol Exp Ther.* Aug. 1998;286(2):657-61.
- Reuter U, et al. "Experimental models of migraine," *Funct Neurol.* 2000;15 Suppl 3:9-18.
- Reuter U. "Anti-CGRP antibodies: a new approach to migraine prevention," *Lancet Neurol.* Sep. 2014;13(9):857-9.

(56)

References Cited

OTHER PUBLICATIONS

- Rolston RK, et al., "Intravenous calcitonin gene-related peptide stimulates net water secretion in rat colon in vivo," *Dig Dis Sci.* Apr. 1989;34(4):612-6.
- Roon KI, et al. "No acute antimigraine efficacy of CP-122,288, a highly potent inhibitor of neurogenic inflammation: results of two randomized, double-blind, placebo-controlled clinical trials," *Ann Neurol.* Feb. 2000;47(2):238-41.
- Roopenian DC, et al. "FcRn: the neonatal Fc receptor comes of age," *Nat Rev Immunol.* Sep. 2007;7(9):715-25.
- Roque AC, et al. "Antibodies and genetically engineered related molecules: production and purification," *Biotechnol Prog.* May-Jun. 2004;20(3):639-54.
- Roskos LK, et al. "The Clinical Pharmacology of Therapeutic Monoclonal Antibodies," *Drug Development Research* 2004 61:108-120.
- Rother RP, et al. "Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria," *Nat Biotechnol.* Nov. 2007;25(11):1256-64.
- Rovero P, et al. "CGRP antagonist activity of short C-terminal fragments of human alpha CGRP, CGRP(23-37) and CGRP(19-37)." *Peptides.* Sep.-Oct. 1992;13(5):1025-7.
- Rudikoff S, et al. "Single amino acid substitution altering antigen-binding specificity," *Proc Natl Acad Sci U S A.* Mar. 1982;79(6):1979-83.
- Ruiz-Gayo M, et al. "Vasodilatory effects of cholecystokinin: new role for an old peptide?" *Regul Pept.* Dec. 10, 2006;137(3):179-84.
- Russo AF, et al., "A Potential Preclinical Migraine Model: CGRP-Sensitized Mice," *Mol Cell Pharmacol.* 2009;1(5):264-270.
- Russo AF. "Calcitonin gene-related peptide (CGRP): a new target for migraine," *Annu Rev Pharmacol Toxicol.* 2015;55:533-52.
- Russo. "CGRP Meeting Abstract Book," The 4th International Meeting on CGRP, Copenhagen, Sep. 2001, 71 pages.
- Russo. "CGRP Meeting Abstract Book," Joint International Symposium on Calcitonin Gene-Related Peptide, Amylin and Calcitonin; 4th Symposium on Adrenomedullin and Preadrenomedullin N-20 Peptide, Zurich, Switzerland, Mar. 2004. 38 pages.
- Ryan AM, et al. "Preclinical safety evaluation of rhuMAbVEGF, an antiangiogenic humanized monoclonal antibody," *Toxicol Pathol.* Jan.-Feb. 1999;27(1):78-86.
- Ryan S. "Medicines for migraine," *Arch Dis Child Educ Pract Ed.* Apr. 2007;92(2):ep50-5.
- Saleh MN, et al. "Phase I trial of the chimeric anti-GD2 monoclonal antibody ch14.18 in patients with malignant melanoma," *Hum Antibodies Hybridomas.* Jan. 1992;3(1):19-24.
- Salonen R, et al. "Triptans: do they differ?" *Curr Pain Headache Rep.* Apr. 2002;6(2):133-9.
- Salvatore CA, et al. "Pharmacological characterization of MK-0974 [N-[3(R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide], a potent and orally active calcitonin gene-related peptide receptor antagonist for the treatment of migraine," *J Pharmacol Exp Ther.* Feb. 2008;324(2):416-21.
- Sars-Nielsen A, et al. "Pharmacological evidence for CGRP uptake into perivascular capsaicin sensitive nerve terminals," *Br J Pharmacol.* Mar. 2001;132(5):1145-53.
- Saphire EO, et al. "Crystal structure of a neutralizing human IgG against HIV-1: a template for vaccine design," *Science.* Aug. 10, 2001;293(5532):1155-9.
- Schaible HG, et al. "Mechanisms of pain in arthritis," *Ann N Y Acad Sci.* Jun. 2002;966:343-54.
- Schelstraete C, et al. "CGRP antagonists: hope for a new era in acute migraine treatment," *Acta Neurol Belg.* Dec. 2009;109(4):252-61.
- Schier R, et al. "Isolation of high-affinity monomeric human anti-c-erbB-2 single chain Fv using affinity-driven selection," *J Mol Biol.* Jan. 12, 1996;255(1):28-43.
- Schier R, et al. "Isolation of picomolar affinity anti-c-erbB-2 single-chain Fv by molecular evolution of the complementarity determining regions in the center of the antibody binding site," *J Mol Biol.* Nov. 8, 1996;263(4):551-67.
- Schifter S. "Circulating concentrations of calcitonin gene-related peptide (CGRP) in normal man determined with a new, highly sensitive radioimmunoassay," *Peptides.* Mar.-Apr. 1991;12(2):365-9.
- Schindler M, et al. "Binding properties of the novel, non-peptide CGRP receptor antagonist radioligand, [(3)H]BIBN4096BS," *Eur J Pharmacol.* May 10, 2002;442(3):187-93.
- Schoenen J, et al. "Almotriptan and its combination with acetaminophen for migraine attacks: a study of efficacy and the influence of auto-evaluated brush allodynia," *Cephalgia.* Oct. 2008;28(10):1095-105.
- Schreiber CP, "The pathophysiology of migraine," *Dis Mon.* Oct. 2006;52(10):385-401.
- Schwenger N, et al. "Interaction of calcitonin gene-related peptide, nitric oxide and histamine release in neurogenic blood flow and afferent activation in the rat cranial dura mater," *Cephalgia.* Jun. 2007;27(6):481-91.
- Schytz HW, et al. "What have we learnt from triggering migraine?" *Curr Opin Neurol.* Jun. 2010;23(3):259-65.
- Seike M, et al. "Increased synthesis of calcitonin gene-related peptide stimulates keratinocyte proliferation in murine UVB-irradiated skin," *J Dermatol Sci.* Feb. 2002;28(2):135-43.
- Selenko N, et al. "CD20 antibody (C2B8)-induced apoptosis of lymphoma cells promotes phagocytosis by dendritic cells and cross-priming of CD8+ cytotoxic T cells," *Leukemia.* Oct. 2001;15(10):1619-26.
- Seong J, et al. "Radiation-induced alteration of pain-related signals in an animal model with bone invasion from cancer," *Ann N Y Acad Sci.* Dec. 2004;1030:179-86.
- Seybold VS. "The role of peptides in central sensitization," *Handb Exp Pharmacol.* 2009;(194):451-91.
- Shaw NE, et al. "The effect of monoclonal antibodies to calcitonin gene-related peptide (CGRP) on CGRP-induced vasodilation in pig coronary artery rings," *Br J Pharmacol.* May 1992;106(1):196-8.
- Sheets MD, et al. "Efficient construction of a large nonimmune phage antibody library: the production of high-affinity human single-chain antibodies to protein antigens," *Proc Natl Acad Sci U S A.* May 26, 1998;95(11):6157-62.
- Sheftell FD, et al. "Naratriptan in the preventive treatment of refractory transformed migraine: a prospective pilot study," *Headache.* Nov.-Dec. 2005;45(10):1400-6.
- Shen YT, et al. "Functional role of alpha-calcitonin gene-related peptide in the regulation of the cardiovascular system," *J Pharmacol Exp Ther.* Aug. 2001;298(2):551-8.
- Shevel E. "The extracranial vascular theory of migraine—a great story confirmed by the facts," *Headache.* Mar. 2011;51(3):409-17.
- Shields RL, et al. "High resolution mapping of the binding site on human IgG1 for Fc gamma RI, Fc gamma RII, Fc gamma RIII, and FcRn and design of IgG1 variants with improved binding to the Fc gamma R," *J Biol Chem.* Mar. 2, 2001;276(9):6591-604.
- Shulkes A, et al. "Production of calcitonin gene related peptide, calcitonin and PTH-related protein by a prostatic adenocarcinoma," *Clin Endocrinol (Oxf).* May 1991;134(5):387-93.
- Silberstein S, et al. "Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group," *Headache.* Jun. 2000;40(6):445-50.
- Silberstein SD, "Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology," *Neurology.* Sep. 26, 2000;55(6):754-62.
- Silberstein SD. "Emerging target-based paradigms to prevent and treat migraine," *Clin Pharmacol Ther.* Jan. 2013;93(1):78-85.
- Silverman AJ, et al. "Mast cells migrate from blood to brain," *J Neurosci.* Jan. 1, 2000;20(1):401-8.
- Simmons LC, et al. "Expression of full-length immunoglobulins in *Escherichia coli*: rapid and efficient production of aglycosylated antibodies," *J Immunol Methods.* May 1, 2002;263(1-2):133-47.
- Sixt ML, et al. "Calcitonin gene-related peptide receptor antagonist olcegepatin acts in the spinal trigeminal nucleus," *Brain.* Nov. 2009;132(Pt 11):3134-41.

(56)

References Cited**OTHER PUBLICATIONS**

- Skofitsch G, et al. "Comparative immunohistochemical distribution of amylin-like and calcitonin gene related peptide like immunoreactivity in the rat central nervous system," *Can J Physiol Pharmacol.* Jul. 1995;73(7):945-58.
- Smillie SJ, et al. "Calcitonin gene-related peptide (CGRP) and its role in hypertension," *Neuropeptides.* Apr. 2011;45(2):93-104.
- Smith KA, et al. "Demystified . . . recombinant antibodies," *J Clin Pathol.* Sep. 2004;57(9):912-7.
- Smith TW, et al. "Reversal of advanced digoxin intoxication with Fab fragments of digoxin-specific antibodies." *N Engl J Med.* Apr. 8, 1976;294(15):797-800.
- Smith-Gill SJ, et al. "Contributions of immunoglobulin heavy and light chains to antibody specificity for lysozyme and two haptens." *J Immunol.* Dec. 15, 1987;139(12):4135-44.
- Solomon S. "Major therapeutic advances in the past 25 years," *Headache.* Apr. 2007;47 Suppl 1:S20-2.
- Song MK, et al. "Light chain of natural antibody plays a dominant role in protein antigen binding." *Biochem Biophys Res Commun.* Feb. 16, 2000;268(2):390-4.
- Spetz AC, et al. "Momentary increase in plasma calcitonin gene-related peptide is involved in hot flashes in men treated with castration for carcinoma of the prostate," *J Urol.* Nov. 2001;166(5):1720-3.
- Sprenger T, et al. "Migraine pathogenesis and state of pharmacological treatment options," *BMC Med.* Nov. 16, 2009;7:71.
- Stensrud P, et al. "Comparative trial of Tenormin (atenolol) and Inderal (propranolol) in migraine," *Headache.* Jul. 1980;20(4):204-7.
- Storer RJ, et al. "Calcitonin gene-related peptide (CGRP) modulates nociceptive trigeminovascular transmission in the cat," *Br J Pharmacol.* Aug. 2004;142(7):1171-81.
- Stovner LJ, et al. "New drugs for migraine," *J Headache Pain.* Dec. 2009;10(6):395-406.
- Strassman AM, et al. "On the origin of headaches," *Endeavour.* 1997;21(3):97-100.
- Strassman AM, et al. "Response properties of dural nociceptors in relation to headache," *J Neurophysiol.* Mar. 2006;95(3):1298-306.
- Subramanian KN, et al. "Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia, MEDI-493 Study Group," *Pediatr Infect Dis J.* Feb. 1998;17(2):110-5.
- Tam SH, et al. "Abciximab (ReoPro, chimeric 7E3 Fab) demonstrates equivalent affinity and functional blockade of glycoprotein IIb/IIIa and alpha(v)beta3 integrins." *Circulation.* Sep. 15, 1998;98(11):1085-91.
- Tamura M, et al. "Structural correlates of an anticarcinoma antibody: identification of specificity-determining residues (SDRs) and development of a minimally immunogenic antibody variant by retention of SDRs only." *J Immunol.* Feb. 1, 2000;164(3):1432-41.
- Tan et al., "Demonstration of the neurotransmitter role of calcitonin gene-related peptides (CGRP) by immunoblockade with anti-CGRP monoclonal antibodies," *Br J Pharmacol.* Mar. 1994;111(3):703-10.
- Tan KK, et al. "Calcitonin gene-related peptide as an endogenous vasodilator: immunoblockade studies in vivo with an anti-calcitonin gene-related peptide monoclonal antibody and its Fab' fragment." *Clin Sci (Lond).* Dec. 1995;89(6):565-73.
- Tanaka H, et al. "Inhibition of calcitonin gene-related peptide (CGRP) has the potential to extend first-phase insulin secretion," *Exp Clin Endocrinol Diabetes.* May 2013;121(5):260-5.
- Taylor AW, et al. "Suppression of nitric oxide generated by inflammatory macrophages by calcitonin gene-related peptide in aqueous humor," *Invest Ophthalmol Vis Sci.* Jul. 1998;39(8):1372-8.
- Tedstone, et al. "The effect of islet amyloid polypeptide (amylin) and calcitonin gene-related peptide on glucose removal in the anaesthetized rat and on insulin secretion from rat pancreatic islets in vitro," *Biosci Rep.* Aug. 1990;10(4):339-45.
- Tepper SJ, Bigal ME, et al. "Botulinum toxin type A in the treatment of refractory headache." In Olsen J, Silberstein SD, Tfelt-Hansen P, eds. *Preventive Pharmacotherapy of Headache Disorders.* Copenhagen: Oxford University Press, 2004, Chapter 20.
- Tepper SJ, et al. "Botulinum neurotoxin type A in the preventive treatment of refractory headache: a review of 100 consecutive cases," *Headache.* Sep. 2004;44(8):794-800.
- Tepper SJ, et al. "Clinical and preclinical rationale for CGRP-receptor antagonists in the treatment of migraine," *Headache.* Sep. 2008;48(8):1259-68.
- Tepper SJ, et al. "Mechanisms of action of the 5-HT1B/1D receptor agonists," *Arch Neurol.* Jul. 2002;59(7):1084-8.
- Teva Pharmaceutical Industries Ltd., Press Release, "Teva to Acquire Labrys Biologics, Inc.," Jun. 3, 2014. 4 pages.
- Tfelt-Hansen P, et al. "Effervescent metoclopramide and aspirin (Migravess) versus effervescent aspirin or placebo for migraine attacks: a double-blind study," *Cephalgia.* Jun. 1984;4(2):107-11.
- Tfelt-Hansen P, et al. "Possible site of action of CGRP antagonists in migraine," *Cephalgia.* Apr. 2011;31(6):748-50.
- Tfelt-Hansen PC. "Verisimilitude (or "truthlikeness") as an alternative to pro and cons: migraine and cluster headache mechanisms," *J Headache Pain.* Oct. 2010;11(5):379-89.
- Theoharides TC, et al. "The role of mast cells in migraine pathophysiology," *Brain Res Brain Res Rev.* Jul. 2005;49(1):65-76.
- Thomas TC, et al. "Inhibition of complement activity by humanized anti-C5 antibody and single-chain Fv," *Mol Immunol.* Dec. 1996;33(17-18):1389-401.
- Tjen-A-Looi S, et al. "CGRP and somatostatin modulate chronic hypoxic pulmonary hypertension," *Am J Physiol.* Sep. 1992;263(3 Pt 2):H681-90.
- Toda M, et al. "Neuronal system-dependent facilitation of tumor angiogenesis and tumor growth by calcitonin gene-related peptide." *Proc Natl Acad Sci U S A.* Sep. 9, 2008;105(36):13550-5.
- Todd J, Schwedt et al: "14th International Headache Congress: Basic Science Highlights", *Headache*, vol. 50, No. 3, Mar. 1, 2010 (Mar. 1, 2010), pp. 520-526.
- Tokuda Y, et al. "Dose escalation and pharmacokinetic study of a humanized anti-HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer," *Br J Cancer.* Dec. 1999;81(8):1419-25.
- Tsujikawa K, et al. "Hypertension and dysregulated proinflammatory cytokine production in receptor activity-modifying protein 1-deficient mice," *Proc Natl Acad Sci U S A.* Oct. 16, 2007;104(42):16702-7.
- Turner LC, et al. "A neural shift theory of migraine," *Neuroepidemiology.* 1993;12(4):249-50.
- Tvedskov JF, et al. "No increase of calcitonin gene-related peptide in jugular blood during migraine," *Ann Neurol.* Oct. 2005;58(4):561-8.
- Tzabazis AZ, et al. "Antihyperalgesic effect of a recombinant herpes virus encoding antisense for calcitonin gene-related peptide." *Anesthesiology.* Jun. 2007;106(6):1196-203.
- Uhr M, et al. "Penetration of endogenous steroid hormones corticosterone, cortisol, aldosterone and progesterone into the brain is enhanced in mice deficient for both mdr1a and mdr1b P-glycoproteins," *J Neuroendocrinol.* Sep. 2002;14(9):753-9.
- Unger J. "Migraine headaches: a historical prospective, a glimpse into the future, and migraine epidemiology," *Dis Mon.* Oct. 2006;52(10):367-84.
- Vajdos FF, et al. "Comprehensive functional maps of the antigen-binding site of an anti-ErbB2 antibody obtained with shotgun scanning mutagenesis." *J Mol Biol.* Jul. 5, 2002;320(2):415-28.
- Van der Schueren BJ, et al. "Calcitonin gene-related peptide-8-37 antagonizes capsaicin-induced vasodilation in the skin: evaluation of a human *in vivo* pharmacodynamic model," *J Pharmacol Exp Ther.* Apr. 2008;325(1):248-55.
- Van Rossum D, et al. "Neuroanatomical localization, pharmacological characterization and functions of CGRP-related peptides and their receptors," *Neurosci Biobehav Rev.* Sep. 1997;21(5):649-78.
- Vater A, et al. "Short bioactive Spiegelmers to migraine-associated calcitonin gene-related peptide rapidly identified by a novel approach: tailored-SELEX." *Nucleic Acids Res.* Nov. 1, 2003;31(21):e130.
- Vaughan TJ, et al. "Human antibodies with sub-nanomolar affinities isolated from a large non-immunized phage display library," *Nat Biotechnol.* Mar. 1996;14(3):309-14.

(56)

References Cited**OTHER PUBLICATIONS**

- Villalón CM, et al. "The role of CGRP in the pathophysiology of migraine and efficacy of CGRP receptor antagonists as acute antimigraine drugs," *Pharmacol Ther.* Dec. 2009;124(3):309-23.
- Vincent A, et al. "Molecular targets for autoimmune and genetic disorders of neuromuscular transmission," *Eur J Biochem.* Dec. 2000;267(23):6717-28.
- Vogler B, et al. "Role of melatonin in the pathophysiology of migraine: implications for treatment," *CNS Drugs.* 2006;20(5):343-50.
- Volcy M, et al. "Botulinum toxin A for the treatment of greater occipital neuralgia and trigeminal neuralgia: a case report with pathophysiological considerations," *Cephalgia.* Mar. 2006;26(3):336-40.
- Von Mehren M, et al. "Monoclonal antibody therapy for cancer," *Annu Rev Med.* 2003;54:343-69.
- Wachter C, et al. "Visceral vasodilatation and somatic vasoconstriction evoked by acid challenge of the rat gastric mucosa: diversity of mechanisms," *J Physiol.* Jul. 15, 1995;486 (Pt 2):505-16.
- Wacnik PW, et al. "Tumor-induced mechanical hyperalgesia involves CGRP receptors and altered innervation and vascularization of DsRed2 fluorescent hindpaw tumors." *Pain.* May 2005;115(1-2):95-106.
- Waeber C, et al. "Migraine as an inflammatory disorder," *Neurology.* May 24, 2005;64(10 Suppl 2):S9-15.
- Walker CS, et al. "Mice lacking the neuropeptide alpha-calcitonin gene-related peptide are protected against diet-induced obesity," *Endocrinology.* Sep. 2010;151(9):4257-69.
- Walker CS, et al. "Regulation of signal transduction by calcitonin gene-related peptide receptors," *Trends Pharmacol Sci.* Oct. 2010;31(10):476-83.
- Ward ES, et al. "Binding activities of a repertoire of single immunoglobulin variable domains secreted from *Escherichia coli*," *Nature.* Oct. 12, 1989;341(6242):544-6.
- Weir AN, et al. "Formatting antibody fragments to mediate specific therapeutic functions," *Biochem Soc Trans.* Aug. 2002;30(4):512-6.
- Welch KM, et al. "Mismatch in how oestrogen modulates molecular and neuronal function may explain menstrual migraine," *Neurol Sci.* May 2006;27 Suppl 2:S190-2.
- Werther WA, et al. "Humanization of an anti-lymphocyte function-associated antigen (LFA)-1 monoclonal antibody and reengineering of the humanized antibody for binding to rhesus LFA-1," *J Immunol.* Dec. 1, 1996;157(11):4986-95.
- Wick EC, et al. "Transient receptor potential vanilloid 1, calcitonin gene-related peptide, and substance P mediate nociception in acute pancreatitis," *Am J Physiol Gastrointest Liver Physiol.* May 2006;290(5):G959-69. Epub Jan. 6, 2006.
- Willats WG. "Phage display: practicalities and prospects," *Plant Mol Biol.* Dec. 2002;50(6):837-54.
- Williamson DJ, et al. "Intravital microscope studies on the effects of neurokinin agonists and calcitonin gene-related peptide on dural vessel diameter in the anaesthetized rat," *Cephalgia.* Jun. 1997;17(4):518-24.
- Williamson DJ, et al. "Neurogenic inflammation in the context of migraine," *Microsc Res Tech.* May 1, 2001;53(3):167-78.
- Williamson DJ, et al. "Sumatriptan inhibits neurogenic vasodilation of dural blood vessels in the anaesthetized rat—intravital microscope studies," *Cephalgia.* Jun. 1997;17(4):525-31.
- Williamson DJ, et al. "The anti-migraine 5-HT(1B/ID) agonist rizatriptan inhibits neurogenic dural vasodilation in anaesthetized guinea-pigs," *Br J Pharmacol.* Aug. 2001;133(7):1029-34.
- Williamson DJ, et al. "The novel anti-migraine agent rizatriptan inhibits neurogenic dural vasodilation and extravasation," *Eur J Pharmacol.* Jun. 5, 1997;328(1):61-4.
- Wimalawansa SJ, et al. "Comparative study of distribution and biochemical characterization of brain calcitonin gene-related peptide receptors in five different species," *Neuroscience.* May 1993;54(2):513-9.
- Wimalawansa SJ, et al. "Validation, role in perioperative assessment, and clinical applications of an immunoradiometric assay for human calcitonin," *Peptides.* 1995;16(2):307-12.
- Wimalawansa SJ. "Amylin, calcitonin gene-related peptide, calcitonin, and adrenomedullin: a peptide superfamily," *Crit Rev Neurobiol.* 1997;11(2-3):167-239.
- Wimalawansa SJ. "Calcitonin gene-related peptide and its receptors: molecular genetics, physiology, pathophysiology, and therapeutic potentials," *Endocr Rev.* Oct. 1996;17(5):533-85.
- Wimalawansa SJ. "Effects of in vivo stimulation on molecular forms of circulatory calcitonin and calcitonin gene-related peptide in man," *Mol Cell Endocrinol.* May 28, 1990;71(1):13-9.
- Winkler K, et al. "Changing the antigen binding specificity by single point mutations of an anti-p24 (HIV-1) antibody," *J Immunol.* Oct. 15, 2000;165(8):4505-14.
- Winter G, et al. "Making antibodies by phage display technology," *Annu Rev Immunol.* 1994;12:433-55.
- Wong G, et al. "Safety and tolerability of LBR-101, a humanized monoclonal antibody that blocks the binding of CGRP to its receptor," *Labrys Biologics Poster*, 1 page, 2013 International Headache Congress.
- Wong HC, et al. "Monoclonal antibody to rat alpha-CGRP: production, characterization, and in vivo immunoneutralization activity," *Hybridoma.* Feb. 1993;12(1):93-106.
- Wong HC, et al. "Preparation of a monoclonal antibody to rat alpha-CGRP for in vivo immunoneutralization of peptides," *Ann N Y Acad Sci.* Jun. 30, 1992;657:525-7.
- Wu D, et al. "Development and potential of non-peptide antagonists for calcitonin-gene-related peptide (CGRP) receptors: evidence for CGRP receptor heterogeneity," *Biochem Soc Trans.* Aug. 2002;30(4):468-73.
- Wu H, et al. "Humanization of a murine monoclonal antibody by simultaneous optimization of framework and CDR residues," *J Mol Biol.* Nov. 19, 1999;294(1):151-62.
- Wu H, et al. "Humanized antibodies and their applications," *Methods.* May 2005;36(1):1-2.
- Wyon Y, et al. "Postmenopausal women with vasomotor symptoms have increased urinary excretion of calcitonin gene-related peptide," *Maturitas.* Nov. 16, 1998;30(3):289-94.
- Xu, F.T. Study on the Mechanism of SP and CGRP in the Chronic Pain and Knee Joint. Master Thesis. Guangxi Medical University. May 2005. (In Chinese with English abstract).
- Yallampalli C, et al. "Calcitonin gene-related peptide in pregnancy and its emerging receptor heterogeneity," *Trends Endocrinol Metab.* Aug. 2002;13(6):263-9.
- Yoshikawa R, et al. "Suppression of ovalbumin-induced allergic diarrhea by diminished intestinal peristalsis in RAMP1-deficient mice," *Biochem Biophys Res Commun.* Jul. 8, 2011;410(3):389-93.
- Yu LC, et al. "Roles of calcitonin gene-related peptide and its receptors in pain-related behavioral responses in the central nervous system," *Neurosci Biobehav Rev.* Sep. 2009;33(8):1185-91.
- Zeller J, et al. "CGRP function-blocking antibodies inhibit neurogenic vasodilation without affecting heart rate or arterial blood pressure in the rat," *Br J Pharmacol.* Dec. 2008;155(7):1093-103. doi: 10.1038/bjp.2008.334. Epub Sep. 8, 2008.
- Zhang L, et al. "Arthritic calcitonin/alpha calcitonin gene-related peptide knockout mice have reduced nociceptive hypersensitivity," *Pain.* Jan. 2001;89(2-3):265-73.
- Zhang M, et al. "Rheumatoid factor specificity of a VH3-encoded antibody is dependent on the heavy chain CDR3 region and is independent of protein A binding," *J Immunol.* Sep. 1, 1998;161(5):2284-9.
- Zhuang X, et al. "Brain mast cell degranulation regulates blood-brain barrier," *J Neurobiol.* Dec. 1996;31(4):393-403.
- Zittel et al., "Role of spinal afferents and calcitonin gene-related peptide in the postoperative gastric ileus in anesthetized rats," *Ann Surg.* Jan. 1994;219(1):79-87.
- Zittel TT, et al. "Calcitonin gene-related peptide and spinal afferents partly mediate postoperative colonic ileus in the rat," *Surgery.* May 1998;123(5):518-27.

(56)

References Cited**OTHER PUBLICATIONS**

- Zuckier LS, et al. "Chimeric human-mouse IgG antibodies with shuffled constant region exons demonstrate that multiple domains contribute to in vivo half-life," *Cancer Res.* Sep. 1, 1998;58(17):3905-8.
- Misura, et al. "The Eptinezumab: CGRP Complex Structure and Characterization of the Ligand Binding Interface," poster Presented at the American Headache Society (AHS) 61st Annual Scientific Meeting Jul. 11-14, 2019.
- Rita Costa A, Elisa Rodrigues M, Henriques M, Azeredo J, Oliveira R. Guidelines to cell engineering for monoclonal antibody production. *Eur J Pharm Biopharm.* 2010;74(2):127-138. doi:10.1016/j.ejpb.2009.10.002.
- Potgieter TI, Cukan M, Drummond JE, et al. Production of monoclonal antibodies by glycoengineered *Pichia pastoris*. *J Biotechnol.* 2009;139(4):318-325. doi:10.1016/j.jbiotec.2008.12.015.
- Trill JJ, Shatzman AR, Ganguly S. Production of monoclonal antibodies in COS and CHO cells. *Curr Opin Biotechnol.* 1995;6(5):553-560. doi: 10.1016/0958-1669(95)80092-1.
- Alder Biopharmaceuticals. "Alder BioPharmaceuticals announces positive eptinezumab Phase 3 results for prevention of frequent episodic migraine." (2017).
- Dodick, David W., et al. "Eptinezumab demonstrated efficacy in sustained prevention of episodic and chronic migraine beginning on day 1 after dosing." *Headache: The Journal of Head and Face Pain* 60.10 (2020): 2220-2231.
- Dodick, David W., et al. "Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial." *The lancet neurology* 13.11 (2014): 1100-1107.
- Edvinsson, L. "The Trigeminovascular pathway: role of CGRP and CGRP receptors in migraine. *Headache.* 57 (Suppl 2): 47-55." (2017).
- George, Judy. "Eptinezumab Effective in Chronic Migraine: Intravenous CGRP blocker shows rapid treatment effect." *MedPageToday*, Apr. 27, 2018.
- Lee, Mi Ji, et al. "Feasibility of serum CGRP measurement as a biomarker of chronic migraine: a critical reappraisal." *The journal of headache and pain* 19.1 (2018): 1-8.
- Maasumi, Kasra, Rebecca L. Michael, and Alan M. Rapoport. "CGRP and migraine: the role of blocking calcitonin gene-related peptide ligand and receptor in the management of migraine." *Drugs* 78 (2018): 913-928.
- Marmura MJ, et al. Preventive migraine treatment with eptinezumab reduced acute headache medication and headache frequency to below diagnostic thresholds in patients with chronic migraine and medication-overuse headache. *Headache: The Journal of Head and Face Pain.* Oct. 2021;61(9):1421-31.
- Peters, Golden L. "Migraine overview and summary of current and emerging treatment options." *Am J Manag Care* 25.2 Suppl (2019): S23-S34.
- Raffaelli, Bianca, and Uwe Reuter. "The biology of monoclonal antibodies: focus on calcitonin gene-related peptide for prophylactic migraine therapy." *Neurotherapeutics* 15.2 (2018): 324-335.
- Silberstein, S. D., et al. "Eptinezumab results for the prevention of episodic migraine over one year in the PROMISE-1 (PRevention of migraine via intravenous Eptinezumab safety and efficacy-1) trial." *Headache.* vol. 58. No. 8. 111 River ST, Hoboken 07030-5774, NJ USA: Wiley, 2018. p. 1298.
- Singh SR, Zhang J, O'Dell C, Hsieh MC, Goldstein J, Liu J, Srivastava A. Effect of polysorbate 80 quality on photostability of a monoclonal antibody. *Aaps Pharmscitech.* Jun. 2012;13:422-30.
- Tepper, Stewart J. "CGRP and headache: a brief review." *Neurological Sciences* 40 (2019): 99-105.
- The Department of Health and Human Services U.S. Food and Drug Administration, The Pediatric Exclusivity Provision, Jan. 2001 Status Report to Congress (Year 2001).
- The International Classification of Headache Disorders, second edition, *Cephalgia*, 24(Suppl 1) 2004 (Year: 2004).
- Warne, Nicholas W. "Development of high concentration protein biopharmaceuticals: the use of platform approaches in formulation development." *European journal of pharmaceutics and biopharmaceutics* 78.2 (2011): 208-212.
- Dodick, David, et al. "A single intravenous administration of ALD403 (eptinezumab) reduces use of triptans among patients with chronic migraine." *Cephalgia.* vol. 37. 1 Olivers Yard, 55 City Road, London EC1Y 1SP, England: Sage Publications Ltd, 2017.
- Lipton, Richard B et al. "Patient-identified most bothersome symptom in preventive migraine treatment with eptinezumab: A novel patient-centered outcome." *Headache* vol. 61,5 (2021): 766-776. doi:10.1111/head.14120.
- Lipton, Richard B et al. "Evaluating the clinical utility of the patient-identified most bothersome symptom measure from PROMISE-2 for research in migraine prevention." *Headache* vol. 62,6 (2022): 690-699. doi:10.1111/head.14295.
- Brandes, Jan Lewis, et al. "Effects of fremanezumab on the use of acute headache medication and associated symptoms of migraine in patients with episodic migraine." *Cephalgia* 40.5 (2020): 470-477.
- Munjal, Sagar, et al. "Most Bothersome Associated Migraine Symptom: Results from 2017 Migraine in America Symptoms and Treatment (MAST) Study (P3. 10-017)." *Neurology* 92-15 supplement (2019): P3-10.
- Silberstein, Stephen D., et al. "Fremanezumab for the preventive treatment of chronic migraine." *New England Journal of Medicine* 377.22 (2017): 2113-2122.
- Database Embase [online] Jan. 1, 2018 (Jan. 1, 2018), Silberstein S: "The impact of fremanezumab on medication overuse in patients with chronic migraine2018", Database accession No. EMB-624431011.

* cited by examiner

Figure 1A - Heavy Chain Protein Sequence

Sequence	FR1	FR2	CDR1	FR2	CDR2
Name					
Ab1	QSLLEESGGGRLLVTPGTRPLTLTCTVSGLDLS	SYMMQ WVRQAPGKGLEWIG	VIGINDNTYYASWAKG		
Ab2	EVQLVESGGGLVQPGGSLRLSCAVSGLDLS	SYMMQ WVRQAPGKGLEWIG	VIGINDNTYYASWAKG		
Ab3	EVQLVESGGGLVQPGGSLRLSCAVSGLDLS	SYMMQ WVRQAPGKGLEWIG	VIGINDNTYYASWAKG		
Ab4	QSLLEESGGGRLLVTPGTRPLTLTCTVSGLDLS	GYMMN WVRQAPGKGLEWIG	VIGINGATYYASWAKG		
Ab5	EVQLVESGGGLVQPGGSLRLSCAVSGLDLS	GYMMN WVRQAPGKGLEWIG	VIGINGATYYASWAKG		
Ab6	EVQLVESGGGLVQPGGSLRLSCAVSGLDLS	GYMMN WVRQAPGKGLEWIG	VIGINGATYYASWAKG		
Ab7	QEQLKESGGGRLLVTPGTSLLTCTVSGLDLS	NHMMQ WVRQAPGKGLEWIG	VVGINGRTYYASWAKG		
Ab8	EVQLVESGGGLVQPGGSLRLSCAVSGLDLS	NHMMQ WVRQAPGKGLEWIG	VVGINGRTYYASWAKG		
Ab9	QSLLEESGGGRLLVTPGTRPLTLTCTVSGIGLS	SYMMQ WVRQSPGRGLEWIG	VIGSDGKTYYYATWAKG		
Ab10	EVQLVESGGGLVQPGGSLRLSCAVSGIGLS	SYMMQ WVRQAPGKGLEWIG	VIGSDGKTYYYATWAKG		
Ab11	QSLLEESGGGRLLVTPGGSSTLTLTCTVSGIDVT	NYMMQ WVRQAPGKGLEWIG	VIGVNGKRYYYASWAKG		
Ab12	EVQLVESGGGLVQPGGSLRLSCAVSGIDVT	NYMMQ WVRQAPGKGLEWIG	VIGVNGKRYYYASWAKG		
Ab13	QSVEEESGGGGLVQPEGSSLTLTCTASGFDES	SNAMM WVRQAPGKGLEWIG	CIYNGDGSTYYASWVNG		
Ab14	EVQLVESGGGLVQPGGSLRLSCAVSGIGLS	SYMMQ WVRQAPGKGLEWIG	VIGSDGKTYYYATWAKG		
Sequence	FR3	FR4	CDR3	FR4	CDR4
Name					
Ab1	RFITISRASSSTIVDLKMTSLTTEDTATYFCAR	GDI	WGPGTILTVVSS		
Ab2	RFITISRDNSKTTTVYLQMNNSLRAEDTAVYFCAR	GDI	WGQGTILTVVSS		
Ab3	RFITISRDNSKTTTVYLQMNNSLRAEDTAVYFCAR	GDI	WGQGTILTVVSS		
Ab4	RFITISKTSSTIVDLKMTSLTTEDTATYFCAR	GDI	WGPGTILTVVSS		
Ab5	RFITISRDNSKTTTVYLQMNNSLRAEDTAVYFCAR	GDI	WGQGTILTVVSS		
Ab6	RFITISRDNSKTTTVYLQMNNSLRAEDTAVYFCAR	GDI	WGQGTILTVVSS		
Ab7	RFITISRASSSTIVDLKMTSLTTEDTATYFCAR	GDI	WGQGTILTVVSS		
Ab8	RFITISRDNSKTTTVYLQMNNSLRAEDTAVYFCAR	GDI	WGQGTILTVVSS		
Ab9	RFITISKTSSTIVDLRMASLTTEDTATYFCAR	GDI	WGPGTILTVVSS		
Ab10	RFITISRDNSSKTTTVYLQMNNSLRAEDTAVYFCAR	GDI	WGQGTILTVVSS		
Ab11	RFITISKTSSTIVDLKMTSLTTEDTATYFCAR	GDI	WGPGTILTVVSS		
Ab12	RFITISRDNSKTTTVYLQMNNSLRAEDTAVYFCAR	GDI	WGQGTILTVVSS		
Ab13	RFISLSKTSSTIVTLQJNSLTTVADTATYYCAR	DLDL	WGPGTILTVVSS		
Ab14	RFITISRDNSKTTTVYLQMNNSLRAEDTAVYFCAR	GDI	WGQGTILTVVSS		

Figure 1B - Heavy Chain Protein Sequence

Figure 1C - Heavy Chain Protein Sequence

Sequence	Constant Region
Ab1	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV
Ab2	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV
Ab3	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV
Ab4	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV
Ab5	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV
Ab6	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV
Ab7	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV
Ab8	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV
Ab9	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV
Ab10	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV
Ab11	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV
Ab12	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV
Ab13	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV
Ab14	ASTKGPSVFLAPSSKKSTSGGTAAALGCLVKDYYFPEPVTVWNNSGALTSGVHTPAVLOSSGLYSLSSVVTVPSSSITGGTQTYICNV

Figure 1D - Heavy Chain Protein Sequence

Sequence	Constant Region
Ab1	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA
Ab2	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA
Ab3	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA
Ab4	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA
Ab5	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA
Ab6	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA
Ab7	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA
Ab8	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA
Ab9	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA
Ab10	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA
Ab11	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA
Ab12	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA
Ab13	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA
Ab14	NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPKPKDTLMSRTPEVTKVVVDVSHEDEPVKENMYVDGVEVHNA

Figure 1E - Heavy Chain Protein Sequence

Sequence	Constant Region
Ab1	KTKPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF
Ab2	KTKPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF
Ab3	KTKPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF
Ab4	KTKPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF
Ab5	KTKPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF
Ab6	KTKPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF
Ab7	KTKPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF
Ab8	KTRPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF
Ab9	KTKPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF
Ab10	KTKPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF
Ab11	KTKPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF
Ab12	KTKPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF
Ab13	KTKPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF
Ab14	KTKPREEQYASTYRVSITVLHQDWLNGKEYKCKVSNKALPAPIEKTIKSKAKGQPREPOVYTLLPPSREEMTKNOVSLSLTCLVKGF

Figure 1F - Heavy Chain Protein Sequence

Sequence	Constant Region
Ab1	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 1)
Ab2	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 41)
Ab3	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 81)
Ab4	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 121)
Ab5	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 161)
Ab6	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 201)
Ab7	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 241)
Ab8	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 281)
Ab9	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 321)
Ab10	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 361)
Ab11	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 401)
Ab12	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 441)
Ab13	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 481)
Ab14	YPSDIAVEMESNGQPENNYKTTPPVLDSDGSFFFLYSKLTVDKSRWQOQNVECSVMHEALHNHYTOKSLSLSPGK (SEQ ID NO: 521)

Figure 2A - Light Chain Protein Sequence

Sequence	Name	FR1	CDR1	CDR2
	Ab1	QVLTQTASeVSAVGSTVTINC	QASQSvYDNNYLIA	WYQOKPGQPPKOLIY
	Ab2	QVLTQSPSSLSASVGDRVTINC	QASQSvYDNNYLIA	SSTSLAS
	Ab3	QVLTQSPSSLSASVGDRVTINC	QASQSvYDNNYLIA	WYQOKPGKVKPQOLIY
	Ab4	QVLTQTPSeVSAVGSTVTINC	QASQSvYHNTYLIA	SSTSLAS
	Ab5	QVLTQSPSSLSASVGDRVTINC	QASQSvYHNTYLIA	WYQOKPGKVKPQOLIY
	Ab6	QVLTQSESSLSASVGDRVTINC	QASQSvYHNTYLIA	DASTLAS
	Ab7	QVLTQTASeVSAVGSTVTINC	QASQSvYHNTYLIA	WYQOKPGQPPKOLIY
	Ab8	QVLTQSPSSLSASVGDRVTINC	QASQSvYHNTYLIA	DASTLAS
	Ab9	QVLTQTPSeVSAVGSTVTINC	QASQSvYHNTYLIA	WYQOKPGKVKPQOLIY
	Ab10	QVLTQSPSSLSASVGDRVTINC	QASQNVYNNNLYIA	SSTSLAS
	Ab11	QVLTQTASeVSPAVGSTVTINC	QASQSVYNNNLYIA	WYQOKPGKVKPQOLIY
	Ab12	QVLTQSPSSLSASVGDRVTINC	RASQSVYNNNLYIA	SSTSLAS
	Ab13	AIvMTQTPSSKSVPVGDTVTINC	QASESLYNNNALA	WFQOKPGQPPKRILY
	Ab14	QVLTQSPSSLSASVGDRVTINC	QASQNVYNNNLYIA	DASKLAS
				SSTSLAS
Sequence	Name	FR3	CDR3	FR4
	Ab1	GVSSRFKGSGSGTQFTLTISDLECADAAATYC	LGSYDCSSGDCFV	FGGGTEVVVKR
	Ab2	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCSSGDCFV	FGGGTKVEIKR
	Ab3	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCSSGDCFV	FGGGTKVEIKR
	Ab4	GVPSRFSGSGSGTQFTLTISGVOCNDAAAYYC	LGSYDCTNGDCFV	FGGGTEVVVKR
	Ab5	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCTNGDCFV	FGGGTKVEIKR
	Ab6	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCTNGDCFV	FGGGTKVEIKR
	Ab7	GVSSRFKGSGSGTQFTLTISDVCDDAAATYC	LGSYDCSTGDCFV	FGGGTEVVVKR
	Ab8	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCSTGDCFV	FGGGTKVEIKR
	Ab9	GVSSRFKGSGSGTQFTLTISDVCDDAAATYC	LGSYDCSRGDCFV	FGGGTEVVVKR
	Ab10	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCSRGDCFV	FGGGTKVEIKR
	Ab11	GVSSRFKGSGSGTQFTLTISDVCDDAAATYC	LGSYDCSNGDCFV	FGGGTEVVVKR
	Ab12	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCSNGDCFV	FGGGTKVEIKR
	Ab13	GVPSRFSGGGSGTQFTLTISGVOCDDAAATYC	GGYRSDSVDGVA	FAGGTEVVVKR
	Ab14	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCSRGDCFV	FGGGTKVEIKR

Figure 2B - Light Chain Protein Sequence

Sequence	Name	FR1	CDR1	CDR2
	Ab1	GVSSRFKGSGSGTQFTLTISDLECADAAATYC	LGSYDCSSGDCFV	FGGGTEVVVKR
	Ab2	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCSSGDCFV	FGGGTKVEIKR
	Ab3	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCSSGDCFV	FGGGTKVEIKR
	Ab4	GVPSRFSGSGSGTQFTLTISGVOCNDAAAYYC	LGSYDCTNGDCFV	FGGGTEVVVKR
	Ab5	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCTNGDCFV	FGGGTKVEIKR
	Ab6	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCTNGDCFV	FGGGTKVEIKR
	Ab7	GVSSRFKGSGSGTQFTLTISDVCDDAAATYC	LGSYDCSTGDCFV	FGGGTEVVVKR
	Ab8	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCSTGDCFV	FGGGTKVEIKR
	Ab9	GVSSRFKGSGSGTQFTLTISDVCDDAAATYC	LGSYDCSRGDCFV	FGGGTEVVVKR
	Ab10	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCSRGDCFV	FGGGTKVEIKR
	Ab11	GVSSRFKGSGSGTQFTLTISDVCDDAAATYC	LGSYDCSNGDCFV	FGGGTEVVVKR
	Ab12	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCSNGDCFV	FGGGTKVEIKR
	Ab13	GVPSRFSGGGSGTQFTLTISGVOCDDAAATYC	GGYRSDSVDGVA	FAGGTEVVVKR
	Ab14	GVPSRFSGSGSGTDFLTITLTISSLOPEDVATYC	LGSYDCSRGDCFV	FGGGTKVEIKR

Figure 2C - Light Chain Protein Sequence

Sequence Name	Constant Region
Ab1	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA
Ab2	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA
Ab3	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA
Ab4	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA
Ab5	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA
Ab6	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA
Ab7	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA
Ab8	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA
Ab9	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA
Ab10	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA
Ab11	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA
Ab12	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA
Ab13	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA
Ab14	TVAAPSVEIIFPPSDEQQLKSGTASVVCLLNNFYPREAKVQWVVDNAIQLQSGNQESVTQTEQDSKDSTYSLSSSTLTLSSKLADYEKHKVYA

Figure 2D - Light Chain Protein Sequence

Sequence Name	Constant Region
Ab1	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 21)
Ab2	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 61)
Ab3	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 101)
Ab4	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 141)
Ab5	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 181)
Ab6	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 221)
Ab7	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 261)
Ab8	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 301)
Ab9	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 341)
Ab10	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 381)
Ab11	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 421)
Ab12	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 461)
Ab13	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 501)
Ab14	CEVTHQGLSSPVTKSENRRGEC (SEQ ID NO: 541)

Figure 3A - Heavy Chain DNA Sequence

Sequence Name	FR1
Ab1	CAGTCGCTGGAGGAGTCCGGGTCTGGCACGCCCTGGGAGGCTTGGTCCACGCCCTGGGAGCACCCTGACACTCACCTGCACAGTCTCGACCTCAGT
Ab2	GAGGTGCAGCTTGTGGAGTCTGGGGAGGCTGGTCCAGCCTGGGGTCCCTGAGACTCCTGTGCACTCTGGACTCGAACCTCAGT
Ab3	CAGTCGCTGGAGGAGTCCGGGTCTGGCACGCCCTGGGAGCACCCTGACACTCACCTGCACAGTCTCGACCTCAGT
Ab4	GAGGTGCAGCTTGTGGAGSTCTGGGGAGGCTTGGTCCAGCCTGGGGTCCCTGAGACTCCTGTGCACTCACCTGCACAGTCTCGACCTCAGT
Ab5	GAGGTGCAGCTTGTGGAGSTCTGGGGAGGCTTGGTCCAGCCTGGGGTCCCTGAGACTCCTGTGCACTCACCTGCACAGTCTCGACCTCAGT
Ab6	GAGGTGCAGCTTGTGGAGTCTGGGGAGGCTTGGTCCAGCCTGGGGTCCCTGAGACTCCTGTGCACTCACCTGCACAGTCTCGACCTCAGT
Ab7	CAGAGGAGCTGAAGGGTCCGGGTGCCCCATCCCTGAGACTCCTGTGCACTCACCTGCACAGTCTCGACCTCAGT
Ab8	GAGCTGCAGCTTGTGGAGSTCTGGGGAGGCTTGGTCCAGCCTGGGGTCCCTGAGACTCCTGTGCACTCACCTGCACAGTCTCGACCTCAGT
Ab9	CAGTCGCTGGAGGAGTCCGGGGTCTGGAGTCTGGGGAGGCTTGGTCCAGCCTGGGGTCCCTGAGACTCCTGTGCACTCACCTGCACAGTCTCGACCTCAGT
Ab10	CAGTCGCTGGAGGAGTCCGGGGTCTGGGGAGGCTTGGTCCAGCCTGGGGTCCCTGAGACTCCTGTGCACTCACCTGCACAGTCTCGACCTCAGT
Ab11	CAGTCGCTGGAGGAGTCCGGGGTCCCTGAGACTCCTGTGCACTCACCTGCACAGTCTCGACCTCAGT
Ab12	GAGGTGCAGCTTGTGGAGTCTGGGGAGGCTTGGTCCAGCCTGGGGTCCCTGAGACTCCTGTGCACTCACCTGCACAGCTCTGGAAATCGACCTCAGT
Ab13	CAGTCGCTGGAGGAGTCCGGGGAGGCTTGGTCCAGCCTGGGGTCCCTGAGACTCCTGTGCACTCACCTGCACAGCTCTGGAAATCGACCTCAGT
Ab14	GAGGTGCAGCTTGTGGAGTCTGGGGAGGCTTGGTCCAGCCTGGGGTCCCTGAGACTCCTGTGCACTCACCTGCACAGCTCTGGAAATCGACCTCAGT

Figure 3B - Heavy Chain DNA Sequence

Sequence Name	CDR1	FR2
Ab1	AGCTACTACATGCAA	TGGGTCCGCCAGGGTCCAGGGAAAGGGGCTGGAAATGGATCGGA
Ab2	AGCTACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAAGGGGCTGGAAATGGATCGGA
Ab3	AGCTACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAAGGGGCTGGAAATGGATCGGA
Ab4	GGCTACTACATGAAAC	TGGGTCCGTCAGGCTCCAGGGAAAGGGGCTGGAAATGGATCGGA
Ab5	GGCTACTACATGAAAC	TGGGTCCGTCAGGCTCCAGGGAAAGGGGCTGGAAATGGATCGGA
Ab6	GGCTACTACATGAAAC	TGGGTCCGTCAGGCTCCAGGGAAAGGGGCTGGAAATGGATCGGA
Ab7	AACCACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAAGGGGCTGGAAATGGATCGGA
Ab8	AACCACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAAGGGGCTGGAAATGGATCGGA
Ab9	AGCTACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAAGGGGCTGGAAATGGATCGGA
Ab10	AGCTACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAAGGGGCTGGAAATGGATCGGA
Ab11	AACCTACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAAGGGGCTGGAAATGGATCGGA
Ab12	AACCTACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAAGGGGCTGGAAATGGATCGGA
Ab13	AGCAATGCAATGTGG	TGGGTCCGTCAGGCTCCAGGGAAAGGGGCTGGAAATGGATCGGA
Ab14	AGCTACTACATGCAA	TGGGTCCGTCAGGCTCCAGGGAAAGGGGCTGGAAATGGATCGGA

Figure 3C - Heavy Chain DNA Sequence

Sequence	CDR2
Name	
Ab1	GTCATTGGTATTGATAACACATACACTACCGGAGCTGGCGAAAGGC
Ab2	GTCATTGGTATTGATAACACATACACTACCGGAGCTGGCGAAAGGC
Ab3	GTCATTGGTATTGATAACACATACACTACCGGAGCTGGCGAAAGGC
Ab4	GTCATTGGTATTGATAACACATACACTACCGGAGCTGGCGAAAGGC
Ab5	GTCATTGGTATTGATAACACATACACTACCGGAGCTGGCGAAAGGC
Ab6	GTCATTGGTATTGATAACACATACACTACCGGAGCTGGCGAAAGGC
Ab7	GTCATTGGTATTGATAACACATACACTACCGGAGCTGGCGAAAGGC
Ab8	GTCATTGGTATTGATAACACATACACTACCGGAGCTGGCGAAAGGC
Ab9	GTCATTGGTATTGATAACACATACACTACCGGAGCTGGCGAAAGGC
Ab10	GTCATTGGTATTGATAACACATACACTACCGGAGCTGGCGAAAGGC
Ab11	GTCATTGGTATTGATAACACATACACTACCGGAGCTGGCGAAAGGC
Ab12	GTCATTGGTATTGATAACACATACACTACCGGAGCTGGCGAAAGGC
Ab13	TGCAATTACAATGGTGTGAGCACATACACGGAGCTGGGTGAATGGC
Ab14	GTCATTGGTATTGATAAGAGATACTACCGGAGCTGGCGAAAGGC

Figure 3D - Heavy Chain DNA Sequence

Sequence	FR3
Name	
Ab1	CGATTCAACCCTCCAGAGCCCTGTCGACCAACGGTGGATCTGAAAATGACCAAGCTCTGACAACCCAGGACACGGCCACCTATTCTGTGCCAGA
Ab2	CGATTCAACCCTCCAGAGACAATTCCAAAGACCAATTCCAAATGACCAACGGTGTATCTCAATGAAACAGCTGAGACTGAGAGCTGAGAGCTGCTGCTAGA
Ab3	CGATTCAACCCTCCAGAGACAATTCCAAAGACCAATTCCAAATGACCAACGGTGTATCTCAATGAAACAGCTGAGAGCTGAGAGCTGCTGCTAGA
Ab4	CGATTCAACCCTCCAGAGACAATTCCAAAGACCAATTCCAAATGACCAACGGTGTATCTCAATGAAACAGCTGAGAGCTGAGAGCTGCTGCTAGA
Ab5	CGATTCAACCCTCCAGAGACAATTCCAAAGACCAATTCCAAATGACCAACGGTGTATCTCAATGAAACAGCTGAGAGCTGAGAGCTGCTGCTAGA
Ab6	CGATTCAACCCTCCAGAGACAATTCCAAAGACCAATTCCAAATGACCAACGGTGTATCTCAATGAAACAGCTGAGAGCTGAGAGCTGCTGCTAGA
Ab7	CGATTCAACCCTCCAGAGACAATTCCAAAGACCAATTCCAAATGACCAACGGTGTATCTCAATGAAACAGCTGAGAGCTGAGAGCTGCTGCTAGA
Ab8	CGATTCAACCCTCCAGAGACAATTCCAAAGACCAATTCCAAATGACCAACGGTGTATCTCAATGAAACAGCTGAGAGCTGAGAGCTGCTGCTAGA
Ab9	CGATTCAACCCTCCAGAGACAATTCCAAAGACCAATTCCAAATGACCAACGGTGTATCTCAATGAAACAGCTGAGAGCTGAGAGCTGCTGCTAGA
Ab10	CGATTCAACCCTCCAGAGACAATTCCAAAGACCAATTCCAAATGACCAACGGTGTATCTCAATGAAACAGCTGAGAGCTGAGAGCTGCTGCTAGA
Ab11	CGATTCAACCCTCCAGAGACAATTCCAAAGACCAATTCCAAATGACCAACGGTGTATCTCAATGAAACAGCTGAGAGCTGAGAGCTGCTGCTAGA
Ab12	CGATTCAACCCTCCAGAGACAATTCCAAAGACCAATTCCAAATGACCAACGGTGTATCTCAATGAAACAGCTGAGAGCTGAGAGCTGCTGCTAGA
Ab13	CGATTCAACCCTCCAGAGACAATTCCAAAGACCAATTCCAAATGACCAACGGTGTATCTCAATGAAACAGCTGAGAGCTGAGAGCTGCTGCTAGA
Ab14	CGATTCAACCCTCCAGAGACAATTCCAAAGACCAATTCCAAATGACCAACGGTGTATCTCAATGAAACAGCTGAGAGCTGCTGCTAGA

Figure 3E - Heavy Chain DNA Sequence

Sequence	Name	CDR3	FR4	Constant Region
Ab1	GGGACATC	TGGGGCCCAGGGCACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC
Ab2	GGGACATC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC
Ab3	GGGACATC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC
Ab4	GGGACATC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC
Ab5	GGGACATC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC
Ab6	GGGACATC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC
Ab7	GGGACATC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC
Ab8	GGGACATC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC
Ab9	GGGACATC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC
Ab10	GGGACATC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC
Ab11	GGGACATC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC
Ab12	GGGACATC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC
Ab13	GATCTTGACTTG	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC
Ab14	GGGACATC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	TGGGGCAAGGGAACCCCTCGTACCGTCTCGAGC	GCCTCCACCAAGGGCCCATCGGTCTCCCCCTGGCACCCCTCC

Figure 3F - Heavy Chain DNA Sequence

Sequence	Name	Constant Region
Ab1	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC
Ab2	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC
Ab3	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC
Ab4	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC
Ab5	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC
Ab6	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC
Ab7	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC
Ab8	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC
Ab9	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC
Ab10	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC
Ab11	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC
Ab12	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC
Ab13	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC
Ab14	AAGAGCACCTCTGGGGCACAGGGCCCTGGCTGGTCAAGGA	TCCCGAACGGGTGACGGGTGTCGTGAACTCAGGC

Figure 3G - Heavy Chain cDNA Sequence

Sequence	Constant Region
Ab1	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGGCCCTCAGCAGCAGC
Ab2	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGCAGCAGC
Ab3	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGCAGCAGC
Ab4	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGCAGCAGC
Ab5	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGCAGCAGC
Ab6	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGCAGCAGC
Ab7	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGCAGCAGC
Ab8	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGCAGCAGC
Ab9	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGCAGCAGC
Ab10	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGCAGCAGC
Ab11	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGCAGCAGC
Ab12	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGCAGCAGC
Ab13	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGCAGCAGC
Ab14	CTGACCAGGGCGGTGCAACACCTTCCGGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCTCAGCAGCAGC

Figure 3H - Heavy Chain DNA Sequence

Sequence	Constant Region
Ab1	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA
Ab2	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA
Ab3	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA
Ab4	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA
Ab5	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA
Ab6	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA
Ab7	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA
Ab8	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA
Ab9	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA
Ab10	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA
Ab11	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA
Ab12	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA
Ab13	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA
Ab14	TGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGAACACCAAGGTGGACAAGAGAGTGAAGCCCAAATCTTGTGACAAA

Figure 3I - Heavy Chain DNA Sequence

Sequence	Constant Region
Ab1	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG
Ab2	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG
Ab3	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG
Ab4	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG
Ab5	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG
Ab6	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG
Ab7	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG
Ab8	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG
Ab9	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG
Ab10	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG
Ab11	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG
Ab12	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG
Ab13	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG
Ab14	ACTCACACATGCCAACCGTCCCCAGCACCTGAACTCCTGGGGGACCCGTCAAGTCCTCCCCAAAACCCNAGGACACCCCTCATG

Figure 3J - Heavy Chain DNA Sequence

Sequence	Constant Region
Ab1	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTGGACATGGTGGGACCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab2	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab3	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab4	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab5	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab6	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab7	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab8	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab9	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab10	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab11	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab12	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab13	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG
Ab14	ATCTCCCGAACCCCTGAGGTACATGGTGGGACGTGAGGCCAGGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTG

Effi ciency 3K = Heavy Chain DNA Sequence

Figure 3L - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG
Ab2	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG
Ab3	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG
Ab4	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG
Ab5	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG
Ab6	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG
Ab7	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG
Ab8	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG
Ab9	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG
Ab10	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG
Ab11	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG
Ab12	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG
Ab13	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG
Ab14	TGGCTGAATGGCAAGGAGTACAAGTGCAGGTCTCCAAACAAAGGCCCTCCAGCCCCATCAGAGAAAACCATCTCCAAAGCCAAGGGAG

Figure 3M - Heavy Chain DNA Sequence

Sequence	Constant Region
Name	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 1	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 2	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 3	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 4	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 5	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 6	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 7	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 8	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 9	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 10	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 11	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 12	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 13	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC
Ab 14	CCCCGAGAACACAGGGTGTACACCCCTGCCCTATCCCCGGGGATGACCAAGAACCAACCAGGTCAAGCTGCCCTGGTCAAAGGCCCTC

Figure 3N - Heavy Chain DNA Sequence

Sequence	Constant Region
Name	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 1	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 2	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 3	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 4	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 5	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 6	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 7	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 8	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 9	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 10	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 11	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 12	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 13	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC
Ab 14	TATCCCGAGGACATGCCGTGGAGTGGAGACAATGGGAGCCGGAAACAACATAAGAACCCAGGCCCTCCCGTGCTGGACTCCGACGGC

Figure 3O - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG
Ab2	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG
Ab3	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG
Ab4	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG
Ab5	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG
Ab6	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG
Ab7	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG
Ab8	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG
Ab9	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG
Ab10	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG
Ab11	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG
Ab12	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG
Ab13	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG
Ab14	TCCCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGGAGGTGGCAAGGGAAACGCTCCTCATGCCCTCCGTTCTCATGCCATGAGGCTCTG

Figure 3P - Heavy Chain DNA Sequence

Sequence Name	Constant Region
Ab1	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 11)
Ab2	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 51)
Ab3	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 91)
Ab4	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 131)
Ab5	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 171)
Ab6	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 211)
Ab7	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 251)
Ab8	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 291)
Ab9	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 331)
Ab10	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 371)
Ab11	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 411)
Ab12	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 451)
Ab13	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 491)
Ab14	CACAAACCACTACACGGCAAAGAGCCCTCCCTGTCTCCGGTAATGA (SEQ ID NO: 531)

Figure 4A - Light Chain DNA Sequence

Sequence	Name	FR1
	Ab1	CAAGTGCACCCAGACTGCATCCCCGTGCTGTGCAGCTGTGGAAAGCACAGTCACCATCAAATTGC
	Ab2	CAAGTGCACCCAGACTCCATCCCCTGCTGCATCTGCAATTGC
	Ab3	CAAGTGCACCCAGACTCCATCCCCTGCTGCAGCTGTGGAAAGCACAGTCACCATCAAATTGC
	Ab4	CAAGTGCACCCAGACTCCATCCCCTGCTGCAGCTGTGGAAAGCACAGTCACCATCAAATTGC
	Ab5	CAAGTGCACCCAGACTCCATCCCCTGCTGCATCTGCAATTGC
	Ab6	CAAGTGCACCCAGACTCCATCCCCTGCTGCATCTGCAATTGC
	Ab7	CAAGTGCACCCAGACTCCATCCCCTGCTGCATCTGCAATTGC
	Ab8	CAAGTGCACCCAGACTCCATCCCCTGCTGCATCTGCAATTGC
	Ab9	CAAGTGCACCCAGACTCCATCCCCTGCTGCATCTGCAATTGC
	Ab10	CAAGTGCACCCAGACTCCATCCCCTGCTGCATCTGCAATTGC
	Ab11	CAGGTGCACCCAGACTGCATCCCCGGTGTCCAGCTGTGGAAAGCACAGTCACCATCAAATTGC
	Ab12	CAAGTGCACCCAGACTCCATCCCCTGCTGCATCTGCAATTGC
	Ab13	GCATCGTAGTGCACCCAGACTCCATCCCCTGCTGCATCTGCAATTGC
	Ab14	CAAGTGCACCCAGACTCCATCCCCTGCTGCATCTGCAATTGC

Figure 4B - Light Chain DNA Sequence

Sequence	Name	CDR1	FR2
	Ab1	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGCAACTGATCTAT
	Ab2	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGTCCTAACGAACCTGATCTAT
	Ab3	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGTCCTAACGAACCTGATCTAT
	Ab4	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGTCCTAACGAACCTGATCTAT
	Ab5	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGTCCTAACGAACCTGATCTAT
	Ab6	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGTCCTAACGAACCTGATCTAT
	Ab7	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGTCCTAACGAACCTGATCTAT
	Ab8	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGTCCTAACGAACCTGATCTAT
	Ab9	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGTCCTAACGAACCTGATCTAT
	Ab10	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGTCCTAACGAACCTGATCTAT
	Ab11	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGTCCTAACGAACCTGATCTAT
	Ab12	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGTCCTAACGAACCTGATCTAT
	Ab13	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGTCCTAACGAACCTGATCTAT
	Ab14	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAACCAAGGGCAGGCCAAAGTCCTAACGAACCTGATCTAT

Figure 4C - Light Chain DNA Sequence

Sequence	CDR2	FR3
Name		GGGGTCTCATCGGGTTCAAGGCCAGTGATCTGGACACAGTTCACTCTCACCA
Ab1	TCTACATCCACTCTGGCATCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGATCTGGACAGATTCACTCTCACCA
Ab2	TCTACATCCACTCTGGCATCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGATCTGGACAGATTCACTCTCACCA
Ab3	TCTACATCCACTCTGGGTCT	GGGGTCCCCATCGGGTCTAGTGGCAGTGATCTGGACAGATTCACTCTCACCA
Ab4	GATGCATCCACTCTGGGTCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGATCTGGACAGATTCACTCTCACCA
Ab5	GATGCATCCACTCTGGCATCT	GGGGTCTCATCGGATTCAGGGCAGTGATCTGGACAGATTCACTCTCACCA
Ab6	GATGCATCCACTCTGGCATCT	GGGGTCTCATCGGATTCAGGGCAGTGATCTGGACAGATTCACTCTCACCA
Ab7	TCTACATCCACTCTGGCATCT	GGGGTCTCATCGGATTCAGGGCAGTGATCTGGACAGATTCACTCTCACCA
Ab8	TCTACATCCACTCTGGCATCT	GGGGTCTCATCGGATTCAGGGCAGTGATCTGGACAGATTCACTCTCACCA
Ab9	TCTACGTTCACTCTGGCATCT	GGGGTCTCATCGGATTCAGGGCAGTGATCTGGACAGATTCACTCTCACCA
Ab10	TCTACATCCACTCTGGCATCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGATCTGGACAGATTCACTCTCACCA
Ab11	TCTACATCCACTCTGGCATCT	GGGGTCTCATCGGGTTCAAGGCCAGTGATCTGGACAGATTCACTCTCACCA
Ab12	TCTACATCCACTCTGGCATCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGATCTGGACAGATTCACTCTCACCA
Ab13	GATGCATCCAAACTGGCATCT	GGGGTCCCCATCGGGTTCAAGGCCAGTGATCTGGACAGATTCACTCTCACCA
Ab14	TCTACATCCACTCTGGCATCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGATCTGGACAGATTCACTCTCACCA

Figure 4D - Light Chain DNA Sequence

Sequence	CDR3
Name	
Ab1	TCAGCGAACCTGGAGTGTGCCACTTACTACTGT
Ab2	TCAGCGAACCTGCAGCTGAAGATGTTGCAACTTATTACTGT
Ab3	TCAGCGAACCTGCAGCTGAAGATGTTGCAACTTATTACTGT
Ab4	TCAGCGGGGGTGCAGCTGAAGATGCTGCCGCTTACTACTGT
Ab5	TCAGCGAACCTGCAGCTGAAGATGTTGCAACTTATTACTGT
Ab6	TCAGCGAACCTGCAGCTGAAGATGTTGCAACTTATTACTGT
Ab7	TCAGCGAACCTGCAGCTGAAGATGTTGCAACTTATTACTGT
Ab8	TCAGCGAACCTGCAGCTGAAGATGTTGCAACTTATTACTGT
Ab9	TCAGCGAACCTGCAGCTGAAGATGTTGCAACTTATTACTGT
Ab10	TCAGCGAACCTGCAGCTGAAGATGTTGCAACTTATTACTGT
Ab11	TCAGCGAACCTGCAGCTGAAGATGTTGCAACTTATTACTGT
Ab12	TCAGCGAACCTGCAGCTGAAGATGTTGCAACTTATTACTGT
Ab13	TCAGTGGGGTGCAGCTGAAGATGTTGCAACTTATTACTGT
Ab14	TCAGCGAACCTGCAGCTGAAGATGTTGCAACTTATTACTGT

Figure 4E - Light Chain DNA Sequence

Sequence	Name	FR4	Constant Region
	Ab1	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG
	Ab2	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG
	Ab3	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG
	Ab4	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG
	Ab5	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG
	Ab6	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG
	Ab7	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG
	Ab8	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG
	Ab9	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG
	Ab10	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG
	Ab11	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG
	Ab12	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG
	Ab13	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG
	Ab14	TTCGGCGGAGGAACCAAGGTGGAAATCAAACGT	ACGGTGGCTGCACCATCTGCTTCACTCTCCGCCATCTGATGAGCAGTTG

Figure 4F - Light Chain DNA Sequence

Sequence	Name	Constant Region
	Ab1	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC
	Ab2	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC
	Ab3	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC
	Ab4	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC
	Ab5	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC
	Ab6	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC
	Ab7	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC
	Ab8	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC
	Ab9	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC
	Ab10	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC
	Ab11	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC
	Ab12	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC
	Ab13	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC
	Ab14	AAATCTGGAACTGGCTCTGTTGTCCTGCTGAATAACTCTATCCCAGAGGGCCAAGTAGCTGGAAGGTGGATAACGCC

Figure 4G - Light Chain DNA Sequence

Sequence Name	Constant Region
Ab 1	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG
Ab 2	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG
Ab 3	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG
Ab 4	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG
Ab 5	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG
Ab 6	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG
Ab 7	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG
Ab 8	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG
Ab 9	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG
Ab 10	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG
Ab 11	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG
Ab 12	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG
Ab 13	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG
Ab 14	TCCAATGGGTAACTCCAGGAGAGTGTACACAGAGCAGGAGACAGCAAGGACACCTAACAGGCCTCACAGCAGCACCCTGACGGCTGAG

Figure 4H - Light Chain DNA Sequence

Sequence Name	Constant Region
Ab 1	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC
Ab 2	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC
Ab 3	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC
Ab 4	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC
Ab 5	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC
Ab 6	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC
Ab 7	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC
Ab 8	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC
Ab 9	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC
Ab 10	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC
Ab 11	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC
Ab 12	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC
Ab 13	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC
Ab 14	CAAAGCAGACTACGAAACACAAAGTCTACGCCCTGGGAAGTCACCCATGGGCCTGAGCTGCCCGTCACAAAGAGCTCAAC

Figure 4I - Light Chain DNA Sequence

Sequence Name	Sequence	ID NO:
Ab1	AGGGGAGAGTGTGTAG	(SEQ ID NO: 31)
Ab2	AGGGGAGAGTGTGTAG	(SEQ ID NO: 71)
Ab3	AGGGGAGAGTGTGTAG	(SEQ ID NO: 111)
Ab4	AGGGGAGAGTGTGTAG	(SEQ ID NO: 151)
Ab5	AGGGGAGAGTGTGTAG	(SEQ ID NO: 191)
Ab6	AGGGGAGAGTGTGTAG	(SEQ ID NO: 231)
Ab7	AGGGGAGAGTGTGTAG	(SEQ ID NO: 271)
Ab8	AGGGGAGAGTGTGTAG	(SEQ ID NO: 311)
Ab9	AGGGGAGAGTGTGTAG	(SEQ ID NO: 351)
Ab10	AGGGGAGAGTGTGTAG	(SEQ ID NO: 391)
Ab11	AGGGGAGAGTGTGTAG	(SEQ ID NO: 431)
Ab12	AGGGGAGAGTGTGTAG	(SEQ ID NO: 471)
Ab13	AGGGGAGAGTGTGTAG	(SEQ ID NO: 511)
Ab14	AGGGGAGAGTGTGTAG	(SEQ ID NO: 551)

Figure 5
Heavy Chain Protein Sequence Features

Antibody	Variable Region Coordinates	SEQ ID: CDR1 NO: Coordinates			SEQ ID: CDR2 NO: Coordinates			SEQ ID: CDR3 NO: Coordinates			SEQ ID: NC:
		30-34	49-64	96-98	50-65	84-98	98-100	46-55	86-98	98-100	
Ab1	1-109	2	30-34		4	49-64	96-98	6	96-98	98	
Ab2	1-111	42	31-35		44	50-65	46	98-100	46	98-100	48
Ab3	1-111	82	31-35		84	50-65	86	98-100	86	98-100	88
Ab4	1-109	122	30-34		124	49-64	126	96-98	126	96-98	128
Ab5	1-111	162	31-35		164	50-65	166	98-100	166	98-100	168
Ab6	1-111	202	31-35		204	50-65	206	98-100	206	98-100	208
Ab7	1-110	242	31-35		244	50-65	246	97-99	246	97-99	248
Ab8	1-111	282	31-35		284	50-65	286	98-100	286	98-100	288
Ab9	1-109	322	30-34		324	49-64	326	96-98	326	96-98	328
Ab10	1-111	362	31-35		364	50-65	366	98-100	366	98-100	368
Ab11	1-109	402	30-34		404	49-64	406	96-98	406	96-98	408
Ab12	1-111	442	31-35		444	50-65	446	98-100	446	98-100	448
Ab13	1-111	482	30-34		484	49-65	486	97-100	486	97-100	488
Ab14	1-111	522	31-35		524	50-65	526	98-100	526	98-100	528

Figure 6
Heavy Chain Protein Sequence Features

Antibody	FR1			FR2			FR3			FR4			SEQ ID NO: Coordinates	Constant Region ID	SEQ ID NO: Coordinates
	SEQ ID NO:	Coordinates	NO:	SEQ ID NO:	Coordinates	NO:	SEQ ID NO:	Coordinates	NO:	SEQ ID NO:	Coordinates	NO:			
Ab1	1-29	3	35-48		5	65-95		7	99-109		9	110-439		10	
Ab2	1-30	43	36-49		45	66-97		47	101-111		49	112-441		50	
Ab3	1-30	83	36-49		85	66-97		87	101-111		89	112-441		90	
Ab4	1-29	123	35-48		125	65-95		127	99-109		129	110-439		130	
Ab5	1-30	163	36-49		165	66-97		167	101-111		169	112-441		170	
Ab6	1-30	203	36-49		205	66-97		207	101-111		209	112-441		210	
Ab7	1-30	243	36-49		245	66-96		247	100-110		249	111-440		250	
Ab8	1-30	283	36-49		285	66-97		287	101-111		289	112-441		290	
Ab9	1-29	323	35-48		325	65-95		327	99-109		329	110-439		330	
Ab10	1-30	363	36-49		365	66-97		367	101-111		369	112-441		370	
Ab11	1-29	403	35-48		405	65-95		407	99-109		409	110-439		410	
Ab12	1-30	443	36-49		445	66-97		447	101-111		449	112-441		450	
Ab13	1-29	483	35-48		485	66-96		487	101-111		489	112-441		490	
Ab14	1-30	523	36-49		525	66-97		527	101-111		529	112-441		530	

Figure 7
Light Chain Protein Sequence Features

	Variable Region Coordinates	SEQ ID NO:	CDR1 Coordinates	SEQ ID NO:	CDR2 Coordinates	SEQ ID NO:	CDR3 Coordinates	SEQ ID NO:
Ab1	1-113	22	23-35	24	51-57	26	90-102	28
Ab2	1-113	62	23-35	64	51-57	66	90-102	68
Ab3	1-113	102	23-35	104	51-57	106	90-102	108
Ab4	1-113	142	23-35	144	51-57	146	90-102	148
Ab5	1-113	182	23-35	184	51-57	186	90-102	188
Ab6	1-113	222	23-35	224	51-57	226	90-102	228
Ab7	1-113	262	23-35	264	51-57	266	90-102	268
Ab8	1-113	302	23-35	304	51-57	306	90-102	308
Ab9	1-113	342	23-35	344	51-57	346	90-102	348
Ab10	1-113	382	23-35	384	51-57	386	90-102	388
Ab11	1-113	422	23-35	424	51-57	426	90-102	428
Ab12	1-113	462	23-35	464	51-57	466	90-102	468
Ab13	1-113	502	24-36	504	52-58	506	91-102	508
Ab14	1-113	542	23-35	544	51-57	546	90-102	548

Figure 8
Light Chain Protein Sequence Features

Antibody	FR1			FR2			FR3			FR4			SEQ ID NO: Coordinates	Constant Region ID	SEQ ID NO: Coordinates
	SEQ ID NO:	Coordinates	NO:	SEQ ID NO:	Coordinates	NO:	SEQ ID NO:	Coordinates	NO:	SEQ ID NO:	Coordinates	NO:			
Ab1	1-22	23	36-50	25	58-89		27	103-113		29	114-219		30		
Ab2	1-22	63	36-50	65	58-89		67	103-113		69	114-219		70		
Ab3	1-22	103	36-50	105	58-89		107	103-113		109	114-219		110		
Ab4	1-22	143	36-50	145	58-89		147	103-113		149	114-219		150		
Ab5	1-22	183	36-50	185	58-89		187	103-113		189	114-219		190		
Ab6	1-22	223	36-50	225	58-89		227	103-113		229	114-219		230		
Ab7	1-22	263	36-50	265	58-89		267	103-113		269	114-219		270		
Ab8	1-22	303	36-50	305	58-89		307	103-113		309	114-219		310		
Ab9	1-22	343	36-50	345	58-89		347	103-113		349	114-219		350		
Ab10	1-22	383	36-50	385	58-89		387	103-113		389	114-219		390		
Ab11	1-22	423	36-50	425	58-89		427	103-113		429	114-219		430		
Ab12	1-22	463	36-50	465	58-89		467	103-113		469	114-219		470		
Ab13	1-23	503	37-51	505	59-90		507	103-113		509	114-219		510		
Ab14	1-22	543	36-50	545	58-89		547	103-113		549	114-219		550		

Figure 9
Heavy Chain DNA Sequence Features

Heavy Chain DNA Sequence Features						
	Variable Region Coordinates	SEQ ID NO:	CDR1 SEQ ID NO:	CDR2 SEQ ID NO:	CDR3 SEQ ID NO:	SEQ ID NO:
Antibody Ab1	1-327	12 88-102	14 145-192	16 286-294	18	
Ab2	1-333	52 91-105	54 148-195	56 292-300	58	
Ab3	1-333	92 91-105	94 148-195	96 292-300	98	
Ab4	1-327	132 88-102	134 145-192	136 286-294	138	
Ab5	1-333	172 91-105	174 148-195	176 292-300	178	
Ab6	1-333	212 91-105	214 148-195	216 292-300	218	
Ab7	1-330	252 91-105	254 148-195	256 289-297	258	
Ab8	1-333	292 91-105	294 148-195	296 292-300	298	
Ab9	1-327	332 88-102	334 145-192	336 286-294	338	
Ab10	1-333	372 91-105	374 148-195	376 292-300	378	
Ab11	1-327	412 88-102	414 145-192	416 286-294	418	
Ab12	1-333	452 91-105	454 148-195	456 292-300	458	
Ab13	1-333	492 88-102	494 145-195	496 289-300	498	
Ab14	1-333	532 91-105	534 148-195	536 292-300	538	

Figure 10
Heavy Chain DNA Sequence Features

Antibody	FR1 Coordinates	SEQ ID NO:	FR2 Coordinates	SEQ ID NO:	FR3 Coordinates	SEQ ID NO:	FR4 Coordinates	SEQ ID NO:	Constant Region	SEQ ID NO:
Ab1	1-87	13	103-144	15	193-285	17	295-327	19	328-1320	20
Ab2	1-90	53	106-147	55	196-291	57	301-333	59	334-1326	60
Ab3	1-90	93	106-147	95	196-291	97	301-333	99	334-1326	100
Ab4	1-87	133	103-144	135	193-285	137	295-327	139	328-1320	140
Ab5	1-90	173	106-147	175	196-291	177	301-333	179	334-1326	180
Ab6	1-90	213	106-147	215	196-291	217	301-333	219	334-1326	220
Ab7	1-90	253	106-147	255	196-288	257	298-330	259	331-1323	260
Ab8	1-90	293	106-147	295	196-291	297	301-333	299	334-1326	300
Ab9	1-87	333	103-144	335	193-285	337	295-327	339	328-1320	340
Ab10	1-90	373	106-147	375	196-291	377	301-333	379	334-1326	380
Ab11	1-87	413	103-144	415	193-285	417	295-327	419	328-1320	420
Ab12	1-90	453	106-147	455	196-291	457	301-333	459	334-1326	460
Ab13	1-87	493	103-144	495	196-288	497	301-333	499	334-1326	500
Ab14	1-90	533	106-147	535	196-291	537	301-333	539	334-1326	540

Figure 11
Light Chain DNA Sequence Features

	Variable Region Coordinates	SEQ ID NO:	CDR1 Coordinates	SEQ ID NO:	CDR2 Coordinates	SEQ ID NO:	CDR3 Coordinates	SEQ ID NO:
Antibody Ab1	1-339	32	67-105	34	151-171	36	268-306	38
Ab2	1-339	72	67-105	74	151-171	76	268-306	78
Ab3	1-339	112	67-105	114	151-171	116	268-306	118
Ab4	1-339	152	67-105	154	151-171	156	268-306	158
Ab5	1-339	192	67-105	194	151-171	196	268-306	198
Ab6	1-339	232	67-105	234	151-171	236	268-306	238
Ab7	1-339	272	67-105	274	151-171	276	268-306	278
Ab8	1-339	312	67-105	314	151-171	316	268-306	318
Ab9	1-339	352	67-105	354	151-171	356	268-306	358
Ab10	1-339	392	67-105	394	151-171	396	268-306	398
Ab11	1-339	432	67-105	434	151-171	436	268-306	438
Ab12	1-339	472	67-105	474	151-171	476	268-306	478
Ab13	1-339	512	70-108	514	154-174	516	271-306	518
Ab14	1-339	552	67-105	554	151-171	556	268-306	558

Figure 12
Light Chain DNA Sequence Features

	FR1	SEQ ID NO:	Coordinates	SEQ ID NO:								
Antibody	Coordinates	SEQ ID NO:										
Ab1	1-66	33	106-150	35	172-267	37	307-339	39	340-660	40		
Ab2	1-66	73	106-150	75	172-267	77	307-339	79	340-660	80		
Ab3	1-66	113	106-150	115	172-267	117	307-339	119	340-660	120		
Ab4	1-66	153	106-150	155	172-267	157	307-339	159	340-660	160		
Ab5	1-66	193	106-150	195	172-267	197	307-339	199	340-660	200		
Ab6	1-66	233	106-150	235	172-267	237	307-339	239	340-660	240		
Ab7	1-66	273	106-150	275	172-267	277	307-339	279	340-660	280		
Ab8	1-66	313	106-150	315	172-267	317	307-339	319	340-660	320		
Ab9	1-66	353	106-150	355	172-267	357	307-339	359	340-660	360		
Ab10	1-66	393	106-150	395	172-267	397	307-339	399	340-660	400		
Ab11	1-66	433	106-150	435	172-267	437	307-339	439	340-660	440		
Ab12	1-66	473	106-150	475	172-267	477	307-339	479	340-660	480		
Ab13	1-69	513	109-153	515	175-270	517	307-339	519	340-660	520		
Ab14	1-66	553	106-150	555	172-267	557	307-339	559	340-660	560		

Responders at all three time-points

FIG. 13

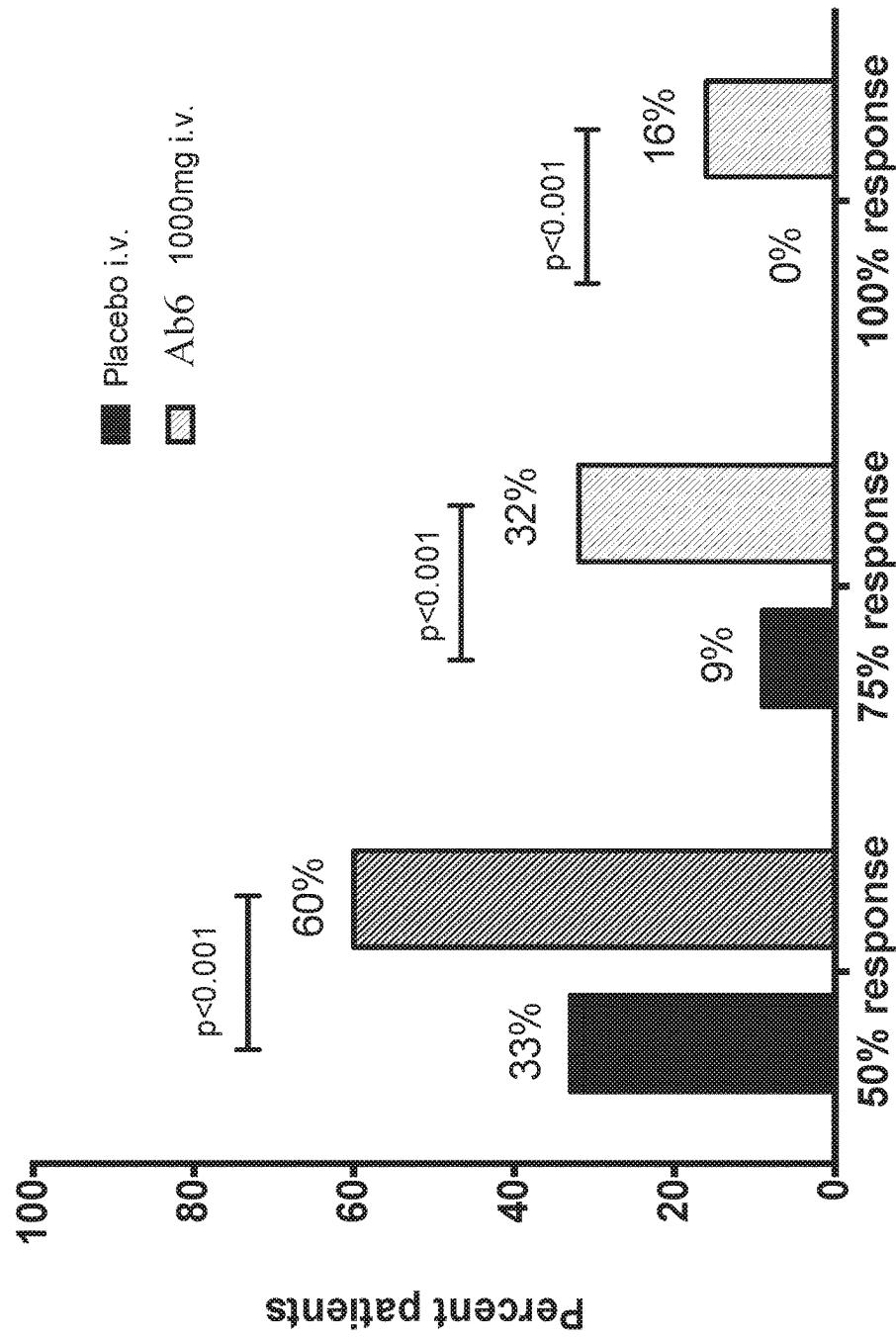


FIG. 14

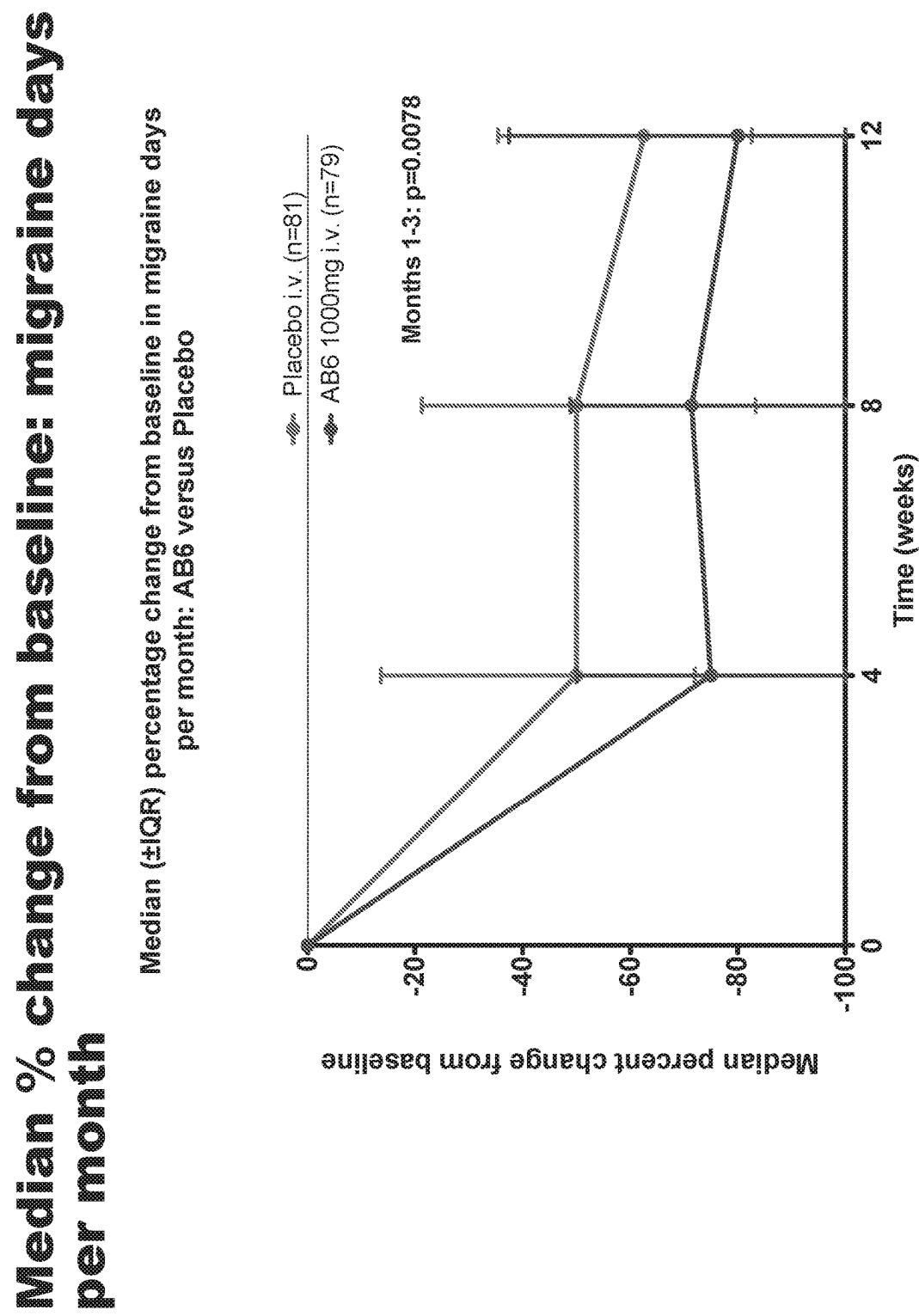


FIG. 15

Median % change from baseline: migraine episodes per month

Median (\pm IQR) percentage change from baseline in migraine episodes per month: AB6 versus Placebo

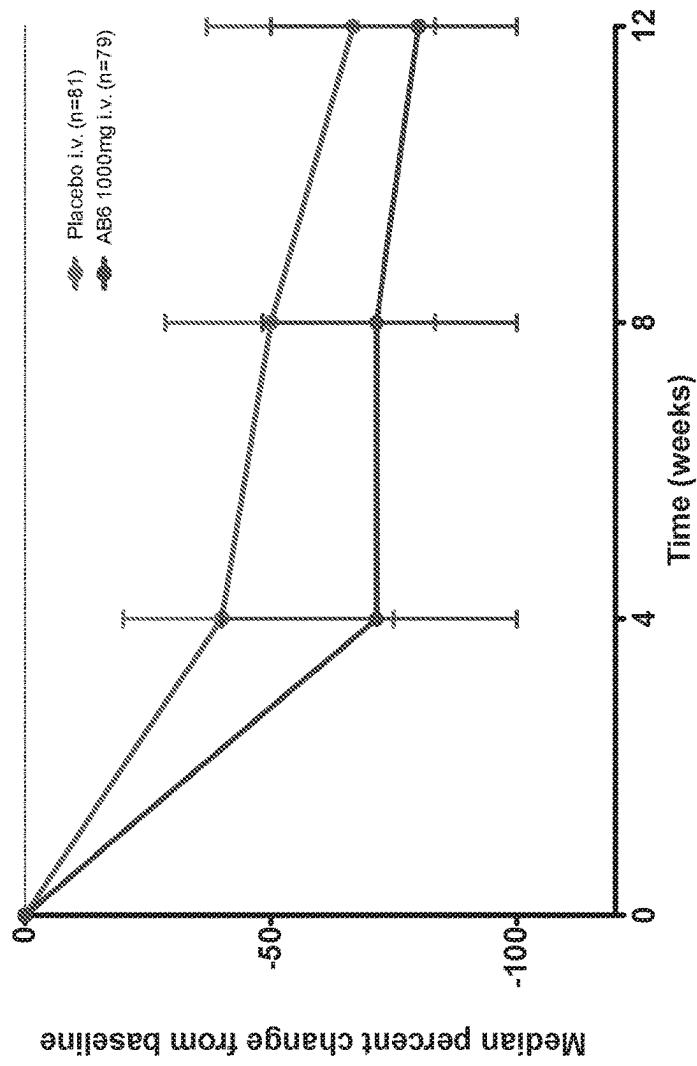


FIG. 16

Median % change from baseline: migraine hours per month

Median (\pm IQR) percentage change from baseline in migraine hours per month: AB6 versus Placebo

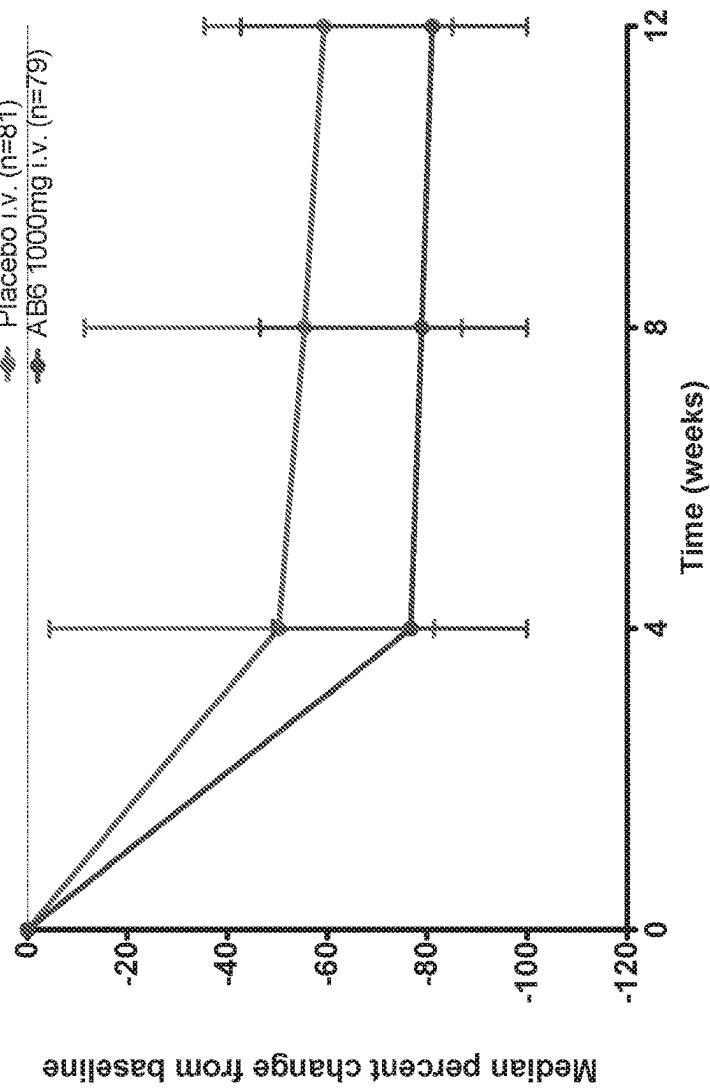


FIG. 17

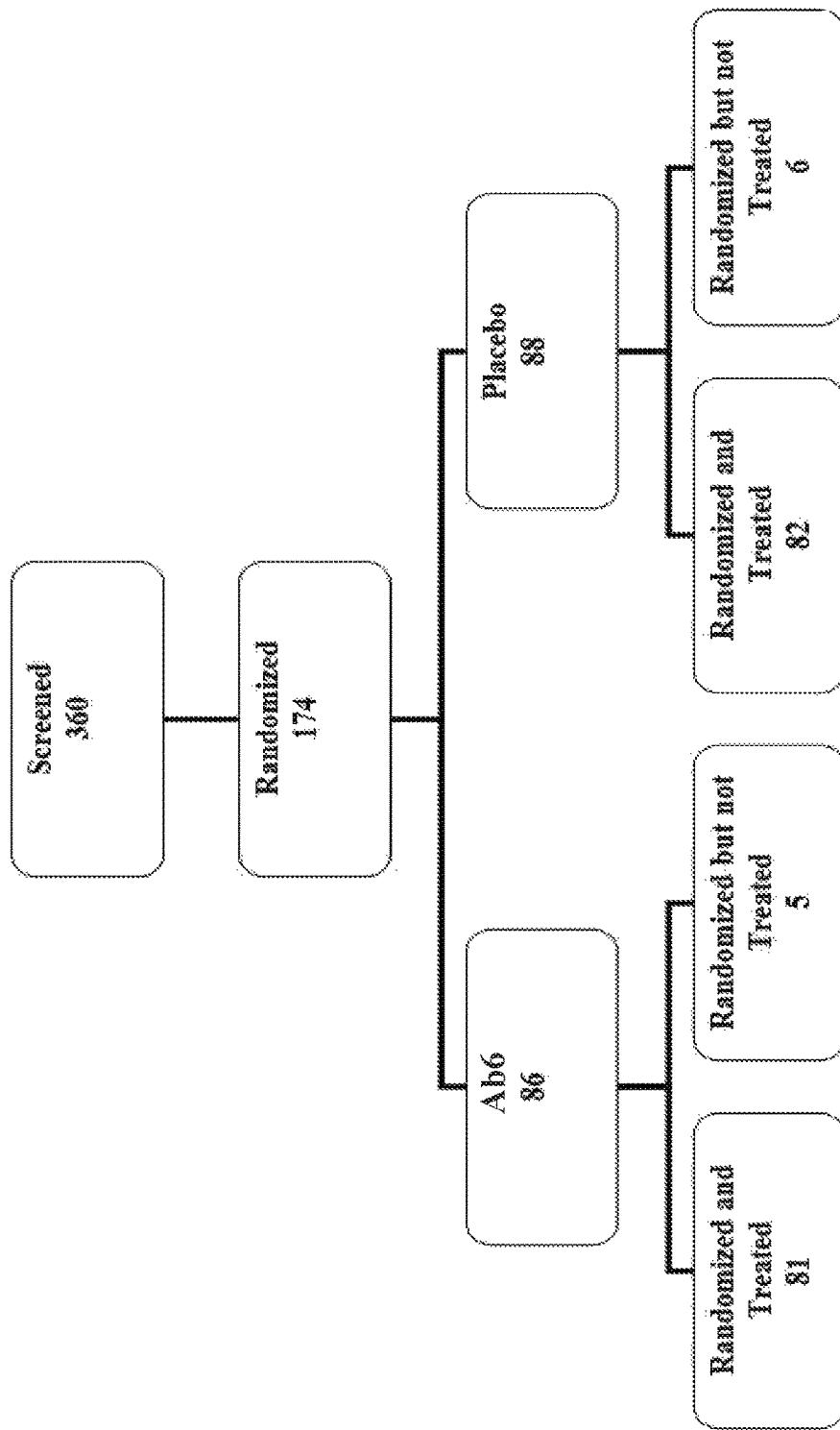
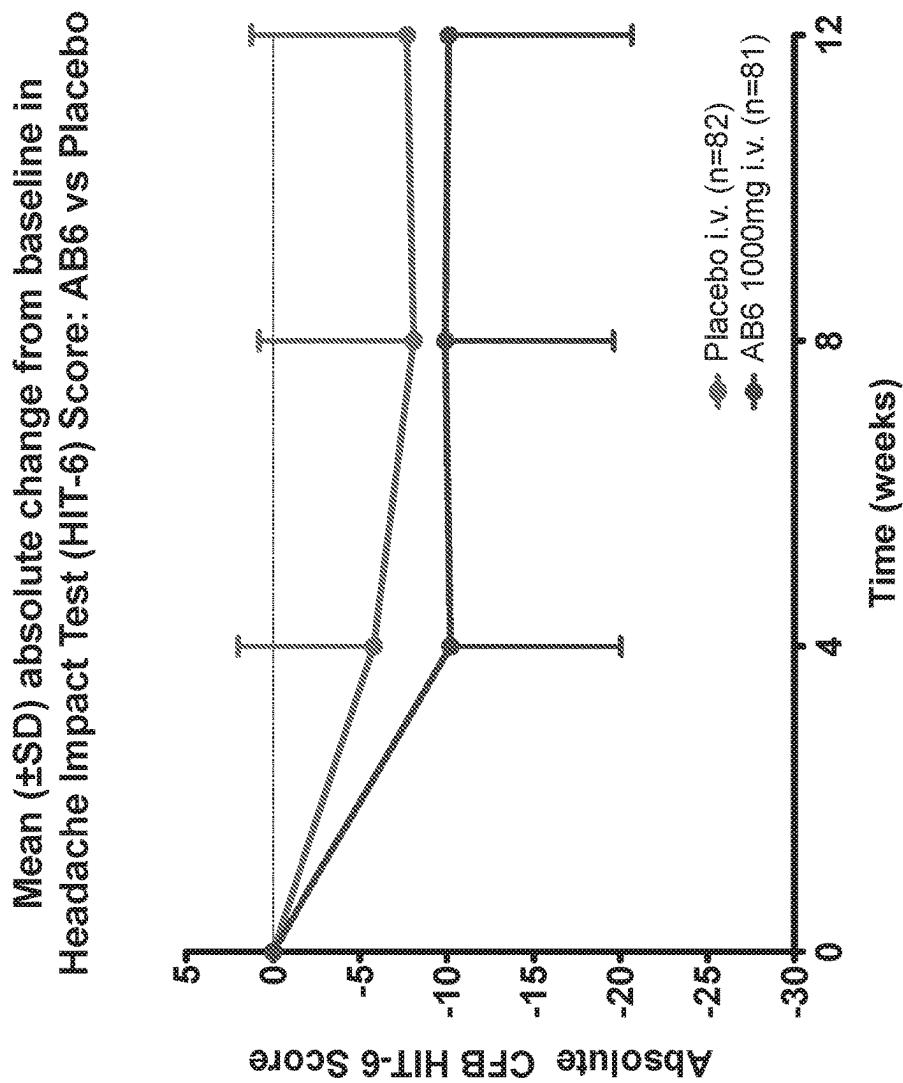


FIG. 18

Mean Change Baseline HIT-6 score



HIT-6 Responder Analysis

FIG. 19

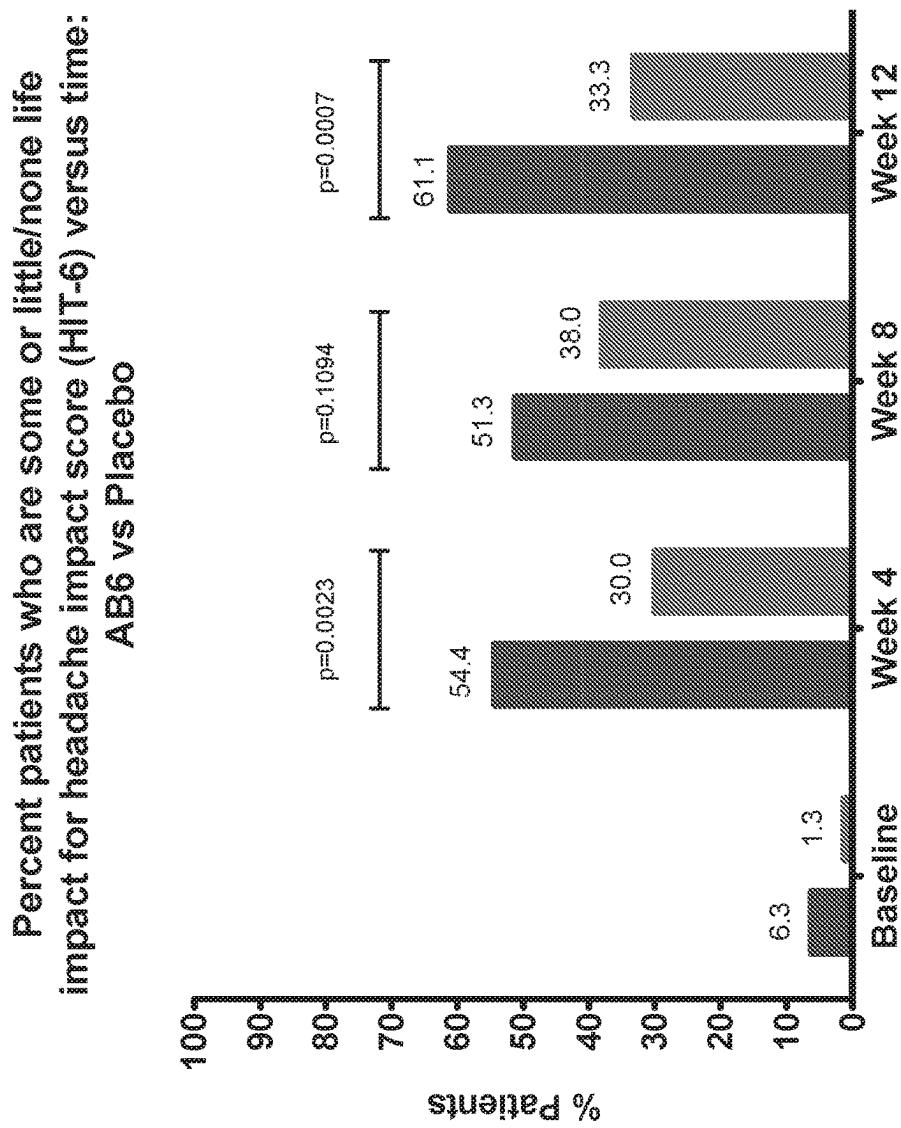


FIG. 20. PK Profile

Ab6 1000 mg I.V. Mean +/- SD

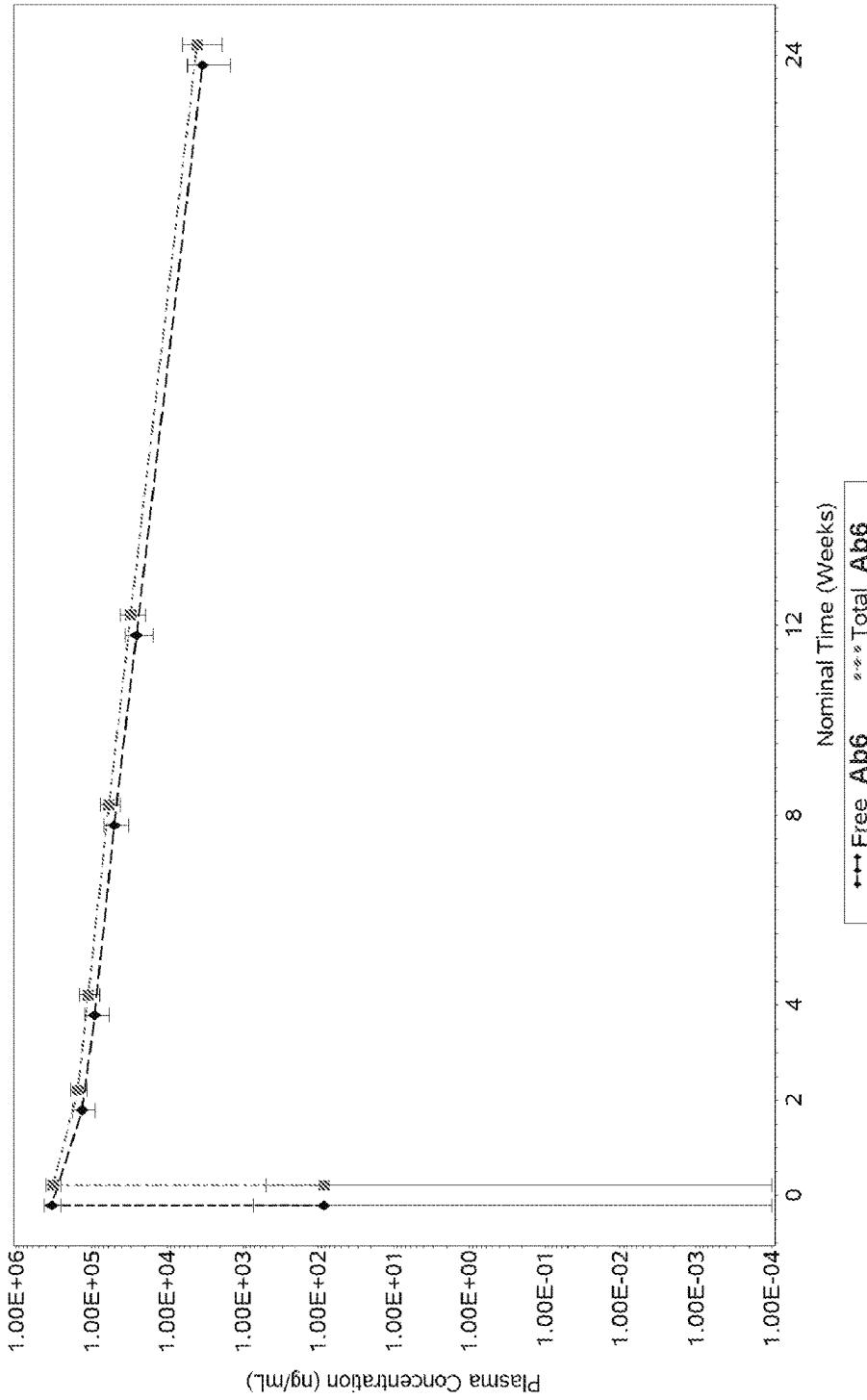


FIG. 21. PK Parameters

Plasma Free Ab6*

	C _{max} (μ g/ml)	AUC _{0-∞} (mg*hr/ml)	Half-Life (Days)	V _Z (L)	CL (ml/hr)
N	81	78	78	78	78
Mean	336	219	31	52	5.0
SD	80	64	8	2.1	1.5

* - Following 1000 mg Ab6 IV single-dose

FIG. 22

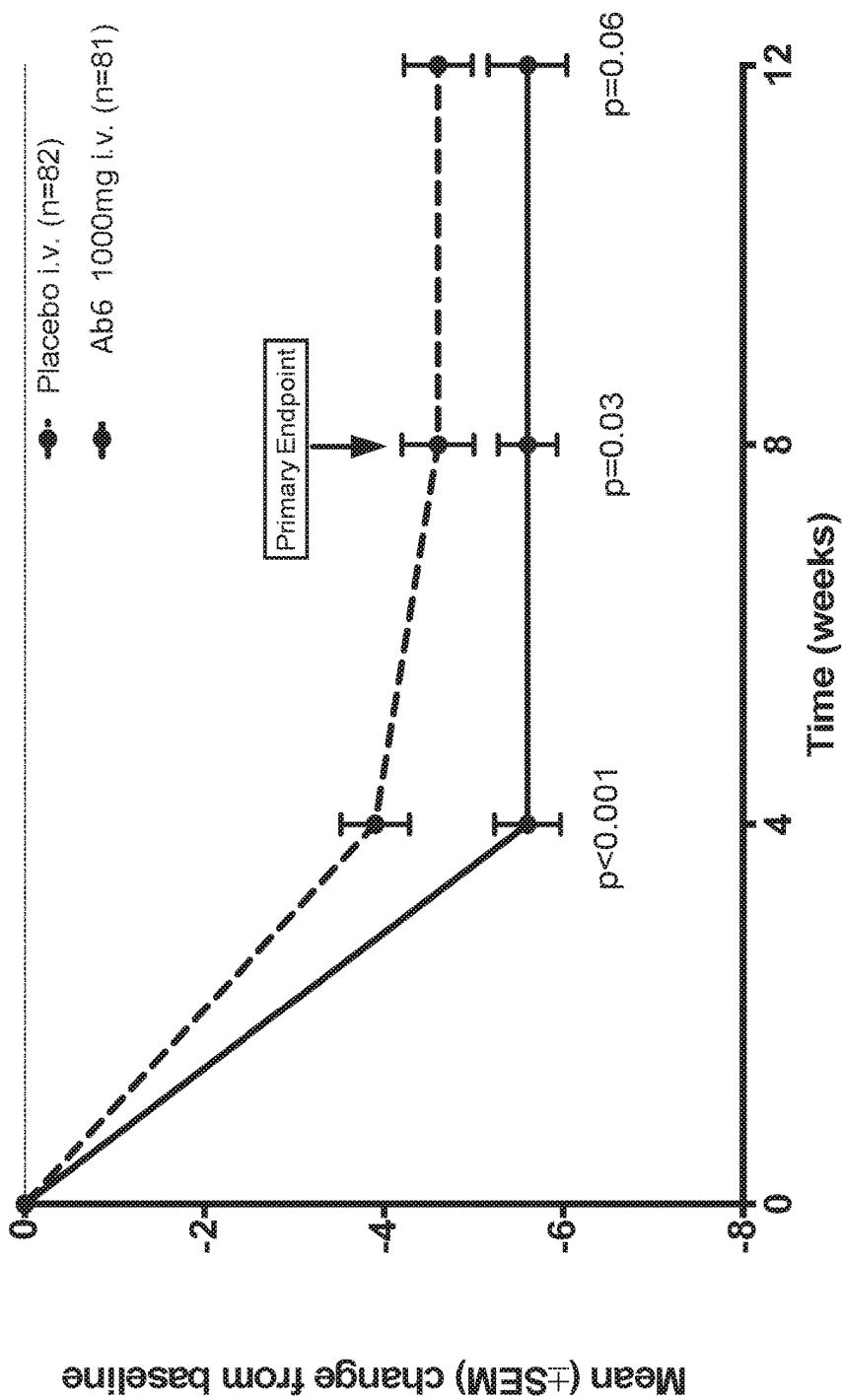


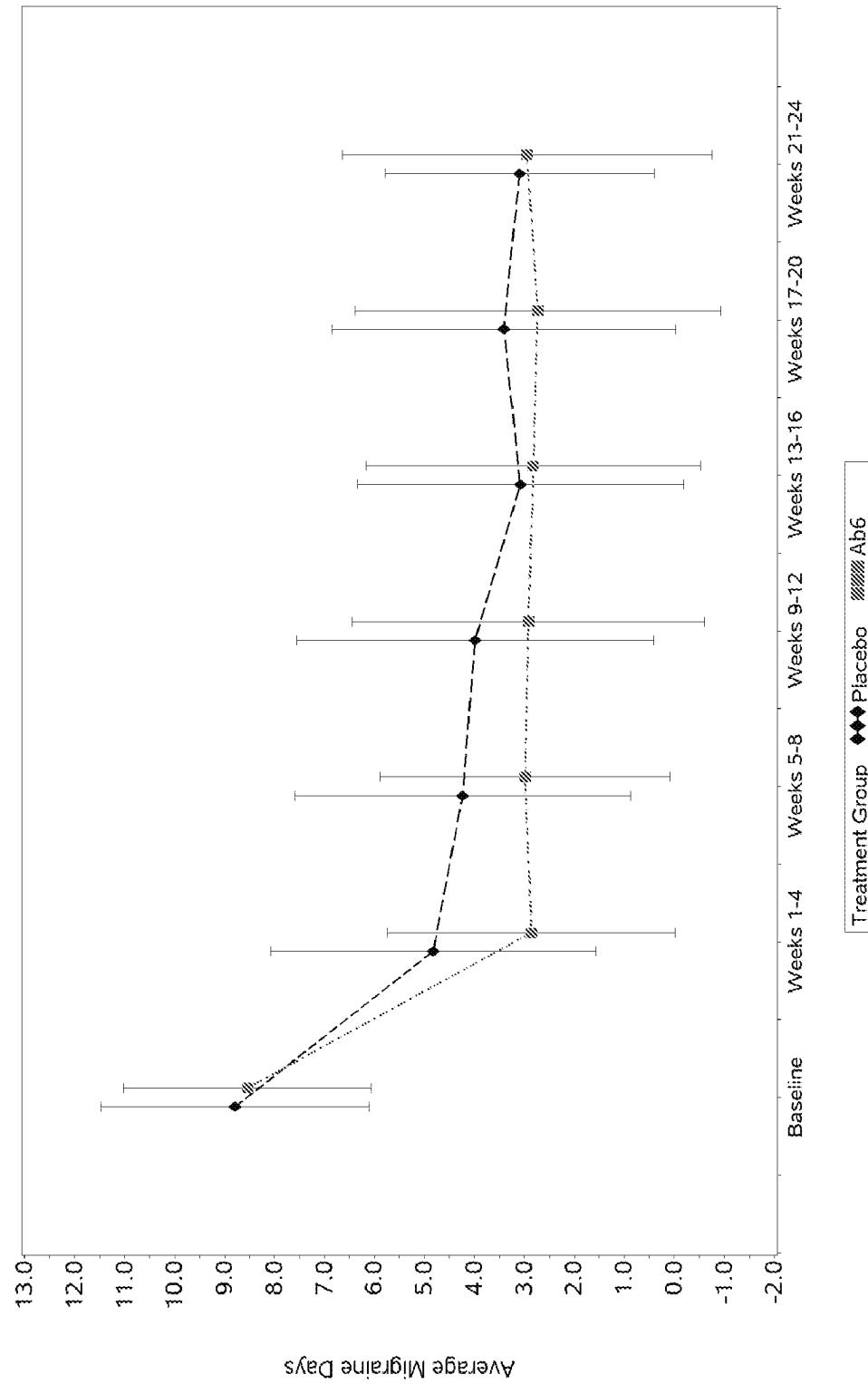
FIG. 23

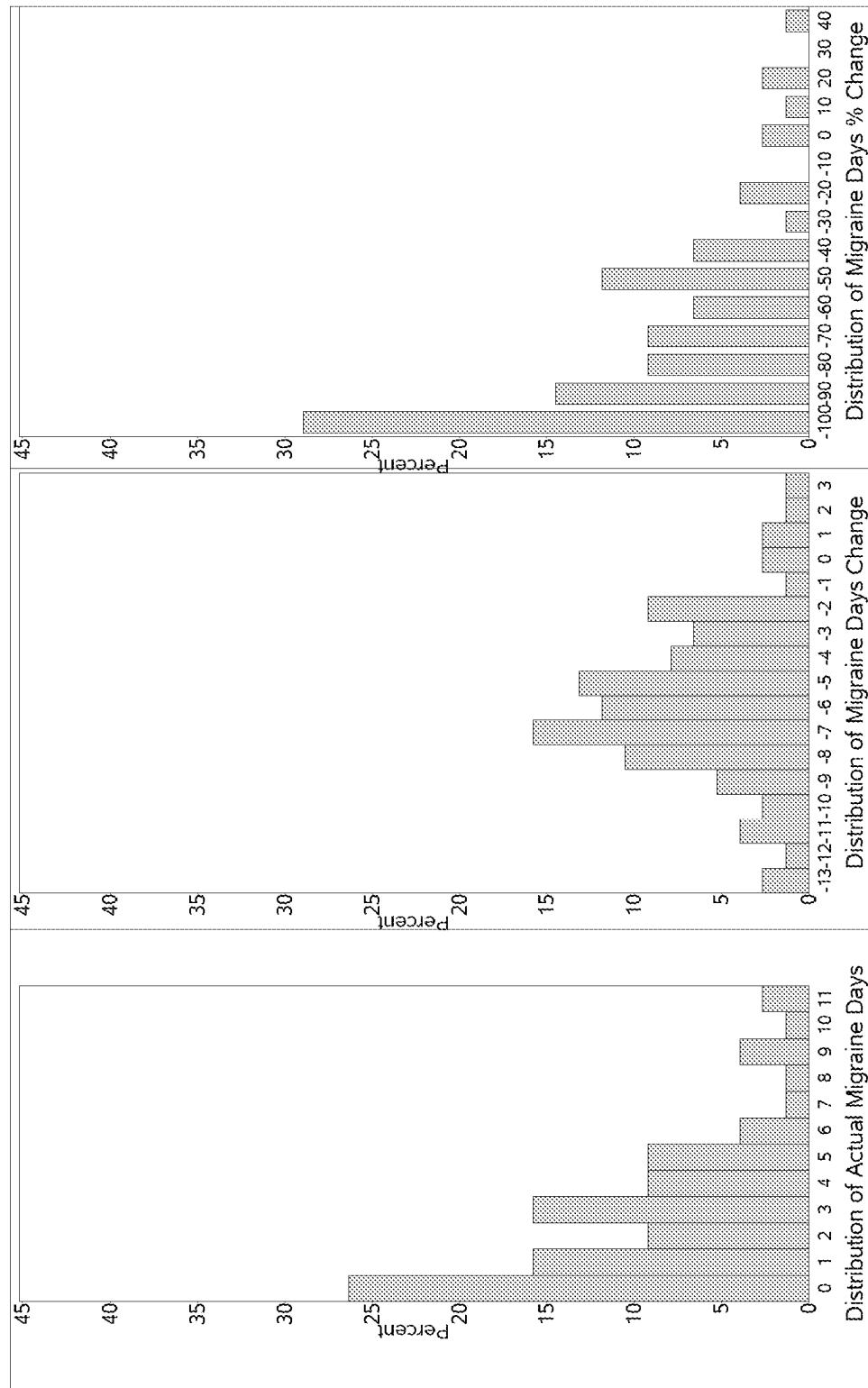
FIG. 24

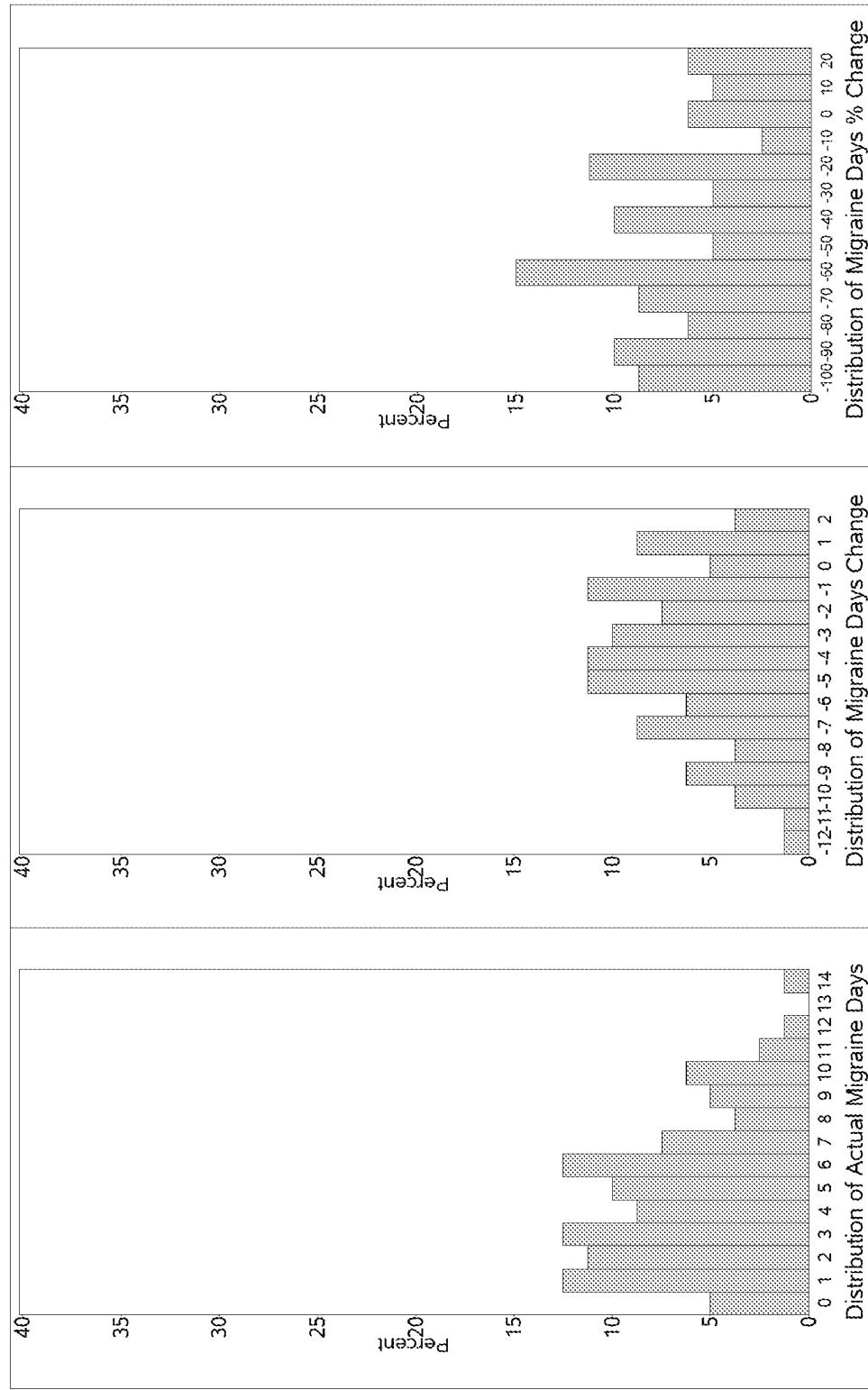
FIG. 25

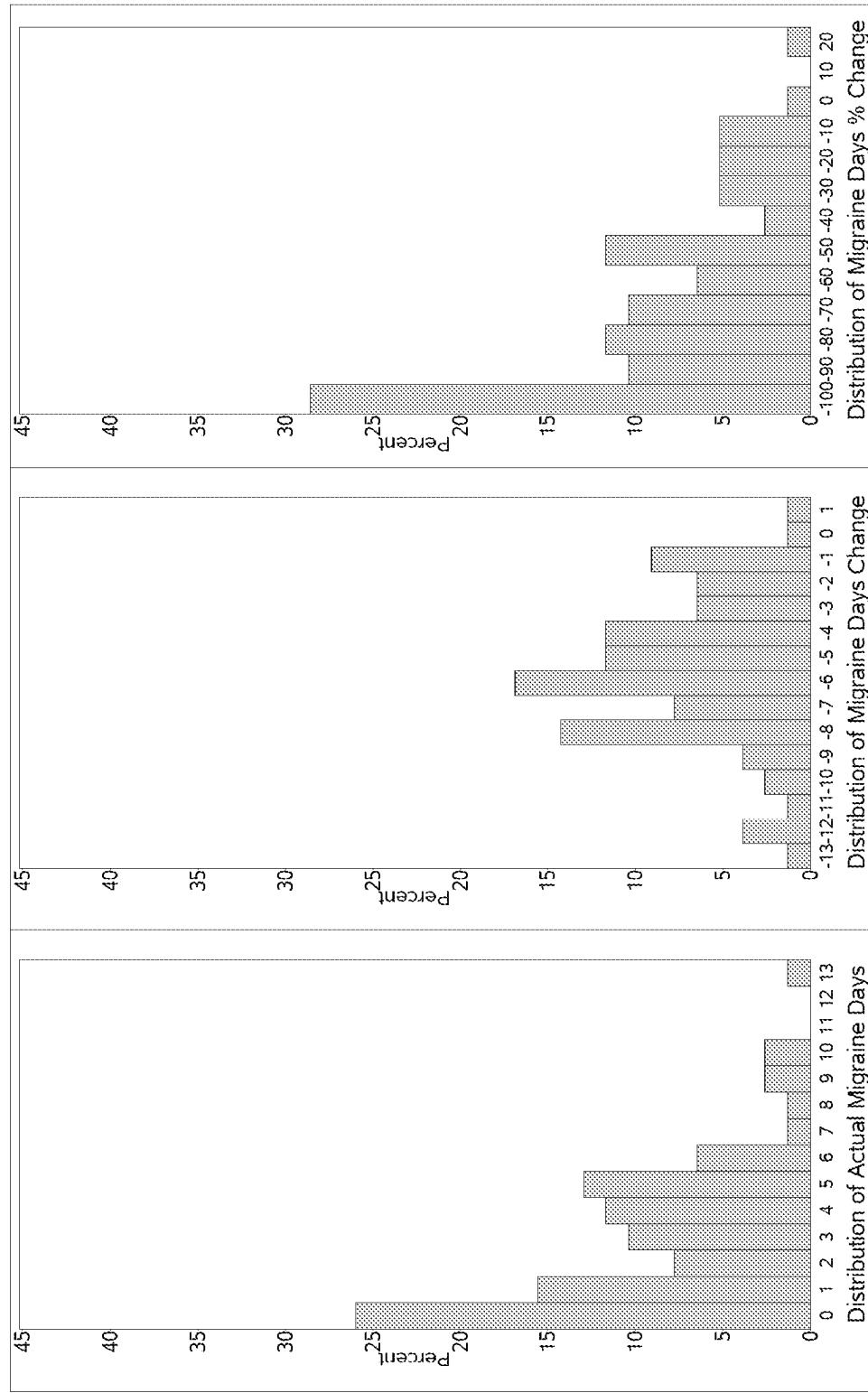
FIG. 26

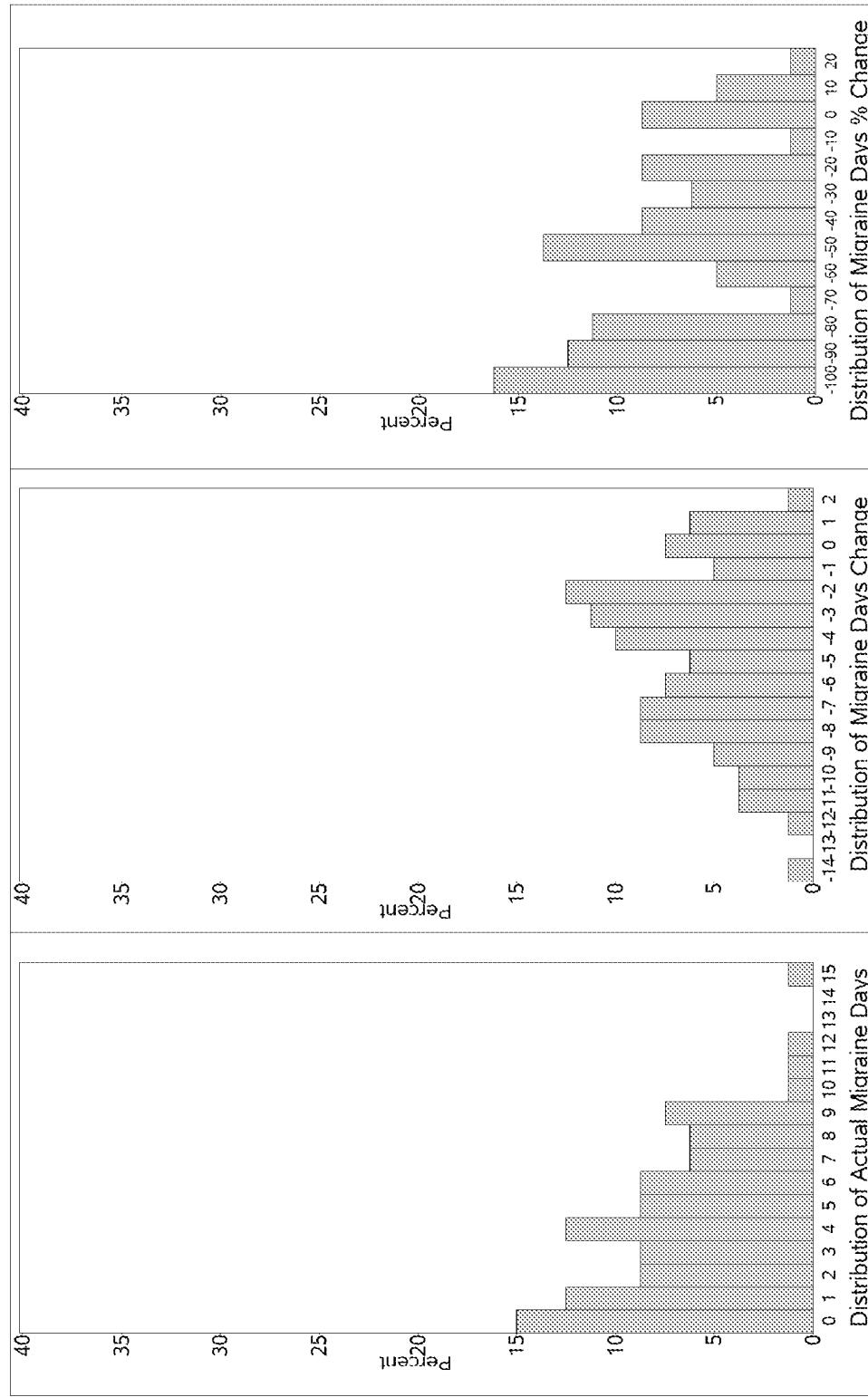
FIG. 27

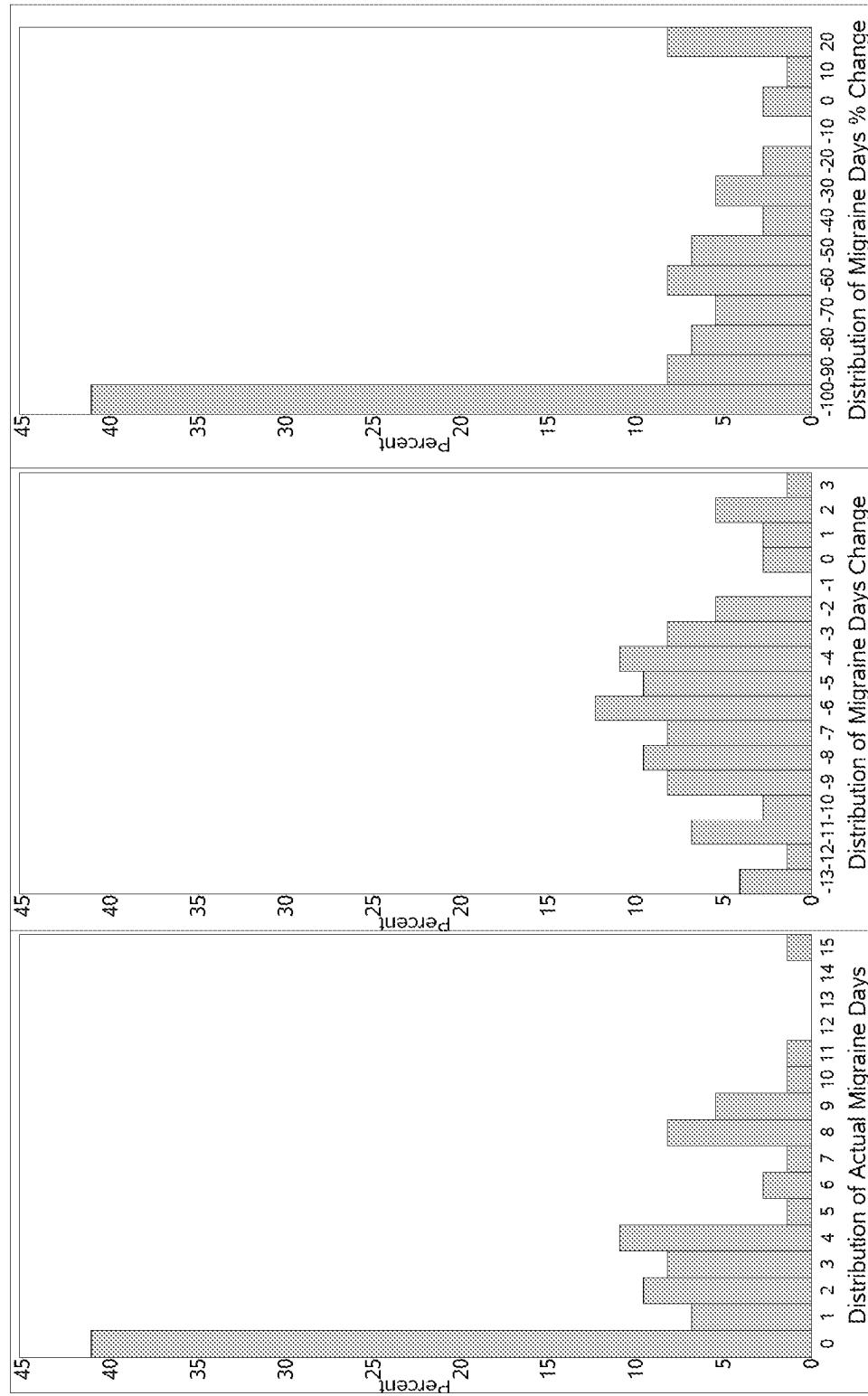
FIG. 28

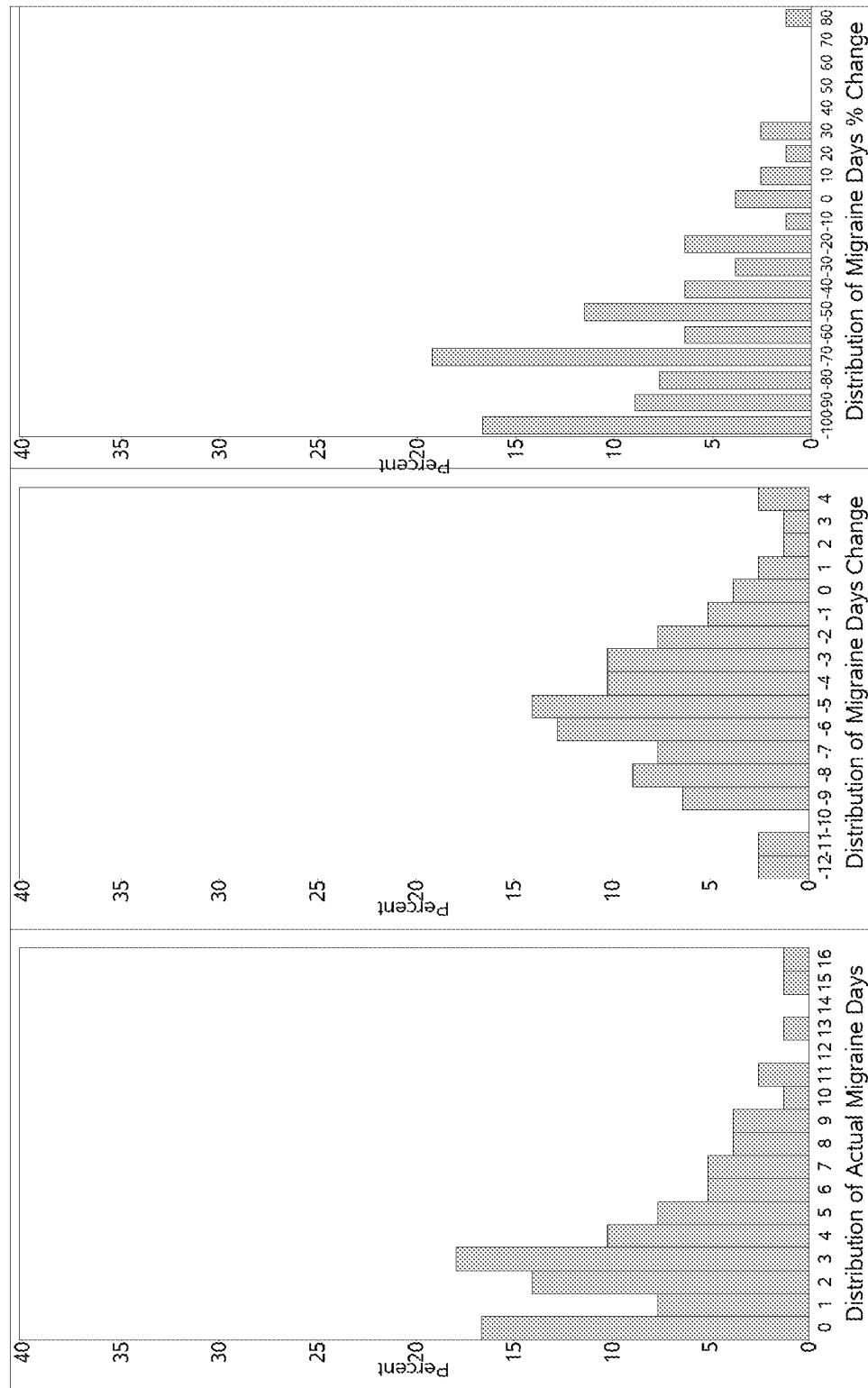
FIG. 29

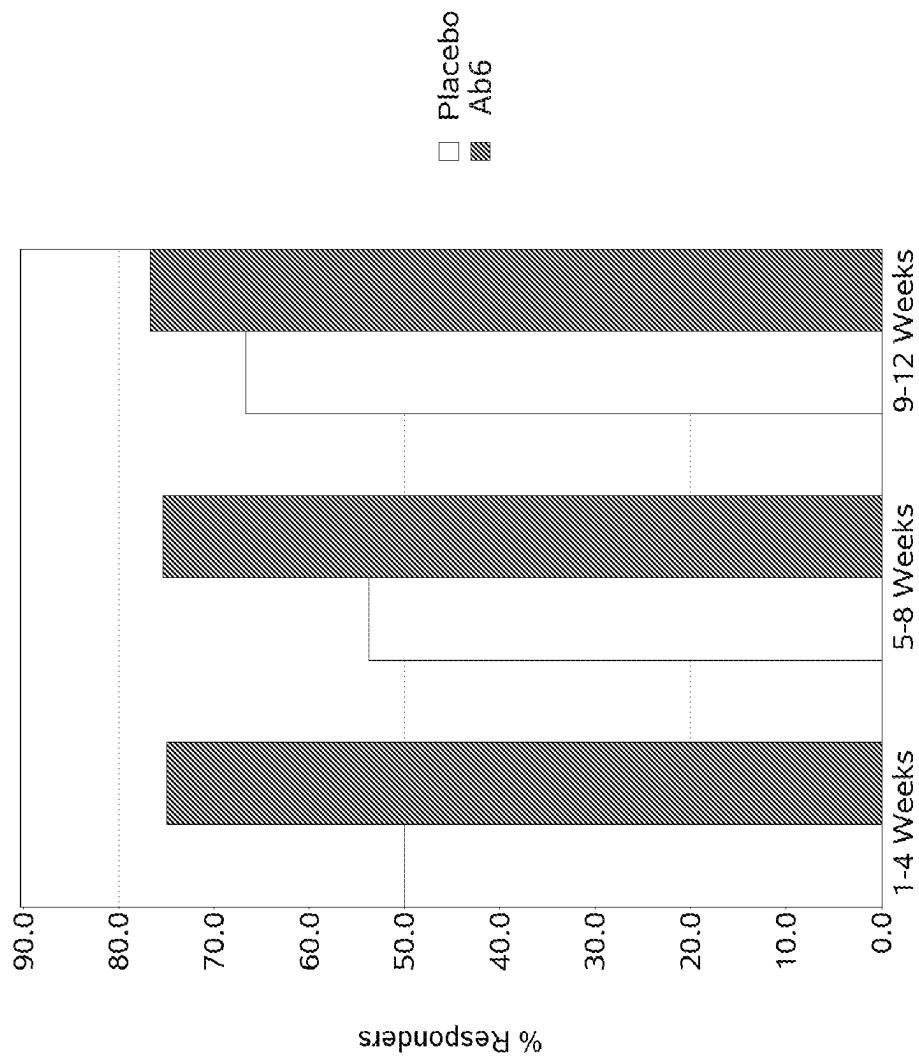
FIG. 30

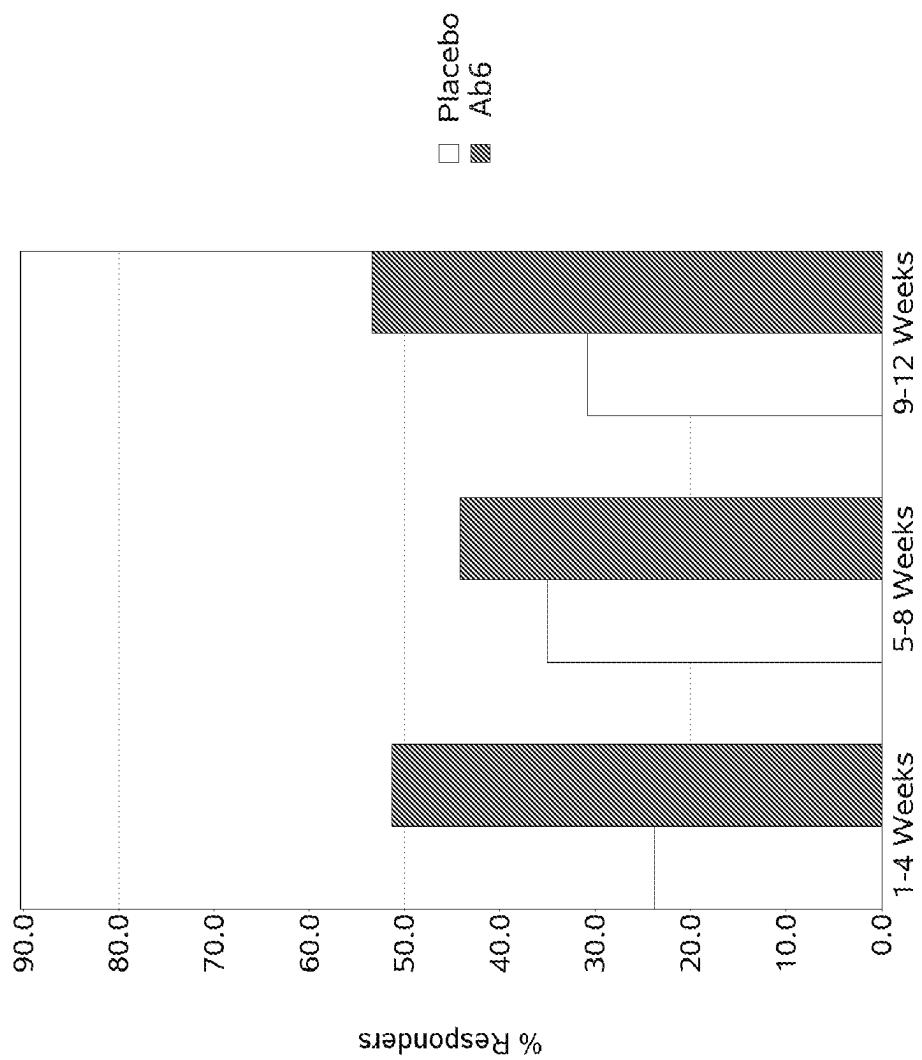
FIG. 31

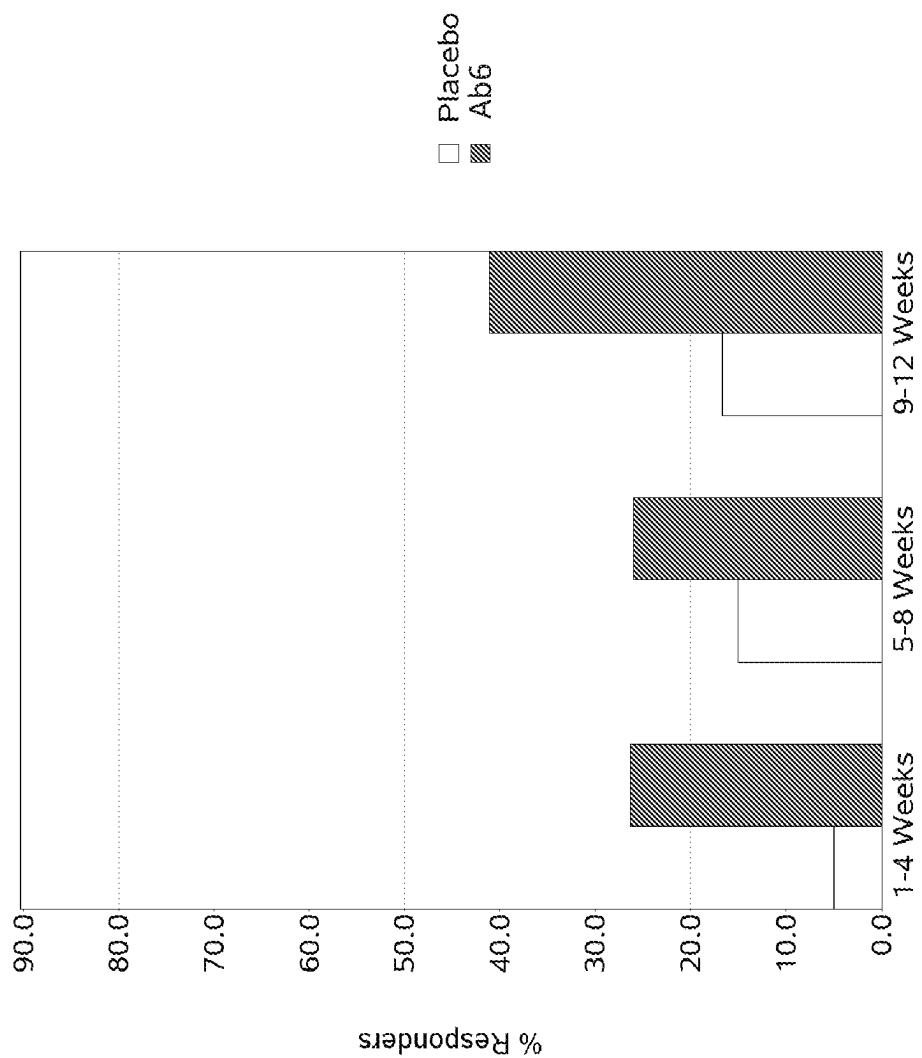
FIG. 32

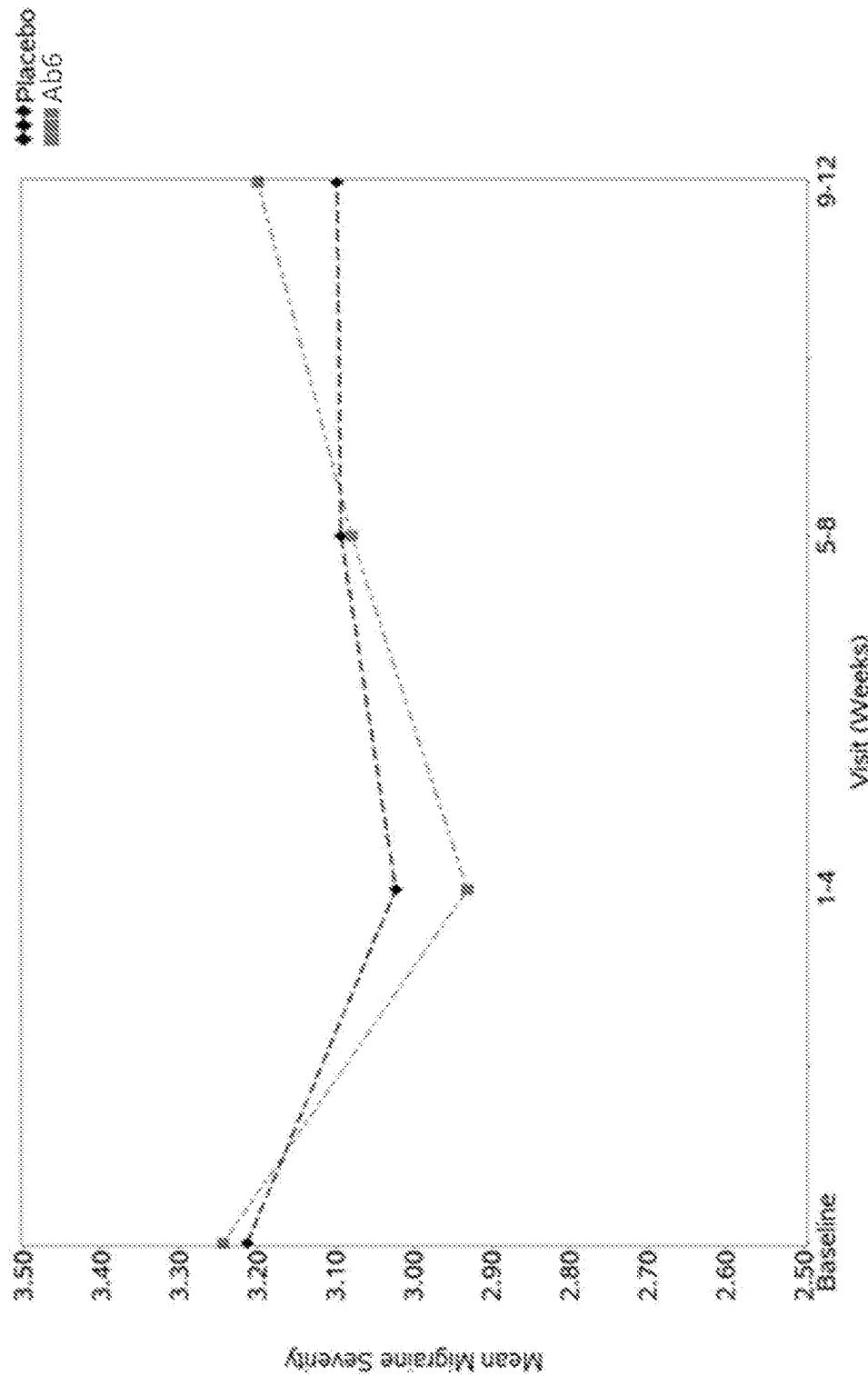
FIG. 33

FIG. 34Mean (\pm SE) Change from Baseline in Study Endpoints

Endpoint ¹	Weeks 1-4		Weeks 3-8		Weeks 9-12	
	Placebo i.v. (n=82)	Abe 1000mg i.v. (n=81)	Placebo i.v. (n=82)	Abe 1000mg i.v. (n=81)	Placebo i.v. (n=82)	Abe 1000mg i.v. (n=81)
Migraine Days	-3.9 (3.5) ²	-5.6 (3.3) ²	-4.6 (3.6)	-5.6 (3.0) ²	-4.6 (3.5)	-5.6 (4.0) ²
Migraine Episodes	-3.0 (2.7)	-3.7 (2.4)	-3.7 (2.9)	-3.8 (2.2)	-3.7 (2.8)	-3.9 (2.6)
Migraine Hours	-33.7 (41.8)	-38.0 (49.1)	-36.1 (45.9)	-34.4 (48.3)	-37.1 (40.0)	-34.6 (60.5)
Average Migraine Severity ³	-0.16 (0.58)	-0.31 (0.58)	-0.10 (0.54)	-0.16 (0.59)	-0.08 (0.54)	-0.11 (0.43)
Headache Frequency	-4.0 (3.8)	-5.6 (3.4)	-5.0 (3.7)	-5.3 (3.5)	-5.1 (3.7)	-5.9 (3.8)
HIT-6 score	-5.8 (7.8)	-10.2 (9.8)	-8.1 (8.9)	-9.9 (9.7)	-7.7 (9.0)	-10.1 (10.6)
MSQ RRP	19.9 (23.8)	29.3 (24.3)	25.3 (24.8)	28.8 (24.7)	22.2 (23.1)	28.5 (24.5)
MSQ RFR	16.3 (23.2)	21.1 (23.9)	20.2 (22.1)	20.9 (23.3)	18.0 (20.5)	21.4 (23.1)
MSQ EFP	19.4 (27.6)	28.1 (28.3)	21.2 (25.1)	23.8 (25.8)	21.1 (25.1)	23.1 (26.8)

¹p<0.001; ²p=0.03; ³p=0.06; ⁴Severity measured on a 4 point scale with 1=mild and 4=severe

FIG. 35

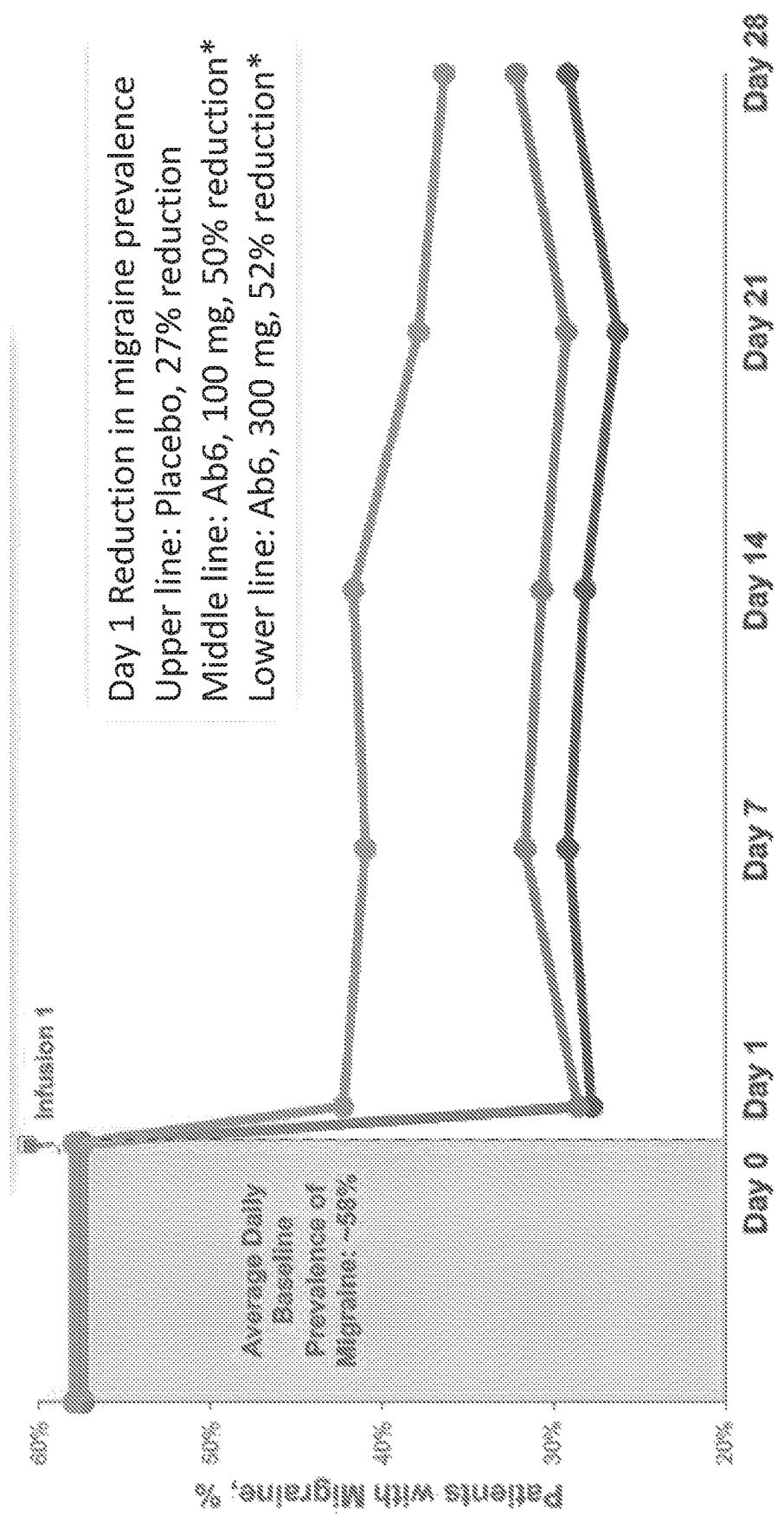


FIG. 36. Chronic migraine $\geq 50\%$ responder rates

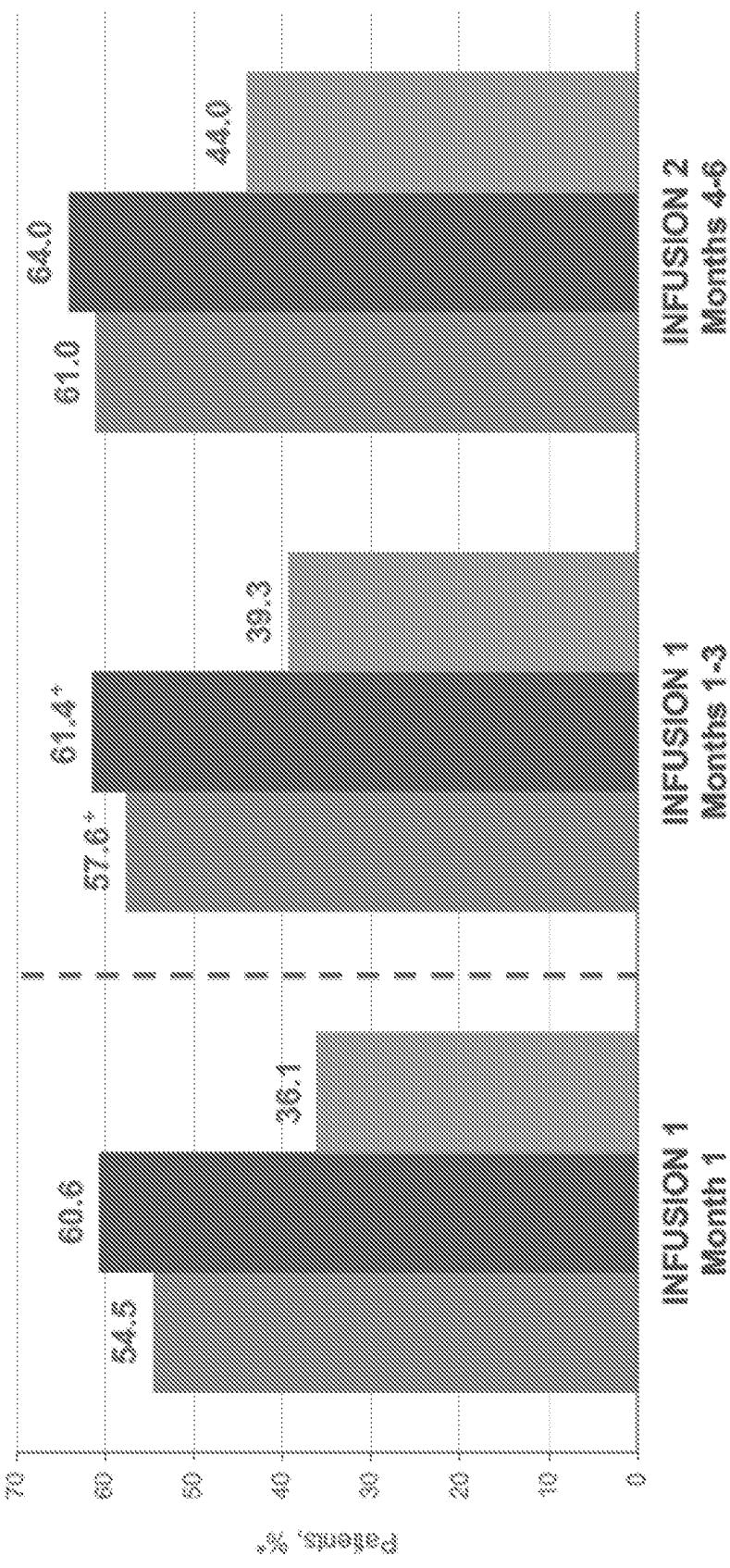


FIG. 37. Chronic migraine $\geq 75\%$ responder rates

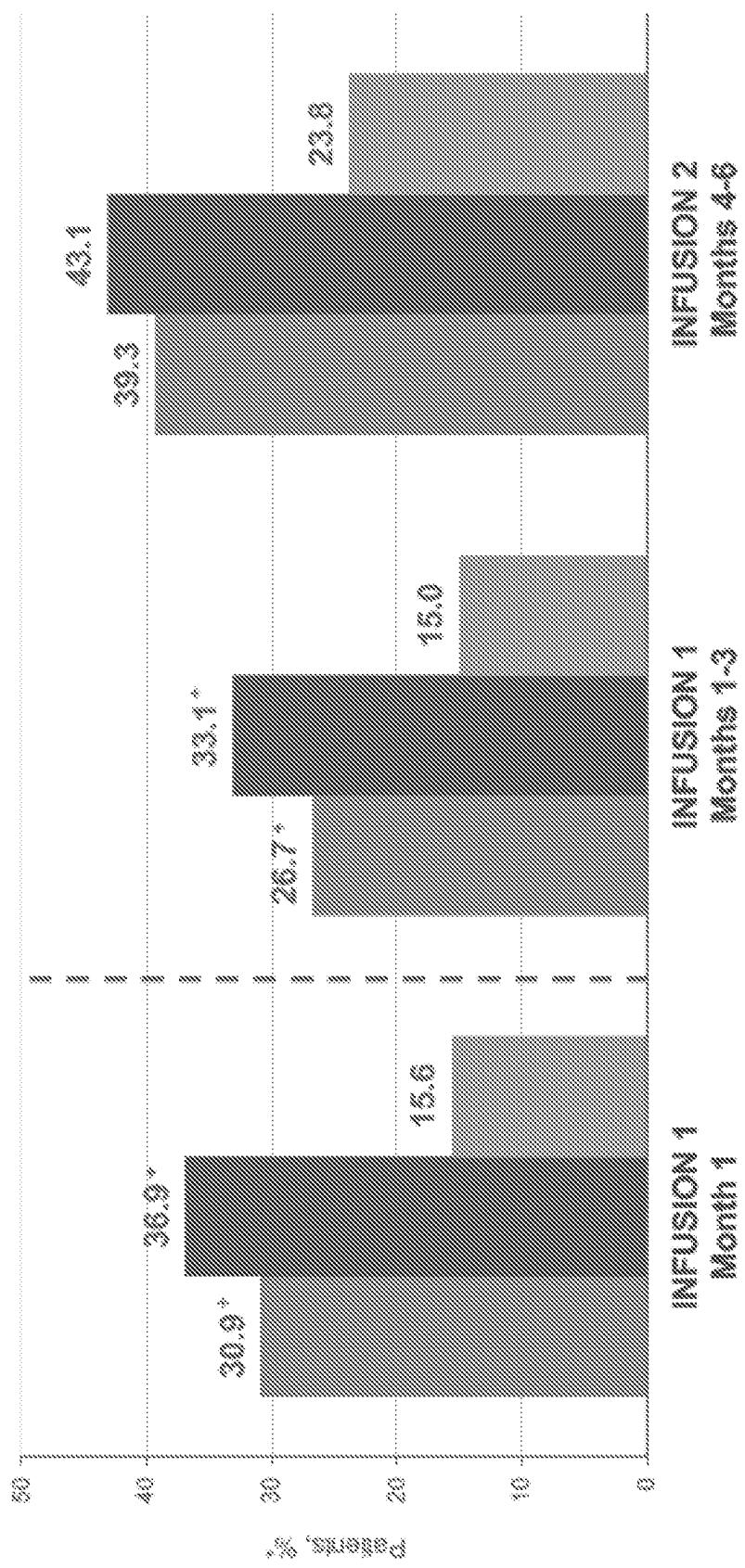


FIG. 38. Chronic migraine 100% responder rates

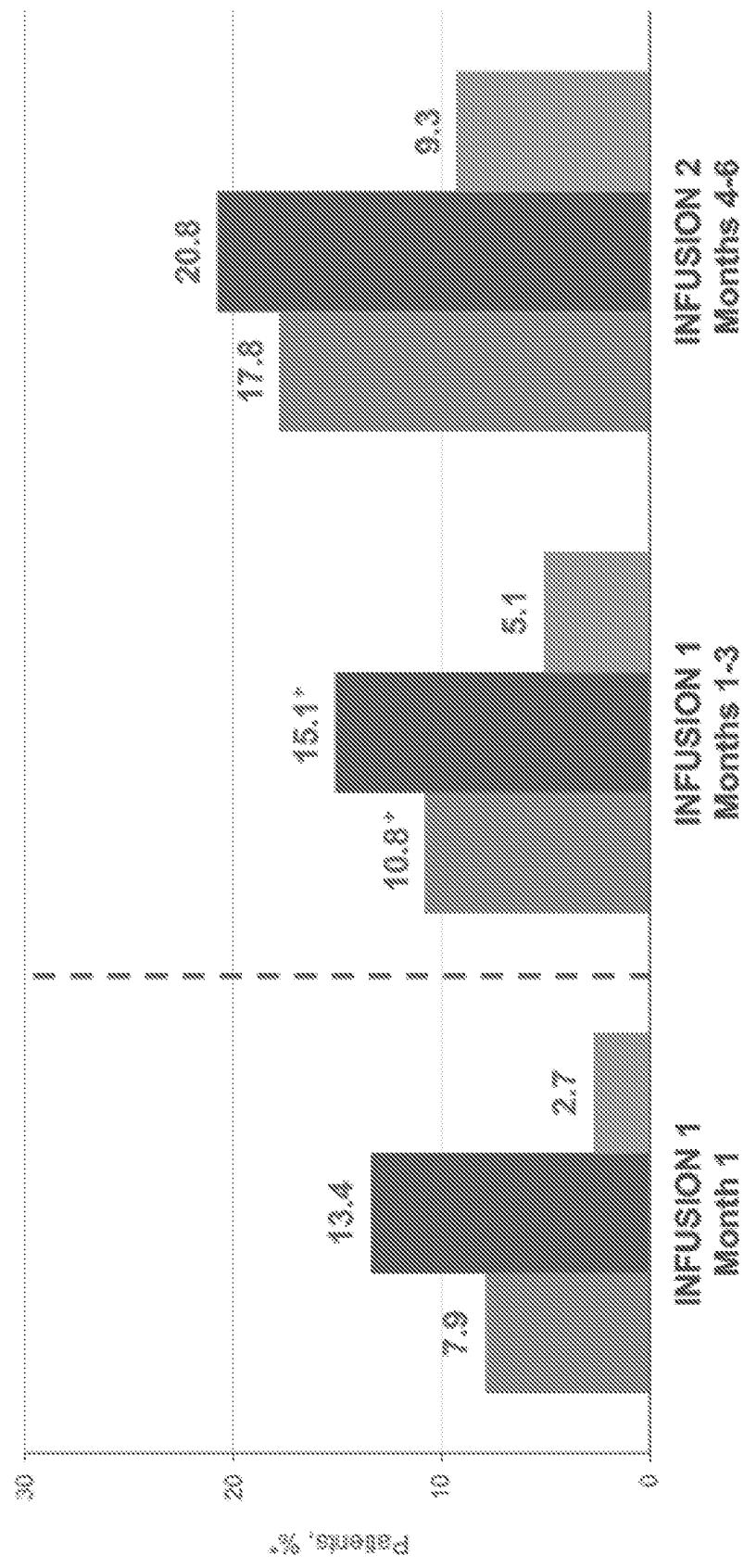


FIG. 39

Subjects, n	366	356	350
Mean age, years (SD)	39.6 (11.3)	41.0 (11.7)	41.0 (10.4)
Mean BMI, kg/m ² (SD)	27.0 (5.6)	26.4 (5.0)	26.3 (5.0)
Female, %	89	86	90
Mean years from migraine diagnosis	17.0	18.3	19.0
Mean duration of chronic migraine, years (SD)	11.6 (10.9)	11.6 (11.7)	12.4 (11.2)
≥1 prophylactic medication, n (%)*	163 (44.5)	161 (45.2)	155 (44.3)
Mean migraine days/month (SD)	16.2 (4.6)	16.1 (4.6)	16.1 (4.8)
Mean headache days/month (SD)	20.6 (3.0)	20.4 (3.1)	20.4 (3.2)

FIG. 40. Difference from placebo in change from baseline in mean migraine days (MMD) over months 1-3 by baseline subgroup

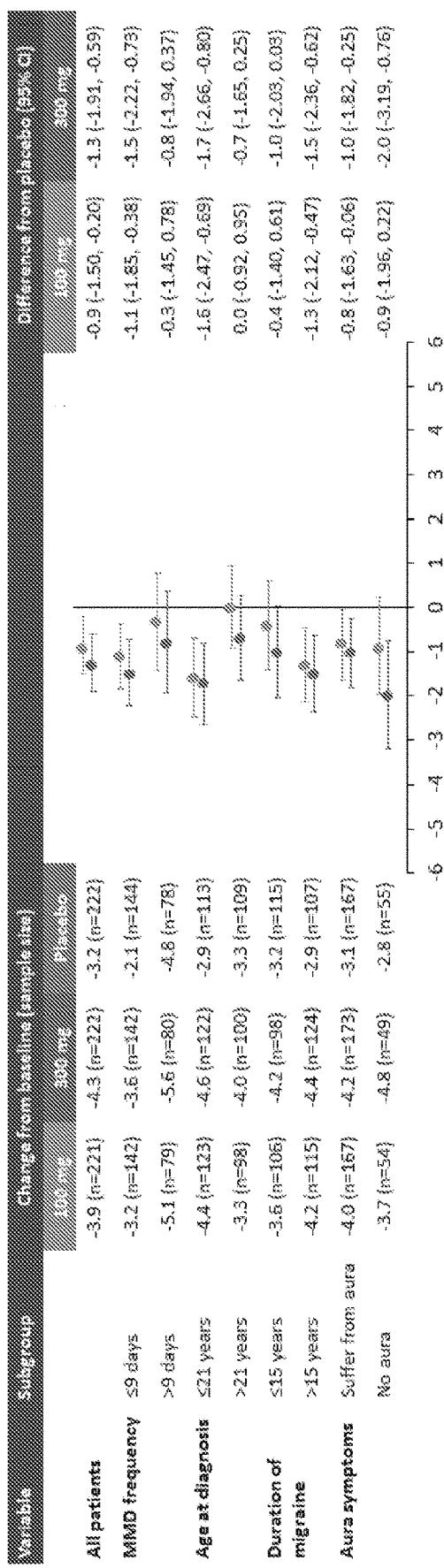
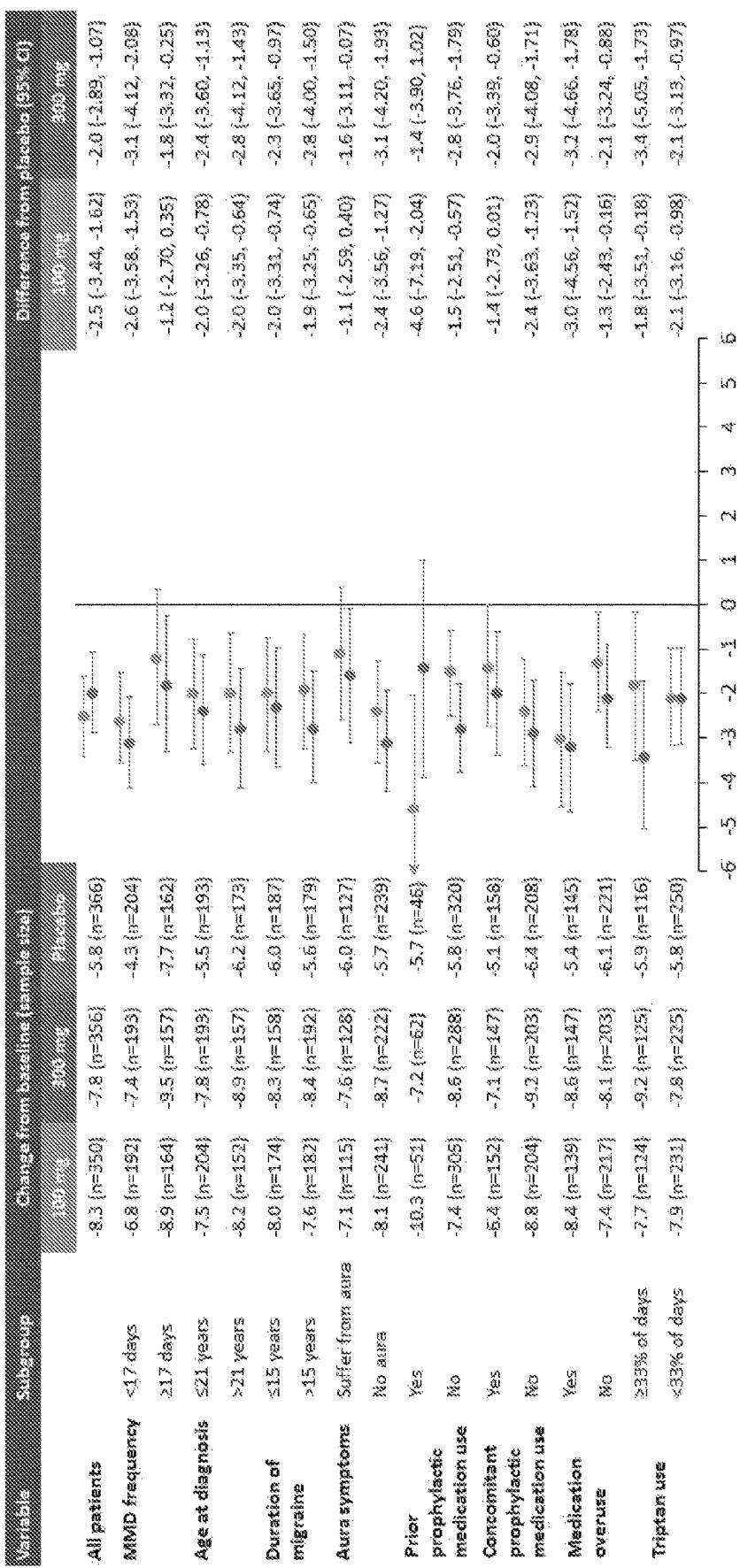


FIG. 41. Difference from placebo in change from baseline in mean migraine days (MMD) over months 1-3 by baseline subgroup



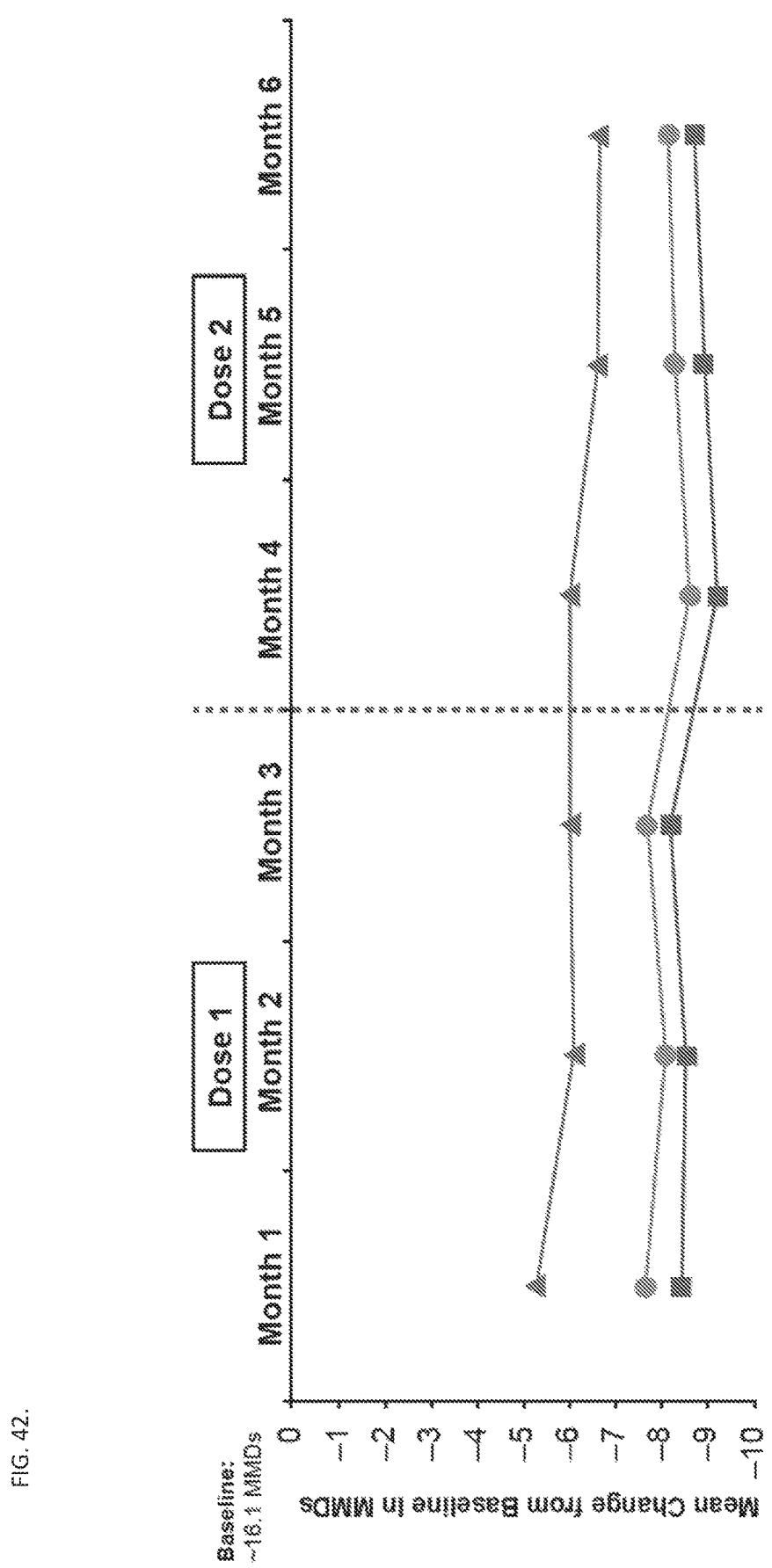


FIG. 43.

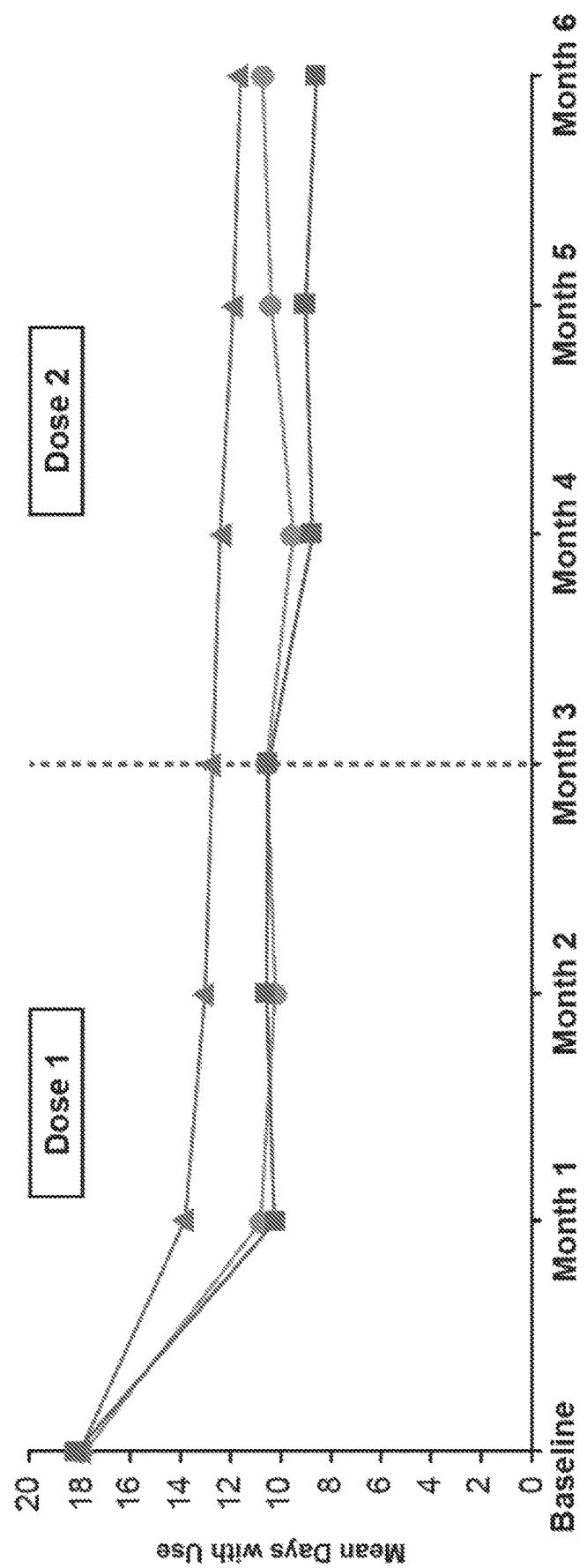


FIG. 44.

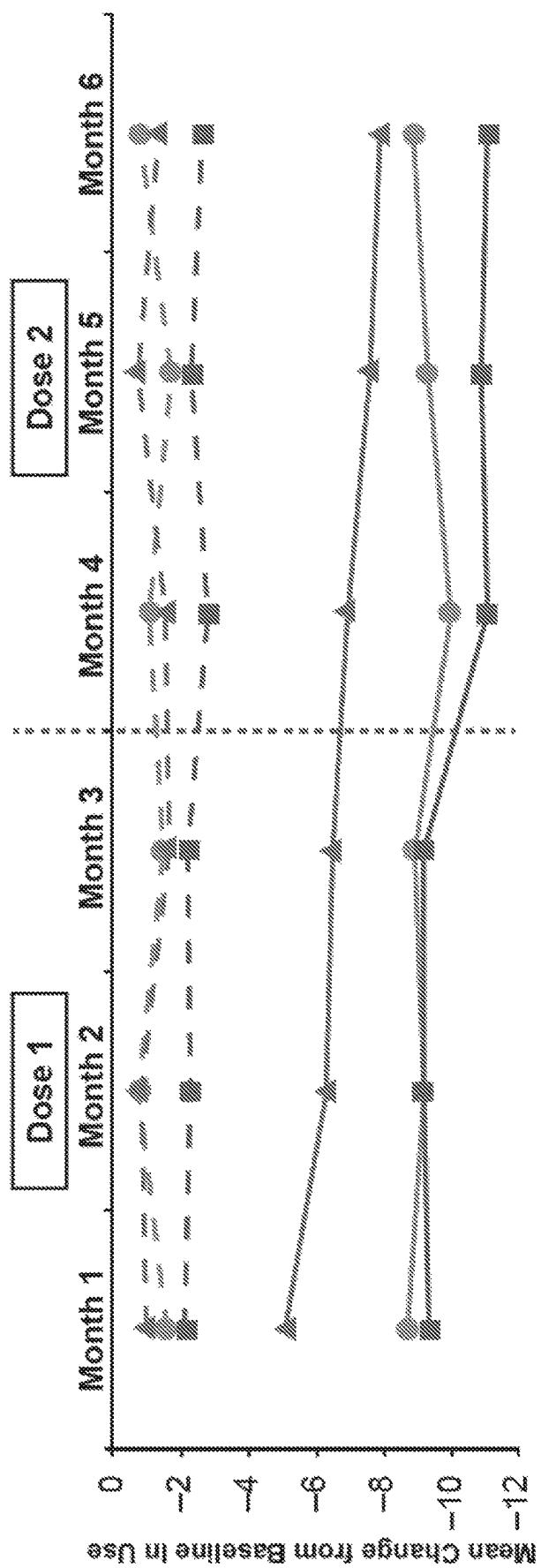


FIG. 45.

	Month 1	Month 6				
	Ab6 100 mg	Ab6 400 mg	Placebo	Ab6 100 mg	Ab6 400 mg	Placebo
Baseline use						
1–9 days/month, n	37	49	49	37	49	49
≥10 days/month, n	264	265	260	264	265	260
≥1 day/month, mean (SD)	18.3 (9.05)	18.4 (9.61)	17.9 (8.60)	18.3 (9.05)	18.4 (9.61)	17.9 (8.60)
Post-baseline use, mean (SD)						
≥1 day/month	10.7 (9.39)	10.2 (9.87)	13.8 (9.52)	10.8 (11.18)	8.6 (9.97)	11.5 (10.16)
Change from baseline, mean (SD)						
≥1 day/month	-7.8 (8.08)	-8.3 (7.64)	-4.5 (7.46)	-8.1 (9.90)	-9.6 (9.92)	-7.0 (9.39)
1–9 days/month	-1.5 (4.44)	-2.3 (4.34)	-1.0 (5.29)	-0.8 (6.63)	-2.6 (4.57)	-1.3 (4.83)
≥10 days/month	-8.7 (8.08)	-9.4 (7.62)	-5.1 (7.63)	-8.9 (9.88)	-11.1 (10.10)	-7.9 (9.64)
Percent change from baseline, mean (SD)						
≥1 day/month	-42.6 (39.98)	-47.0 (40.90)	-22.4 (52.02)	-40.7 (60.66)	-52.9 (48.97)	-34.7 (58.48)
1–9 days/month	-31.8 (67.95)	-47.3 (65.38)	-9.5 (10.52)	1.4 (132.84)	-45.0 (73.05)	-11.2 (108.44)
≥10 days/month	-44.1 (34.24)	-47.0 (34.73)	-24.8 (36.17)	-45.3 (44.91)	-54.5 (42.52)	-38.5 (44.63)

FIG. 46.

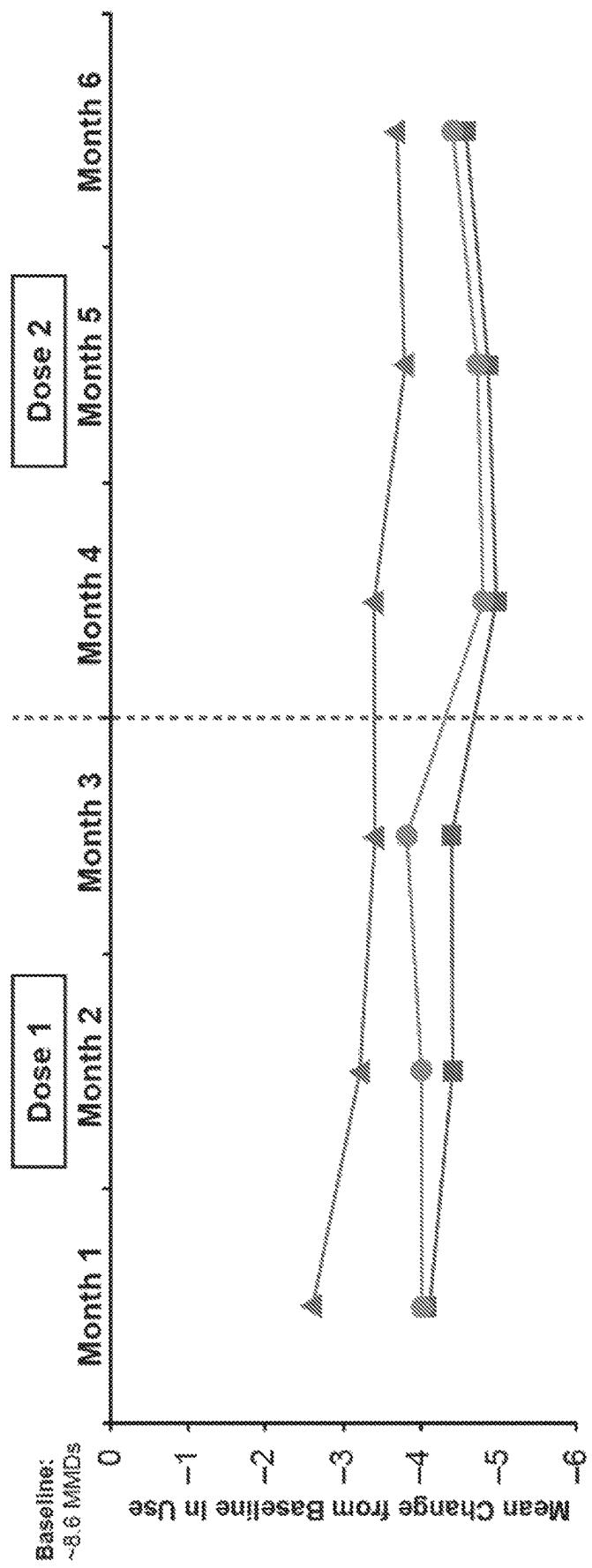


FIG. 47.

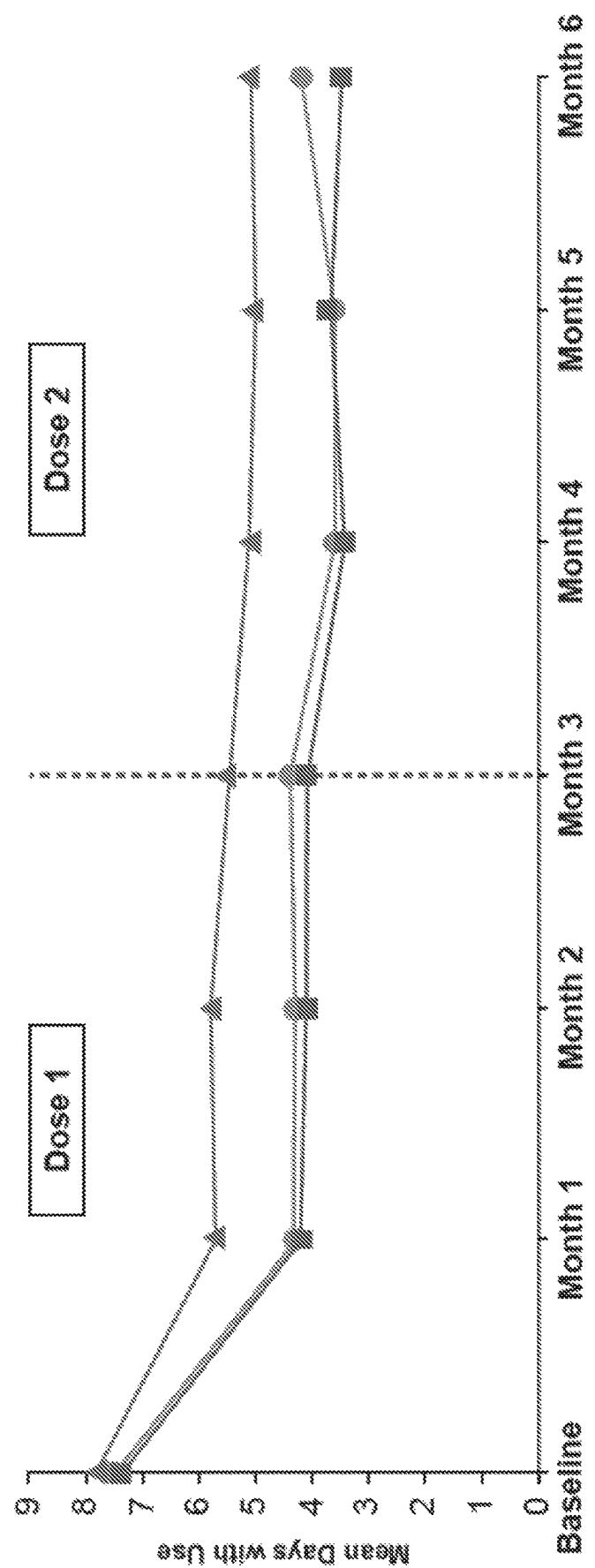


FIG. 48.

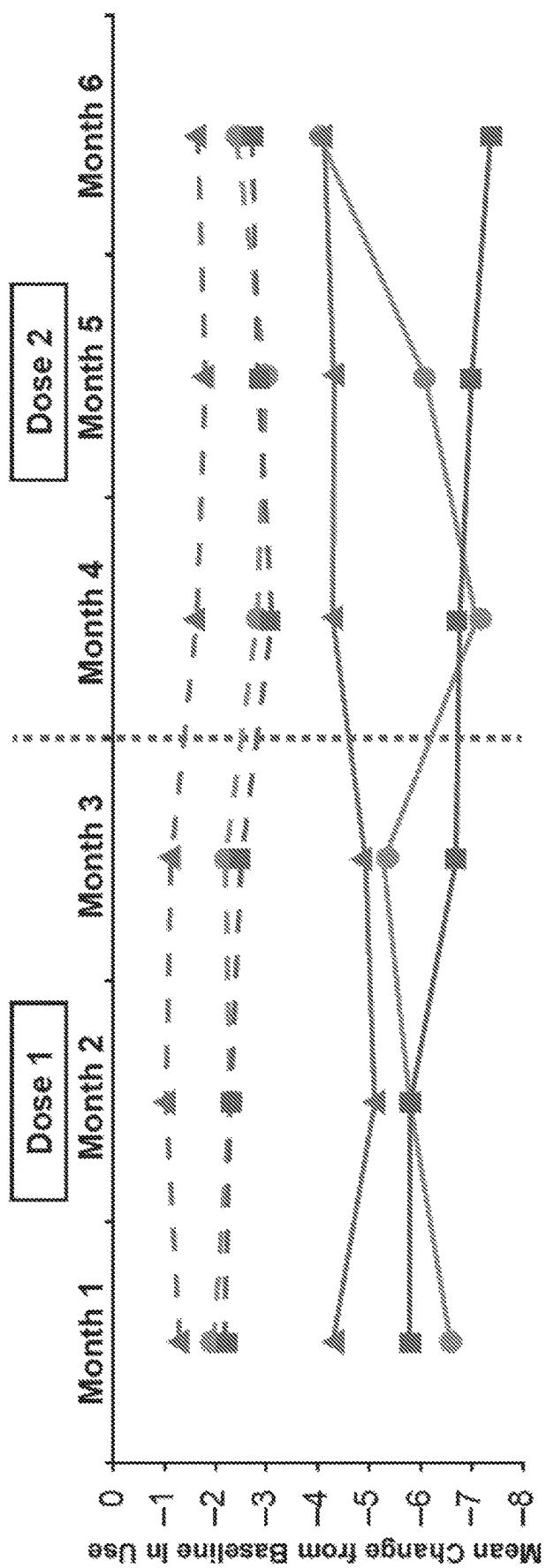


FIG. 49. Summary of Acute Medication Days by Subgroups of Episodic Migraine Patients with Baseline Acute Medication Use

	Month 1			Month 6		
	Ab6 100 mg	Ab6 400 mg	Placebo	Ab6 100 mg	Ab6 400 mg	Placebo
Baseline use						
1-9 days/month, n	117	111	108	117	111	108
>10 days/month, n	42	41	44	42	41	44
>1 day/month, mean (SD)	7.5 (4.97)	7.5 (4.58)	7.8 (4.98)	7.5 (4.97)	7.5 (4.58)	7.8 (4.98)
Post-baseline use, mean (SD)						
≥1 day/month	4.3 (3.99)	4.2 (4.45)	5.7 (5.04)	4.2 (5.87)	3.5 (3.92)	5.1 (5.19)
Change from baseline, mean (SD)						
≥1 day/month	-3.3 (4.14)	-3.2 (4.20)	-2.2 (4.68)	-2.8 (4.92)	-4.1 (4.60)	-2.3 (4.69)
1-9 days/month	-2.0 (2.91)	-2.2 (3.57)	-1.3 (3.10)	-2.4 (3.11)	-2.7 (3.83)	-1.6 (3.52)
>10 days/month	-6.6 (5.11)	-5.8 (4.66)	-4.3 (6.82)	-4.0 (8.60)	-7.4 (4.60)	-4.1 (6.60)
Percent change from baseline, mean (SD)						
≥1 day/month	-36.9 (63.96)	-39.4 (77.71)	-22.4 (60.27)	-45.4 (62.28)	-50.9 (59.88)	-22.5 (95.61)
1-9 days/month	-33.9 (72.22)	-37.0 (88.45)	-19.7 (64.62)	-50.1 (59.65)	-48.2 (68.26)	-18.2 (107.55)
>10 days/month	-45.1 (30.26)	-45.9 (34.95)	-29.1 (47.94)	-29.2 (69.14)	-57.2 (32.59)	-33.9 (52.53)

**ACUTE TREATMENT AND RAPID
TREATMENT OF HEADACHE USING
ANTI-CGRP ANTIBODIES**

RELATED APPLICATIONS

This application is a divisional of U.S. patent application Ser. No. 16/736,925, filed Jan. 8, 2020, which claims priority to Provisional Appl. No. 62/872,989, filed Jul. 11, 2019, Provisional Appl. No. 62/842,162, filed May 2, 2019, and Provisional Appl. No. 62/789,828, filed Jan. 8, 2019, the disclosures of each of which are hereby incorporated by reference in their entireties,

**REFERENCE TO AN ELECTRONIC SEQUENCE
LISTING**

The contents of the electronic sequence listing (1143257.008602.xml; Size: 771,649 bytes; and Date of Creation: Feb. 22, 2023) is herein incorporated by reference in its entirety.

BACKGROUND

Field

This invention pertains to methods of acute treatment of headache disorders, such as migraine, using antibodies and fragments thereof (including Fab fragments) that specifically bind to human Calcitonin Gene Related Peptide (hereinafter "CGRP"). The invention also pertains to rapid treatment of headache, e.g., chronic migraine, using antibodies and fragments thereof (including Fab fragments) that specifically bind to human Calcitonin Gene Related Peptide (hereinafter "CGRP").

Description of Related Art

Calcitonin Gene Related Peptide (CGRP) is produced as a multifunctional neuropeptide of 37 amino acids in length. Two forms of CGRP, the CGRP-alpha and CGRP-beta forms, exist in humans and have similar activities. CGRP-alpha and CGRP-beta differ by three amino acids in humans, and are derived from different genes. CGRP is released from numerous tissues such as trigeminal nerves, which when activated release neuropeptides within the meninges, mediating neurogenic inflammation that is characterized by vaso-dilation, vessel leakage, and mast-cell degradation. Durham, P. L., *New Eng. J. Med.*, 350 (11):1073-75 (2004). Biological effects of CGRP are mediated via the CGRP receptor (CGRP-R), which consists of a seven-transmembrane component, in conjunction with receptor-associated membrane protein (RAMP). CGRP-R further requires the activity of the receptor component protein (RCP), which is essential for an efficient coupling to adenylate cyclase through G proteins and the production of cAMP. Doods, H., *Curr. Op. Invest. Drugs*, 2(9):1261-68 (2001).

Migraines are neurovascular disorder affecting approximately 10% of the adult population in the U.S., and are typically accompanied by intense headaches. CGRP is believed to play a prominent role in the development of migraines. In fact several companies, i.e., Amgen, Eli Lilly, Teva and Alder Biopharmaceuticals (recently acquired by Lundbeck A/S) have developed anti-CGRP and anti-CGRP-R antibodies for use in treating or preventing migraine headaches. The present assignee has previously filed patent applications related to anti-CGRP antibodies and

uses thereof including published PCT Application WO/2012/162243 filed May 21, 2012 entitled "ANTI-CGRP COMPOSITIONS AND USE THEREOF", published PCT Application WO/2012/162257 filed May 21, 2012, entitled "USE OF ANTI-CGRP ANTIBODIES AND ANTIBODY FRAGMENTS TO PREVENT OR INHIBIT PHOTOPHOBIA OR LIGHT AVERSION IN SUBJECTS IN NEED THEREOF, ESPECIALLY MIGRAINE SUFFERERS" published PCT Application WO/2012/162253, filed May 21, 2012, entitled "USE OF ANTI-CGRP OR ANTI-CGRP-R ANTIBODIES OR ANTIBODY FRAGMENTS TO TREAT OR PREVENT CHRONIC AND ACUTE FORMS OF DIARRHEA" and published PCT Application WO/2015/003122, filed Jul. 3, 2014, entitled "REGULATION OF GLUCOSE METABOLISM USING ANTI-CGRP ANTIBODIES" all of which applications are incorporated by reference in their entirety.

BRIEF SUMMARY

The present disclosure provides methods of acute treatment of headache, comprising administering to a patient in need an effective amount of at least one anti-CGRP antibody or antibody fragment or an anti-CGRP-R antibody or anti-body fragment or one or more formulations comprising said antibody or antibody fragment as disclosed herein. Said antibody may be administered while said patient has a headache. Said antibody administration may be initiated within 1-6 hours of the onset of said headache. Said headache may comprise migraine, e.g., episodic migraine or chronic migraine. Said headache may comprise medication overuse headache. Said anti-CGRP antibody or antibody fragment optionally comprises any one of Ab1-Ab14 or a Fab fragment thereof, such as Ab6 or a Fab fragment thereof, e.g., having the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208; or having the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively. Said anti-CGRP antibody may comprise the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202. Said anti-CGRP antibody may comprise the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212. Said anti-CGRP antibody may comprise the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566. Said anti-CGRP antibody may comprise the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567. Said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, e.g., human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells. Said anti-CGRP antibody may comprise the antibody

expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions. Any of the aforementioned anti-CGRP antibodies or antibody fragments, preferably Ab6, may be optionally comprised in a formulation as disclosed herein, e.g., comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8. The administered dosage of said antibody may be between about 100 mg and about 300 mg, such as about 100 mg, about 300 mg, 100 mg, or 300 mg. The dosage may be administered by different means, e.g., intravenously, e.g., in a saline solution such as 0.9% sodium chloride in a suitable volume, such as 100 mL.

Said patient may exhibit less than 25 headache days per month, less than 20 headache days per month, less than 15 headache days per month, or less than 10 headache days per month. For example, said patient may exhibit less than 14 headache days, less than headache 13 days, less than headache 12 days, less than headache 11 days, less than 10 headache days, less than 9 headache days, less than 8 headache days, less than 7 headache days, or less than 6 headache days per month. Said patient may exhibit between 2-15 headache days, e.g., 3-14 headache days, 4-13 headache days, 5-12 headache days, 6-11 headache days, or 7-10 headache days/month.

Said patient may exhibit less than 10 migraines per month, such as between 1-9 migraines per month, such as between 2-8 migraines per month, between 3-7 migraine per month, between 4-6 migraine per month, or about 5 migraines per month. Said patient may exhibit fewer than 1 migraine per month on average, e.g., on average one migraine every 2 months, one every 3 months, one every 4 or 6 months, or intermediate values such as 2 every 3 months, etc. Said migraine may be diagnosed in accord with the ICHD-3 guidelines.

In exemplary embodiments, said headache may comprise medication overuse headache. Said medication overuse headache may be determined based on meeting the following criteria: (a) headache occurring on 15 or more days/month in a patient with a pre-existing headache disorder; and (b) overuse for more than 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache.

Said overuse may comprise use of an ergot alkaloid (e.g., ergotamine) on 10 or more days/month, use of a triptan on 10 or more days/month, use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic) on 15 or more days/month, use of one or more combination-analgesics (as further described below) on 10 or more days/month, use of one or more opioids on 10 or more days/month, or use of a combination of two or more drug classes (as further described below) on 10 or more days/month.

In the methods herein, said triptan may include, without limitation thereto, any one of or any combination of triptans such as sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, among others.

Said medication overuse headache may comprise ergotamine-overuse headache, triptan-overuse headache, non-

opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication.

Said non-opioid analgesic-overuse headache may comprise paracetamol (acetaminophen)-overuse headache, non-steroidal anti-inflammatory drug (NSAID)-overuse headache such as acetylsalicylic acid (aspirin)-overuse headache or ibuprofen-overuse headache, or another non-opioid analgesic-overuse headache.

Said ergotamine-overuse headache may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular use of an ergot alkaloid such as ergotamine on 10 or more days/month for more than 3 months.

In the methods herein, said ergot alkaloid may comprise ergotamine, nicergoline, methysergide, or dihydroergotamine, or may comprise an ergot derivative.

Said triptan-overuse headache may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular use of one or more triptans on 10 or more days/month for more than 3 months.

Said non-opioid analgesic-overuse headache may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular use of one or more non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), ibuprofen, another NSAID, or another non-opioid analgesic) on 15 or more days/month for more than 3 months.

In the methods herein, said NSAID may comprise any NSAID or combination thereof, including without limitation thereto, ibuprofen, naproxen, or indomethacin.

Said combination-analgesic-overuse headache may comprise headache occurring on 15 or more days/month developing as a consequence of regular use of one or more combination-analgesics on 10 or more days/month for more than 3 months. In the context of medication overuse headache, the term combination-analgesic refers to formulations combining drugs of two or more classes, each with analgesic effects (for example, paracetamol and codeine) or analgesics in combination with agents acting as adjuvants (for example, caffeine). Commonly overused combination-analgesics combine non-opioid analgesics with at least one opioid, barbiturate such as butalbital and/or caffeine. In exemplary embodiments, the combination-analgesic overuse-headache is due to the combination of acetaminophen, aspirin, and caffeine, e.g., EXCEDRIN® or EXCEDRIN MIGRAINE®. Other known combination analgesics comprise an analgesic in combination with at least one non-analgesic, e.g., with a vasoconstrictor drug such as pseudoephedrine for sinus-related preparations, antihistamine drug used to treat allergy sufferers, etc.

Said opioid-overuse headache may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular use of one or more opioids 10 or more days/month for more than 3 months.

Said medication-overuse headache attributed to multiple drug classes not individually overused may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a result of regular intake of any combination of ergotamine, triptans,

non-opioid analgesics and/or opioids on a total of at least 10 days/month for more than 3 months without overuse of any single drug or drug class alone.

In the methods herein, said opioid may be any one or any combination of opioid drugs, including without limitation thereto, oxycodone, tramadol, butorphanol, morphine, codeine, hydrocodone, thebaine, oripavine, mixed opium alkaloids such as papaveretum, diacetylmorphine, nicomorphine, dipropanoylemorphine, diacetyl-dihydromorphine, acetylpropionylmorphine, desomorphine, methyldesorphine, dibenzoylmorphine, ethylmorphine, heterocodeine, buprenorphine, etorphine, hydromorphone, oxymorphone, fentanyl, alphamethylfentanyl, alfentanil, sufentanil, remifentanil, carfentanyl, ohmfentanyl, pethidine (meperidine), ketobemidone, MPPP, allylprodine, prodine, PEPAP, promedol, diphenylpropylamine, propoxyphene, dextropropoxyphene, dextromoramide, bezitramide, piritramide, among others.

Said medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a result of regular intake of any combination of ergotamine, triptans, non-opioid analgesics and/or opioids on at least 10 days/month for more than 3 months, wherein the identity, quantity and/or pattern of use or overuse of these classes of drug is not reliably established.

Said medication-overuse headache attributed to other medication may comprise headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a result of regular intake of one or more medications other than those described above, taken for acute or symptomatic treatment of headache, on at least 10 days/month for more than 3 months.

The amount and duration of medication use may be determined utilizing known methods, such as the usage reported by the patient or a relative, a diary, medical records, drug purchase history, prescription fulfilment, biomarkers of medication use, incidence of medication toxicity, incidence of medication overdose, and/or other indicators of a patient's medication use.

The present disclosure provides methods of treating or preventing probable medication overuse headache, comprising administering to a patient in need an effective amount of an anti-CGRP antibody or anti-CGRP antibody fragment or one or more formulations comprising said anti-CGRP antibody or anti-CGRP antibody fragment as disclosed herein. Said anti-CGRP antibody optionally comprises any one of Ab1-Ab14, such as Ab6, e.g., having the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208; or having the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively. Said anti-CGRP antibody may comprise the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202. Said anti-CGRP antibody may comprise the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212. Said anti-CGRP antibody may comprise the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566. Said anti-CGRP antibody may

comprise the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567. Said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, e.g., human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells. Said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions. Any of the aforementioned anti-CGRP antibodies or antibody fragments, preferably Ab6, may be optionally comprised in a formulation as disclosed herein, e.g., comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8. The administered dosage of said antibody may be between about 100 mg and about 300 mg, such as about 100 mg, about 300 mg, 100 mg, or 300 mg. The dosage may be administered by different means, e.g., intravenously, e.g., in a saline solution such as 0.9% sodium chloride in a suitable volume, such as 100 mL. Probable medication overuse headache refers to criteria (a) and (b) not being entirely fulfilled, e.g., having at least 80% or at least 90% of the specified number of headache days and/or medication use days per month, and/or over a shorter time period such as at least 2 months, optionally in the absence of another ICHD-3 diagnosis.

Said medication-overuse headache (such as ergotamine-overuse headache, triptan-overuse headache, non-opioid analgesic-overuse headache, opioid-overuse headache, combination-analgesic-overuse headache, medication-overuse headache attributed to multiple drug classes not individually overused, medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes, or medication-overuse headache attributed to other medication) may be diagnosed according to the third edition of the International Classification of Headache Disorders (ICHD-3). See Headache Classification Committee of the International Headache Society (IHS), The International Classification of Headache Disorders, 3rd edition, Cephalgia. 55 2018 January; 38(1):1-211, which is hereby incorporated by reference in its entirety.

Herein, the criterion that a headache occurs "as a consequence of" over use of a medication or medications refers to the apparent association between the medication(s) overuse and the headache, e.g., that the medication(s) overuse and headache are present at the above-specified frequency such that causation may be presumed.

The present disclosure also provides methods of treating chronic migraine, comprising intravenously administering to a patient in need thereof a first dosage comprising between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody preferably com-

prises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566, wherein in the first 24 hours after administration of said first dosage the patient exhibits at least a 50% reduction in migraine prevalence.

In another aspect, the disclosure provides methods of treating chronic migraine, comprising intravenously administering to a patient in need thereof a first dosage comprising between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody preferably comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566, wherein on the first day following the day of administration the patient exhibits at least a 50% reduction in migraine prevalence.

In some exemplary embodiments the dosage, e.g., the first dosage, of said anti-CGRP antibody may be 100 mg.

In other exemplary embodiments the dosage, e.g., the first dosage, of said anti-CGRP antibody may be 300 mg.

The method may further comprise intravenously administering 100 mg of said anti-CGRP antibody every 10^{-14} weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

The method may further comprise intravenously administering 300 mg of said anti-CGRP antibody every 10^{-14} weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

The antibody may be provided or administered in a formulation as disclosed herein, e.g., comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8.

Prior to said first dosage, the patient may exhibit between about 10 and about 22 migraine days per month, such as between about 13 and about 19 migraine days per month, such as about 16 migraine days per month.

Prior to said first dosage, the patient may exhibit between about 14 and about 27 headache days per month, such as between about 17 and about 24 headache days per month, such as about 20 or about 21 headache days per month.

Said patient may have been diagnosed with migraine at least 10 years prior to said first dosage, such as at least 15 years prior to said first dosage, such as at least 18 or at least 19 years prior to said first dosage.

Said patient may have been diagnosed with chronic migraine at least 5 years prior to said first dosage, such as at least 8 years prior to said first dosage, such as at least 11 or at least 12 years prior to said first dosage.

The patient may have a headache when administered said first dosage.

The patient may have a migraine, such as a migraine with aura, when administered said first dosage.

Said patient may have a reduction in the number of migraine days by at least 50% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

Said patient may have a reduction in the number of migraine days by at least 75% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

Said patient may have a reduction in the number of migraine days by 100% in the one month period after being

administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

Said patient may have a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

Said patient may have a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

Said patient may have a reduction in the number of migraine days by 100% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

The method may further comprise administering, e.g., intravenously, a second dose of said anti-CGRP antibody to said patient within about 10^{-14} weeks, preferably 11-13 weeks, more preferably about 12 weeks or about 3 months, after said first dose.

Said first dose may comprise about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

Said patient may be a chronic migraine patient or episodic migraine patient at risk of developing medication overuse headache. Said patient may use acute headache medication on at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 day(s) per month. Said patient may use acute headache medication on at least 10 days per month. Optionally said acute medication use is determined over a baseline period of at least 28 days. Said acute medication use may be reported by the patient, a caregiver, or based on records. Said acute medication may comprise use of ergot alkaloids, triptans, non-opioid analgesics, acetaminophen, aspirin, NSAIDs, non-opioid analgesics, combination-analgesics, or opioids.

Prior to said administration, the patient may exhibit between about 15 and about 30 migraine days per month, such as between about 16 and about 28 migraine days per month, such as between about 17 and about 26 migraine days per month, such as about 16 migraine days per month.

Prior to said administration, the patient may exhibit between about 15 and about 27 headache days per month, such as between about 17 and about 24 headache days per month, such as about 20 or about 21 headache days per month.

Said patient may have been diagnosed with migraine at least 10 years prior to said administration, such as at least 15 years prior to said administration, such as at least 18 or at least 19 years prior to said administration.

Said patient may have been diagnosed with chronic migraine at least 5 years prior to said administration, such as at least 8 years prior to said administration, such as at least 11 or at least 12 years prior to said administration.

Said patient may have a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

Said patient may have a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

Said patient may have a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

Said patient may have a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

Said patient may have a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

Said patient may have a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

The method may further comprise administering, e.g., intravenously, a second dose of said anti-CGRP antibody to said patient within about 10^{-14} weeks, preferably 11-13 weeks, more preferably about 12 weeks or about 3 months, after said administration.

Said administration may comprise about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

Said anti-CGRP antibody may be aglycosylated or if glycosylated only may contain only mannose residues.

Said anti-CGRP antibody may consist of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566. Said anti-CGRP antibody may consist of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the variable light chain of SEQ ID NO: 222 and/or the variable heavy chain of SEQ ID NO: 202. In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the variable light chain encoded by SEQ ID NO: 232 and/or the variable heavy chain encoded by SEQ ID NO: 212.

In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the light chain of SEQ ID NO: 221 and/or the heavy chain of SEQ ID NO: 201 or SEQ ID NO: 566. In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the light chain encoded by SEQ ID NO: 231 and/or the heavy chain encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

In some embodiments, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the VL polypeptide of SEQ ID NO: 222 and the VH polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, e.g., human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells.

In some embodiments, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy

chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions.

In some embodiments any of the aforementioned anti-CGRP antibodies or antibody fragments may be comprised in a formulation as disclosed herein, e.g., comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8. The antibody or fragment may be administered by different means, e.g., intravenously, e.g., in a saline solution such as 0.9% sodium chloride in a suitable volume, such as 100 mL.

In some embodiments, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody or antibody fragment is administered, e.g., intravenously.

In other embodiments, about 100 mg of said anti-CGRP antibody or antibody fragment is administered.

In other embodiments, about 300 mg of said anti-CGRP antibody or antibody fragment is administered, e.g., intravenously.

In exemplary embodiments, the anti-human CGRP antibody or antibody fragment is administered, e.g., intravenously at a frequency which is at most every 10^{-14} weeks, preferably every 11-13 weeks, more preferably every 3 months or every 12 weeks, wherein the antibody dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 10^{-14} weeks, preferably every 11-13 weeks, more preferably every 3 months or every 12 weeks. The phrase "the antibody dosage is administered in a single formulation or divided into different formulations" refers to the administration of the recited amount of antibody within a relatively short period of time, e.g., within a period of several hours, e.g., 1 to 8 hours, about one day, within about two days, or within about one week, which may be by the same or different routes (e.g., i.v., i.m., and/or s.c.), sites of administration. The term "different formulations" in this context refers to antibody dosages that are administered at different times and/or at different sites and/or different routes, irrespective of whether the dosages are the same or different with respect to the chemical composition of the pharmaceutical formulation in which each dosage is administered; for example, the concentration, excipients, carriers, pH, and the like may be the same or different between the different administered dosages.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 8 weeks or every 2 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 10^{-14} weeks, preferably every 11-13 weeks, more preferably every 12 weeks or every 3 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 16 weeks or every 4 months.

11

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 20 weeks or every 5 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 24 weeks or every 6 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 28 weeks or every 7 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 32 weeks or every 8 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 36 weeks or every 9 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 40 weeks or every 8 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 44 weeks or every 9 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 48 weeks or every 10 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 52 weeks or every 11 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 56 weeks or every 12 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 15-18 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 18-21 months.

In other exemplary embodiments, the anti-human CGRP antibody dosage or antibody fragment used in the afore-mentioned methods is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 2 years.

12

In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods is administered systemically.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment used in the afore-mentioned methods is administered by a mode of administration is selected from intravenous, intramuscular, intravenous, intrathecal, intracranial, topical, intranasal, and oral. In a preferred embodiment, the anti-human CGRP antibody or antibody fragment used in the afore-mentioned methods is administered intravenously.

In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods has an in vivo half-life of at least 10 days.

15 In other exemplary embodiments, the anti-human CGRP antibody has an in vivo half-life of at least 15 days.

In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods has an in vivo half-life of at least 20 days.

20 In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods has an in vivo half-life of at least 20-30 days.

In other exemplary embodiments, the anti-human CGRP antibody is administered at a dosage of between about 100 mg and about 300 mg has an in vivo half-life of $\pm 20\%$ of at least about (284 \pm 44 hours).

In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods binds to human α - and β -CGRP.

25 In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 30 days after antibody administration.

In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 60 days after antibody administration.

30 In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in inhibition of vasodilation induced by topically applied capsaicin at least 90 days after antibody administration.

In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 120 days after antibody administration.

35 In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 150 days after antibody administration.

40 In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin at least 180 days after antibody administration.

In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of vasodilation induced by topically applied capsaicin more than 180 days after antibody administration.

45 In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in sustained pharmacodynamic (PK) activity, within 5% of the maximal response (Imax) (as compared to lower antibody doses).

In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in sustained pharmacodynamic (PK) activity which is maintained for at least 2-3 months after antibody administration, wherein PK analysis of the anti-human CGRP antibody is derived from plasma concentrations.

13

In other exemplary embodiments, the administered anti-human CGRP antibody dosage is between about 100 mg and about 300 mg or more which is administered no more frequently than every 2 months.

The present invention is additionally directed to the use of specific antibodies and fragments thereof having binding specificity for CGRP, in particular antibodies having desired epitopic specificity, high affinity or avidity and/or functional properties. A preferred embodiment of the invention is directed to usage of chimeric or humanized antibodies and fragments thereof (including Fab fragments) capable of binding to CGRP and/or inhibiting the biological activities mediated by the binding of CGRP to the CGRP receptor ("CGRP-R") e.g., wherein such antibodies optionally are derived from recombinant cells engineered to express same, optionally yeast or mammalian cells, further optionally *Pichia pastoris* and CHO cells.

In another preferred embodiment of the invention, full length antibodies and Fab fragments thereof are contemplated that inhibit the CGRP-alpha-, CGRP-beta-, and rat CGRP-driven production of cAMP. In a further preferred embodiment of the invention, full length and Fab fragments thereof are contemplated that reduce vasodilation in a recipient following administration.

The invention also contemplates usage of conjugates of anti-CGRP antibodies and binding fragments thereof conjugated to one or more functional or detectable moieties. The invention also contemplates usage of chimeric or humanized anti-CGRP or anti-CGRP/CGRP-R complex antibodies and binding fragments thereof. In one embodiment, binding fragments include, but are not limited to, Fab, Fab', F(ab')₂, Fv, scFv fragments, SMIPs (small molecule immunopharmaceuticals), camelbodies, nanobodies, and IgNAR.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

FIGS. 1A-1F provide the polypeptide sequences of the full-length heavy chain for antibodies Ab1-Ab14 with their framework regions (FR), complementarity determining regions (CDRs), and constant region sequences delimited.

FIGS. 2A-2D provide the polypeptide sequences of the full-length light chain for antibodies Ab1-Ab14 with their framework regions (FR), complementarity determining regions (CDRs), and constant region sequences delimited.

FIGS. 3A-3P provide exemplary polynucleotide sequences encoding the full-length heavy chain for antibodies Ab1-Ab14 with their framework regions (FR), complementarity determining regions (CDRs), and constant region coding sequences delimited.

FIGS. 4A-4I provide exemplary polynucleotide sequences encoding the full-length light chain for antibodies Ab1-Ab14 with their framework regions (FR), complementarity determining regions (CDRs), and constant region coding sequences delimited.

FIG. 5 provides the polypeptide sequence coordinates within the full-length heavy chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

FIG. 6 provides the polypeptide sequence coordinates within the full-length heavy chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

FIG. 7 provides the polypeptide sequence coordinates within the full-length light chain polypeptide sequences of

14

antibodies Ab1-Ab14 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

FIG. 8 provides the polypeptide sequence coordinates within the full-length light chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

FIG. 9 provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length heavy chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

FIG. 10 provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length heavy chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

FIG. 11 provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length light chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

FIG. 12 provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length light chain polypeptide sequences of antibodies Ab1-Ab14 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

FIG. 13 shows the number of subjects in a human clinical trial described in Example 2 who were either treated with Ab6 (treatment group) or placebo groups who showed a 50, 75 or 100% reduction in migraines at each monitoring point throughout the period. The right bar in each group corresponds to patients receiving 1000 mg Ab6 and the left bar in each group corresponds to matched placebo controls. In each response rate group the patients receiving Ab6 had a significantly greater response rate than placebo-treated controls, with p values of 0.0155, 0.0034, and 0.0006 in each respective group as indicated. The administered antibody was produced in *P. pastoris* and consisted of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201.

FIG. 14 shows the median (\pm QR) % change from baseline in the number of migraine days per month in the placebo and Ab6-treated group over the 12 weeks post-treatment. (p=0.0078). The upper (red) line and lower (blue) line show results for placebo-treated controls and patients administered 1000 mg Ab6, respectively.

FIG. 15 shows the median (\pm QR) % change from baseline in the number of migraine episodes per month in the placebo and Ab6-treated group over the 12 weeks post-treatment. The upper (red) line and lower (blue) line show results for placebo-treated controls and patients administered 1000 mg Ab6, respectively.

FIG. 16 shows the median (\pm QR) % change from baseline in the number of migraine hours per month in the placebo and Ab6-treated group over the 12 weeks post-treatment. The upper (red) line and lower (blue) line show results for placebo-treated controls and patients administered 1000 mg Ab6, respectively.

FIG. 17 summarizes the screening of patients, allocation into the treatment and control groups, and loss of patients through follow-up.

FIG. 18 compares the HIT-6 responder analysis for the Ab6-treated and placebo groups at baseline, week 4 after treatment, week 8 after treatment and week 12 after treatment.

FIG. 19 shows the percentage of patients for whom the HIT-6 analysis indicated that the effect of headaches was only “some” or “little/none” at baseline and after Ab6 administration. At baseline most patients had either “substantial” or “severe” impact from migraines. At each subsequent time point, a significantly greater percentage of patients administered 1000 mg Ab6 had only “some” or “little/none” HIT-6 impact (left bar in each group, colored blue) as compared to placebo controls (right bar in each group, colored red).

FIG. 20 contains the pharmacokinetic (PK) profile for Ab6 administered intravenously at a single dosage of 1000 mg.

FIG. 21 contains plasma-free pharmacokinetic (PK) parameters N (number of patients), mean, and standard deviation (SD) for a single 1000 mg intravenous dosage of Ab6. The parameters shown in the table and the units are C_{max} ($\mu\text{g/mL}$), $AUC_{0-\infty}$ ($\text{mg}^*\text{hr/mL}$), half-life (days), V_z (L) and C_L (mL/hr).

FIG. 22 shows the change (mean+SEM) change from baseline in migraine days per month for Ab6 (1000 mg i.v.) versus placebo as a single dose for the study described in Example 2.

FIG. 23 shows the average migraine days (+/-SD) over time for the full analysis population for the study described in Example 2. Normalization was applied to visit intervals where eDiaries were completed for 21-27 days by multiplying the observed frequency by the inverse of the completion rate.

FIG. 24 shows the distribution of migraine days actual and change for the Ab6 treatment group during weeks 1-4 for the study described in Example 2.

FIG. 25 shows the distribution of migraine days actual and change for the placebo group during weeks 1-4 for the study described in Example 2.

FIG. 26 shows the distribution of migraine days actual and change for the Ab6 treatment group during weeks 5-8 for the study described in Example 2.

FIG. 27 shows the distribution of migraine days actual and change for the placebo group during weeks 5-8 for the study described in Example 2.

FIG. 28 shows the distribution of migraine days actual and change for the Ab6 treatment group during weeks 9-12 for the study described in Example 2.

FIG. 29 shows the distribution of migraine days actual and change for the placebo group during weeks 9-12 for the study described in Example 2.

FIG. 30 shows the 50% responder rate for the Ab6 and placebo treatment groups for the study described in Example 2. Subjects with $\geq 50\%$ reduction in migraine frequency were considered to be a 50% responder. Normalization was applied to visit intervals where eDiary was completed for 21-27 days by multiplying the observed frequency by the inverse of the completion rate.

FIG. 31 shows the 75% responder rate for the Ab6 and placebo treatment groups for the study described in Example 2. Subjects with $\geq 75\%$ reduction in migraine frequency were considered to be a 75% responder. Normalization was applied as described with FIG. 30.

FIG. 32 shows the 100% responder rate for the Ab6 and placebo treatment group for the study described in Example 2. Subjects with 100% reduction in migraine frequency were

considered to be a 100% responder. Normalization was applied as described with FIG. 30.

FIG. 33 shows the mean migraine severity over time for the full analysis population for the study described in Example 2. On the scale used, a mean migraine score of 3 represents “moderate pain.”

FIG. 34 summarizes the change from baseline in measured attributes for the placebo and treatment groups in the study described in Example 2.

FIG. 35 shows the percentages of patients with migraine in the 300 mg, 100 mg, and placebo treatment groups at days 1, 7, 14, 21, and 28 in the clinical trial described in Example 3. The uppermost line shows results for placebo, the lowest line shows results for the 300 mg dosage, and the middle line shows results for the 100 mg dosage.

FIG. 36 show the percentage of patients in the 300 mg and 100 mg treatment groups achieving a 50% reduction in migraine days in month 1, over months 1-3 (after the 1st infusion), and over months 4-5 (after the 2nd infusion) in the clinical trial described in Example 3. In each graph, the data bars, from left to right, show results for the 100 mg, 300 mg, and placebo groups. Statistical significance is as shown. ++ indicates a statistically significant difference from placebo; + indicates a statistically significant difference from placebo (unadjusted); and § indicates a statistically significant difference from placebo (post hoc).

FIG. 37 show the percentage of patients in the 300 mg and 100 mg treatment groups achieving a 75% reduction in migraine days in month 1, over months 1-3 (after the 1st infusion), and over months 4-5 (after the 2nd infusion) in the clinical trial described in Example 3. Data order and statistical significance labels are as indicated with FIG. 36.

FIG. 38 show the percentage of patients in the 300 mg and 100 mg treatment groups achieving a 100% reduction in migraine days in month 1, over months 1-3 (after the 1st infusion), and over months 4-5 (after the 2nd infusion) in the clinical trial described in Example 3. Data order and statistical significance labels are as indicated with FIG. 36.

FIG. 39 summarizes the characteristics of patients in each treatment group in the clinical trial described in Example 3.

* According to the American Academy of Neurology/American Headache Society guidelines for migraine preventative treatment (medications identified by clinical review of coded medical data); SD, standard deviation; BMI, body mass index.

FIG. 40. Difference from placebo in change from baseline in mean migraine days (MMD) over months 1-3 by baseline subgroup for a human clinical trial of chronic migraine patients. In the graph, the data point refers to the mean value and the line shows the 95% confidence interval (CI) of the change from placebo for the 100 mg (upper line) or 300 mg (lower line) treatment group, for each subgroup as labeled at the far left.

FIG. 41. Difference from placebo in change from baseline in mean migraine days (MMD) over months 1-3 by baseline subgroup for a human clinical trial of episodic migraine patients. The graph is labeled as in FIG. 40.

FIG. 42. Change from baseline in mean migraine days (MMDs) across 2 dose intervals in chronic migraine patients with at least 1 day of acute medication use per month at baseline. Triangle: placebo (n=366). Circle: 100 mg Ab6 per dose (n=356). Square: 300 mg Ab6 per dose (n=350).

FIG. 43. Mean days with acute medication use in chronic migraine patients with at least one day per month of acute medication use at baseline. Triangle: placebo (n=366). Circle: 100 mg Ab6 per dose (n=356). Square: 300 mg Ab6 per dose (n=350).

FIG. 44. Change from baseline in acute medication use by subgroups of chronic migraine patients with differing baseline days of acute medication use. Solid lines: patients with 10 or more days of acute medication use per month at baseline. Dashed lines: patients with at least 1 and less than 10 days of acute medication use per month at baseline. Triangle: placebo. Circle: 100 mg Ab6 per dose. Square: 300 mg Ab6 per dose.

FIG. 45. Summary of Acute Medication Days by Subgroups of Chronic Migraine Patients with Baseline Acute Medication Use.

FIG. 46. Change from baseline in mean migraine days (MMDs) across 2 dose intervals in episodic migraine patients with at least 1 day of acute medication use per month at baseline. Triangle: placebo (n=222). Circle: 100 mg Ab6 per dose (n=221). Square: 300 mg Ab6 per dose (n=222).

FIG. 47. Mean days with acute medication use in episodic migraine patients with at least one day per month of acute medication use at baseline. Triangle: placebo (n=222). Circle: 100 mg Ab6 per dose (n=221). Square: 300 mg Ab6 per dose (n=222).

FIG. 48. Change from baseline in acute medication use by subgroups of episodic migraine patients with differing baseline days of acute medication use. Solid lines: patients with 10 or more days of acute medication use per month at baseline. Dashed lines: patients with at least 1 and less than 10 days of acute medication use per month at baseline. Triangle: placebo. Circle: 100 mg Ab6 per dose. Square: 300 mg Ab6 per dose.

FIG. 49. Summary of Acute Medication Days by Subgroups of Episodic Migraine Patients with Baseline Acute Medication Use.

DETAILED DESCRIPTION

Use of anti-CGRP antibodies for treatment of medication overuse headache is described herein. Additionally, anti-CGRP antibodies are demonstrated herein to be effective for treatment of chronic migraine. The treatment was shown to have a very rapid onset of efficacy, with relief from migraine observed on the first day following administration.

Definitions

It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, and reagents described, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. As used herein the singular forms “a”, “and”, and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a cell” includes a plurality of such cells and reference to “the protein” includes reference to one or more proteins and equivalents thereof known to those skilled in the art, and so forth. All technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise.

As used herein, the term “medication overuse headache” refers to a headache that meets the criteria for that condition specified in ICHD-3 (Headache Classification Committee of the International Headache Society (IHS), The International Classification of Headache Disorders, 3rd edition, Cephalgia. 2018 January; 38(1):1-211). The term includes subtypes of medication overuse headache, as defined in the

ICHD-3, such as triptan-overuse headache, non-opioid analgesic overuse headache, opioid overuse headache, etc.

As used herein, the term “reduction in migraine prevalence” refers to a reduction (e.g., a stated percentage reduction, such as 50%) in the likelihood of a patient having a migraine in the stated period, such as the 18 hour, 20 hour, 24 hour, 28 hour, or 30 hour period, preferably the 24 hour period, after a first dosage of an antibody, or on the first day following the day of antibody administration (i.e., on the first full day following the day on which the antibody administration is completed). It is to be understood that a given patient may or may not have a migraine during that period, as the reduction in likelihood may be observable over a large number of patients irrespective of the outcome for an individual patient.

As used herein, the term “chronic migraine” refers to a condition wherein a patient exhibits, on average, at least 15 migraine days and/or headache per month. The term “episodic migraine” refers to a condition wherein a patient exhibits, on average, less than 15 headache and/or migraine days per month.

As used herein, the term “diagnosed with chronic migraine” refers to a patient meeting the clinical criteria for chronic migraine, whether or not a formal diagnosis of that patient was performed.

As used herein, the term “intravenously administering” refers to a mode of administration wherein a substance, e.g., an antibody, is introduced directly into the circulation of that patient, most typically into the venous circulation. The substance may be introduced in a carrier fluid, such as an aqueous solution, e.g., normal saline. The substance may be administered in a single formulation or in multiple formulations, as long as the administration is completed over a short period of time (e.g., within 1 day, preferably within 12 hours, more preferably within 6 hours, and most preferably within 1-2 hours).

As used herein, the term “the baseline number of migraine days” refers to the number of migraine days exhibited by a patient in a specified time period, e.g., prior to treatment. For example, the baseline number of migraine days may be determined over a period of one month, or longer, e.g., by recording each day whether or not a migraine occurred.

As used herein, the term “migraine days per month” refers to the number of days per month on which a patient has a migraine, i.e., at any time during that day, the patient has symptoms that meet the clinical definition of migraine. The number of migraine days per month may be determined by recording each day whether or not a migraine occurred.

As used herein, the term “headache days per month” refers to the number of days per month on which a patient has a headache, i.e., at any time during that day, the patient has symptoms that meet the clinical definition of a headache. The number of headache days per month may be determined by recording each day whether or not a headache occurred.

Calcitonin Gene Related Peptide (CGRP): As used herein, CGRP encompasses not only the following *Homo sapiens* CGRP-alpha and *Homo sapiens* CGRP-beta amino acid sequences available from American Peptides (Sunnyvale CA) and Bachem (Torrance, CA):

CGRP-alpha:	ACDTATCVTHR-LAGLLSRSGGVVKNNFVPTNVGSKAF-NH ₂ (SEQ ID NO: 561), wherein the terminal phenylalanine is amidated;
CGRP-beta:	ACNTATCVTHR-LAGLLSRSGGMVKSNFVPTNVGSKAF-NH ₂ (SEQ ID NO: 562), wherein the terminal phenylalanine is amidated; but also any membrane-bound forms of these

CGRP amino acid sequences, as well as mutants (mutations), splice variants, isoforms, orthologs, homologues and variants of this sequence.

Expression Vector: These DNA vectors contain elements that facilitate manipulation for the expression of a foreign protein within the target host cell, e.g., a yeast or mammalian cell such as *Pichia pastoris* or CHO cells. Conveniently, manipulation of sequences and production of DNA for transformation is first performed in a bacterial host, e.g. *E. coli*, and usually vectors will include sequences to facilitate such manipulations, including a bacterial origin of replication and appropriate bacterial selection marker. Selection markers encode proteins necessary for the survival or growth of transformed host cells grown in a selective culture medium. Host cells not transformed with the vector containing the selection gene will not survive in the culture medium. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media. Exemplary vectors and methods for transformation of yeast are described, for example, in Burke, D., Dawson, D., & Steams, T. (2000). Methods in yeast genetics: a Cold Spring Harbor Laboratory course manual. Plainview, N.Y.: Cold Spring Harbor Laboratory Press.

Expression vectors for use in yeast or mammalian cells will generally further include yeast or mammalian specific sequences, including a selectable auxotrophic or drug marker for identifying transformed yeast strains or transformed mammalian cells. A drug marker may further be used to amplify copy number of the vector in the host cell.

The polypeptide coding sequence of interest is operably linked to transcriptional and translational regulatory sequences that provide for expression of the polypeptide in host cells, e.g., *Pichia pastoris* or CHO cells. These vector components may include, but are not limited to, one or more of the following: an enhancer element, a promoter, and a transcription termination sequence. Sequences for the secretion of the polypeptide may also be included, e.g. a signal sequence, and the like. A yeast or mammalian origin of replication is optional, as expression vectors are often integrated into the host cell genome. In one embodiment of the invention, the polypeptide of interest is operably linked, or fused, to sequences providing for optimized secretion of the polypeptide from yeast diploid cells.

Nucleic acids are “operably linked” when placed into a functional relationship with another nucleic acid sequence. For example, DNA for a signal sequence is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. Generally, “operably linked” means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites or alternatively via a PCR/recombination method familiar to those skilled in the art (Gateway® Technology; Invitrogen, Carlsbad California). If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

Promoters are untranslated sequences located upstream (5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control the transcription and

translation of particular nucleic acid sequences to which they are operably linked. Such promoters fall into several classes: inducible, constitutive, and repressible promoters (that increase levels of transcription in response to absence of a repressor). Inducible promoters may initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, e.g., the presence or absence of a nutrient or a change in temperature.

The promoter fragment may also serve as the site for homologous recombination and integration of the expression vector into the same site in the host genome; alternatively a selectable marker is used as the site for homologous recombination. Examples of suitable promoters from *Pichia* include the AOX1 and promoter (Cregg et al. (1989) *Mol. Cell. Biol.* 9:1316-1323); ICL1 promoter (Menendez et al. (2003) *Yeast* 20(13):1097-108); glyceraldehyde-3-phosphate dehydrogenase promoter (GAP) (Waterham et al. (1997) *Gene* 186(1):37-44); and FLD1 promoter (Shen et al. (1998) *Gene* 216(1):93-102). The GAP promoter is a strong constitutive promoter and the AOX and FLD1 promoters are inducible.

Other yeast promoters include ADH1, alcohol dehydrogenase II, GAL4, PHO3, PHO5, Pyk, and chimeric promoters derived therefrom. Additionally, non-yeast promoters may be used in the invention such as mammalian, insect, plant, reptile, amphibian, viral, and avian promoters. Most typically the promoter will comprise a mammalian promoter (potentially endogenous to the expressed genes) or will comprise a yeast or viral promoter that provides for efficient transcription in yeast systems.

Examples of mammalian promoters include cytomegalovirus (CMV) derived promoters, chicken 3-actin (CBM) derived promoters, adenomatous polyposis coli (APC) derived promoters, leucine-rich repeat containing G protein-coupled receptor 5 (LGR5) promoters, CAG promoter, Beta actin promoter, elongation factor-1 (EF1) promoter, early growth response 1 (EGR-1) promoter, eukaryotic initiation factor 4A (EIF4A1) promoter, simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, as well as human gene promoters such as, but not limited to, the actin promoter, the myosin promoter, the hemoglobin promoter, and the creatine kinase promoter, among others. Combinations of two or more of the foregoing promoters may also be used. Further, inducible promoters may be used. The use of an inducible promoter provides a molecular switch capable of turning on expression of the polynucleotide sequence which it is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Examples of inducible promoters include, but are not limited to a metallothionein promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

The polypeptides of interest may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, e.g. a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the polypeptide coding sequence that is inserted into the vector. The heterologous signal sequence selected preferably is one that is recognized and processed through one of the standard pathways available within the host cell. The *S. cerevisiae* alpha factor pre-pro signal has proven effective in the secretion of a variety of recombinant proteins from *P.*

pastoris. Other yeast signal sequences include the alpha mating factor signal sequence, the invertase signal sequence, and signal sequences derived from other secreted yeast polypeptides. Additionally, these signal peptide sequences may be engineered to provide for enhanced secretion in diploid yeast expression systems. Secretion signals for use in mammalian as well as yeast cells include mammalian signal sequences, which may be heterologous to the protein being secreted, or may be a native sequence for the protein being secreted. Signal sequences include pre-peptide sequences, and in some instances may include propeptide sequences. Many such signal sequences are known in the art, including the signal sequences found on immunoglobulin chains, e.g., K28 preprotoxin sequence, PHA-E, FACE, human MCP-1, human serum albumin signal sequences, human Ig heavy chain, human Ig light chain, and the like. For example, see Hashimoto et. al. *Protein Eng* 11(2) 75 (1998); and Kobayashi et. al. *Therapeutic Apheresis* 2(4) 257 (1998).

Transcription may be increased by inserting a transcriptional activator sequence into the vector. These activators are cis-acting elements of DNA, usually about from 10 to 300 bp, which act on a promoter to increase its transcription. Transcriptional enhancers are relatively orientation and position independent, having been found 5' and 3' to the transcription unit, within an intron, as well as within the coding sequence itself. The enhancer may be spliced into the expression vector at a position 5' or 3' to the coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells may also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from 3' to the translation termination codon, in untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA.

Construction of suitable vectors containing one or more of the above-listed components employs standard ligation techniques or PCR/recombination methods. Isolated plasmids or DNA fragments are cleaved, tailored, and re-ligated in the form desired to generate the plasmids required or via recombination methods. For analysis to confirm correct sequences in plasmids constructed, the ligation mixtures are used to transform host cells, and successful transformants selected by antibiotic resistance (e.g. ampicillin or Zeocin) where appropriate. Plasmids from the transformants are prepared, analyzed by restriction endonuclease digestion and/or sequenced.

As an alternative to restriction and ligation of fragments, recombination methods based on att sites and recombination enzymes may be used to insert DNA sequences into a vector. Such methods are described, for example, by Landy (1989) *Ann. Rev. Biochem.* 58:913-949; and are known to those of skill in the art. Such methods utilize intermolecular DNA recombination that is mediated by a mixture of lambda and *E. coli*-encoded recombination proteins. Recombination occurs between specific attachment (att) sites on the interacting DNA molecules. For a description of att sites see Weisberg and Landy (1983) Site-Specific Recombination in Phage Lambda, in *Lambda II*, Weisberg, ed. (Cold Spring Harbor, NY: Cold Spring Harbor Press), pp. 211-250. The DNA segments flanking the recombination sites are switched, such that after recombination, the att sites are

hybrid sequences comprised of sequences donated by each parental vector. The recombination can occur between DNAs of any topology.

Att sites may be introduced into a sequence of interest by ligating the sequence of interest into an appropriate vector; generating a PCR product containing att B sites through the use of specific primers; generating a cDNA library cloned into an appropriate vector containing att sites; and the like.

Folding, as used herein, refers to the three-dimensional structure of polypeptides and proteins, where interactions between amino acid residues act to stabilize the structure. Proper folding is typically the arrangement of a polypeptide that results in optimal biological activity, and in the case of antibodies can conveniently be monitored by assays for activity, e.g. antigen binding.

The expression host may be further modified by the introduction of sequences encoding one or more enzymes that enhance folding and disulfide bond formation, i.e. foldases, chaperonins, etc. Such sequences may be constitutively or inducibly expressed in the yeast host cell, using vectors, markers, etc. as known in the art. Preferably the sequences, including transcriptional regulatory elements sufficient for the desired pattern of expression, are stably integrated in the yeast genome through a targeted methodology.

For example, the eukaryotic PDI is not only an efficient catalyst of protein cysteine oxidation and disulfide bond isomerization, but also exhibits chaperone activity. Co-expression of PDI can facilitate the production of active proteins having multiple disulfide bonds. Also of interest is the expression of BIP (immunoglobulin heavy chain binding protein); cyclophilin; and the like. In one embodiment of the invention, each of the haploid parental strains expresses a distinct folding enzyme, e.g. one strain may express BIP, and the other strain may express PDI or combinations thereof.

The terms "desired protein" or "desired antibody" are used interchangeably and refer generally to a parent antibody specific to a target, i.e., CGRP or a chimeric or humanized antibody or a binding portion thereof derived therefrom as described herein. The term "antibody" is intended to include any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where one or more non-covalent binding interactions stabilize the complex between the molecular structure and the epitope. The archetypal antibody molecule is the immunoglobulin, and all types of immunoglobulins, IgG, IgM, IgA, IgE, IgD, etc., from all sources, e.g. human, rodent, rabbit, cow, sheep, pig, dog, other mammals, chicken, other avians, etc., are considered to be "antibodies." A preferred source for producing antibodies useful as starting material according to the invention is rabbits. Numerous antibody coding sequences have been described; and others may be raised by methods well-known in the art. Examples thereof include chimeric antibodies, human antibodies and other non-human mammalian antibodies, humanized antibodies, single chain antibodies (such as scFvs), camelbodies, nanobodies, IgNAR (single-chain antibodies derived from sharks), small-modular immuno-pharmaceuticals (SMIPs), and antibody fragments such as Fabs, Fab', F(ab')₂ and the like. See Streitsov V A, et al., Structure of a shark IgNAR antibody variable domain and modeling of an early-developmental isotype, *Protein Sci.* 2005 November; 14(11):2901-9. Epub 2005 Sep. 30; Greenberg A S, et al., A new antigen receptor gene family that undergoes rearrangement and extensive somatic diversification in sharks, *Nature*. 1995 Mar. 9; 374(6518):168-73; Nuttall S D, et al., Isolation of the new antigen receptor from

wobbegong sharks, and use as a scaffold for the display of protein loop libraries, *Mol Immunol.* 2001 August; 38(4): 313-26; Hamers-Casterman C, et al., Naturally occurring antibodies devoid of light chains, *Nature.* 1993 Jun 3; 363(6428):446-8; Gill D S, et al., Biopharmaceutical drug discovery using novel protein scaffolds, *Curr Opin Biotechnol.* 2006 December; 17(6):653-8. *Epib.* 2006 Oct. 19.

For example, antibodies or antigen binding fragments may be produced by genetic engineering. In this technique, as with other methods, antibody-producing cells are sensitized to the desired antigen or immunogen. The messenger RNA isolated from antibody producing cells is used as a template to make cDNA using PCR amplification. A library of vectors, each containing one heavy chain gene and one light chain gene retaining the initial antigen specificity, is produced by insertion of appropriate sections of the amplified immunoglobulin cDNA into the expression vectors. A combinatorial library is constructed by combining the heavy chain gene library with the light chain gene library. This results in a library of clones which co-express a heavy and light chain (resembling the Fab fragment or antigen binding fragment of an antibody molecule). The vectors that carry these genes are co-transfected into a host cell. When antibody gene synthesis is induced in the transfected host, the heavy and light chain proteins self-assemble to produce active antibodies that can be detected by screening with the antigen or immunogen.

Antibody coding sequences of interest include those encoded by native sequences, as well as nucleic acids that, by virtue of the degeneracy of the genetic code, are not identical in sequence to the disclosed nucleic acids, and variants thereof. Variant polypeptides can include amino acid (aa) substitutions, additions or deletions. The amino acid substitutions can be conservative amino acid substitutions or substitutions to eliminate non-essential amino acids, such as to alter a glycosylation site, or to minimize misfolding by substitution or deletion of one or more cysteine residues that are not necessary for function. Variants can be designed so as to retain or have enhanced biological activity of a particular region of the protein (e.g., a functional domain, catalytic amino acid residues, etc.). Variants also include fragments of the polypeptides disclosed herein, particularly biologically active fragments and/or fragments corresponding to functional domains. Techniques for in vitro mutagenesis of cloned genes are known. Also included in the subject invention are polypeptides that have been modified using ordinary molecular biological techniques so as to improve their resistance to proteolytic degradation or to optimize solubility properties or to render them more suitable as a therapeutic agent.

Chimeric antibodies may be made by recombinant means by combining the variable light and heavy chain regions (V_L and V_H), obtained from antibody producing cells of one species with the constant light and heavy chain regions from another. Typically chimeric antibodies utilize rodent or rabbit variable regions and human constant regions, in order to produce an antibody with predominantly human domains. The production of such chimeric antibodies is well known in the art, and may be achieved by standard means (as described, e.g., in U.S. Pat. No. 5,624,659, incorporated herein by reference in its entirety). It is further contemplated that the human constant regions of chimeric antibodies of the invention may be selected from IgG1, IgG2, IgG3, and IgG4 constant regions.

Humanized antibodies are engineered to contain even more human-like immunoglobulin domains, and incorporate only the complementarity-determining regions of the ani-

mal-derived antibody. This is accomplished by carefully examining the sequence of the hyper-variable loops of the variable regions of the monoclonal antibody, and fitting them to the structure of the human antibody chains. 5 Although facially complex, the process is straightforward in practice. See, e.g., U.S. Pat. No. 6,187,287, incorporated fully herein by reference.

In addition to entire immunoglobulins (or their recombinant counterparts), immunoglobulin fragments comprising 10 the epitope binding site (e.g., Fab', F(ab')₂, or other fragments) may be synthesized. "Fragment," or minimal immunoglobulins may be designed utilizing recombinant immunoglobulin techniques. For instance "Fv" immunoglobulins for use in the present invention may be produced by synthesizing a fused variable light chain region and a variable 15 heavy chain region. Combinations of antibodies are also of interest, e.g. diabodies, which comprise two distinct Fv specificities. In another embodiment of the invention, SMIPs (small molecule immunopharmaceuticals), camelbodies, 20 nanobodies, and IgNAR are encompassed by immunoglobulin fragments.

Immunoglobulins and fragments thereof may be modified post-translationally, e.g. to add effector moieties such as 25 chemical linkers, detectable moieties, such as fluorescent dyes, enzymes, toxins, substrates, bioluminescent materials, radioactive materials, chemiluminescent moieties and the like, or specific binding moieties, such as streptavidin, avidin, or biotin, and the like may be utilized in the methods and compositions of the present invention. Examples of 30 additional effector molecules are provided infra.

A polynucleotide sequence "corresponds" to a polypeptide sequence if translation of the polynucleotide sequence in accordance with the genetic code yields the polypeptide sequence (i.e., the polynucleotide sequence "encodes" the 35 polypeptide sequence), one polynucleotide sequence "corresponds" to another polynucleotide sequence if the two sequences encode the same polypeptide sequence.

A "heterologous" region or domain of a DNA construct is 40 an identifiable segment of DNA within a larger DNA molecule that is not found in association with the larger molecule in nature. Thus, when the heterologous region encodes a mammalian gene, the gene will usually be flanked by DNA that does not flank the mammalian genomic DNA in the genome of the source organism. Another example of a 45 heterologous region is a construct where the coding sequence itself is not found in nature (e.g., a cDNA where the genomic coding sequence contains introns, or synthetic sequences having codons different than the native gene). Allelic variations or naturally-occurring mutational events 50 do not give rise to a heterologous region of DNA as defined herein.

A "coding sequence" is an in-frame sequence of codons that (in view of the genetic code) correspond to or encode a 55 protein or peptide sequence. Two coding sequences correspond to each other if the sequences or their complementary sequences encode the same amino acid sequences. A coding sequence in association with appropriate regulatory sequences may be transcribed and translated into a polypeptide. A polyadenylation signal and transcription termination 60 sequence will usually be located 3' to the coding sequence. A "promoter sequence" is a DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. Promoter sequences typically contain additional sites for 65 binding of regulatory molecules (e.g., transcription factors) which affect the transcription of the coding sequence. A coding sequence is "under the control" of the promoter

sequence or "operatively linked" to the promoter when RNA polymerase binds the promoter sequence in a cell and transcribes the coding sequence into mRNA, which is then in turn translated into the protein encoded by the coding sequence.

Vectors are used to introduce a foreign substance, such as DNA, RNA or protein, into an organism or host cell. Typical vectors include recombinant viruses (for polynucleotides) and liposomes (for polypeptides). A "DNA vector" is a replicon, such as plasmid, phage or cosmid, to which another polynucleotide segment may be attached so as to bring about the replication of the attached segment. An "expression vector" is a DNA vector which contains regulatory sequences which will direct polypeptide synthesis by an appropriate host cell. This usually means a promoter to bind RNA polymerase and initiate transcription of mRNA, as well as ribosome binding sites and initiation signals to direct translation of the mRNA into a polypeptide(s). Incorporation of a polynucleotide sequence into an expression vector at the proper site and in correct reading frame, followed by transformation of an appropriate host cell by the vector, enables the production of a polypeptide encoded by said polynucleotide sequence.

"Amplification" of polynucleotide sequences is the in vitro production of multiple copies of a particular nucleic acid sequence. The amplified sequence is usually in the form of DNA. A variety of techniques for carrying out such amplification are described in a review article by Van Brunt (1990, *Bio/Technol.*, 8(4):291-294). Polymerase chain reaction or PCR is a prototype of nucleic acid amplification, and use of PCR herein should be considered exemplary of other suitable amplification techniques.

The general structure of antibodies in vertebrates now is well understood (Edelman, G. M., *Ann. N.Y. Acad. Sci.*, 190: 5 (1971)). Antibodies consist of two identical light polypeptide chains of molecular weight approximately 23,000 daltons (the "light chain"), and two identical heavy chains of molecular weight 53,000-70,000 (the "heavy chain"). The four chains are joined by disulfide bonds in a "Y" configuration wherein the light chains bracket the heavy chains starting at the mouth of the "Y" configuration. The "branch" portion of the "Y" configuration is designated the F_{ab} region; the stem portion of the "Y" configuration is designated the Fc region. The amino acid sequence orientation runs from the N-terminal end at the top of the "Y" configuration to the C-terminal end at the bottom of each chain. The N-terminal end possesses the variable region having specificity for the antigen that elicited it, and is approximately 100 amino acids in length, there being slight variations between light and heavy chain and from antibody to antibody.

The variable region is linked in each chain to a constant region that extends the remaining length of the chain and that within a particular class of antibody does not vary with the specificity of the antibody (i.e., the antigen eliciting it). There are five known major classes of constant regions that determine the class of the immunoglobulin molecule (IgG, IgM, IgA, IgD, and IgE corresponding to γ , μ , α , δ , and ϵ (gamma, mu, alpha, delta, or epsilon) heavy chain constant regions). The constant region or class determines subsequent effector function of the antibody, including activation of complement (Kabat, E. A., *Structural Concepts in Immunology and Immunochemistry*, 2nd Ed., p. 413-436, Holt, Rinehart, Winston (1976)), and other cellular responses (Andrews, D. W., et al., *Clinical Immunobiology*, pp 1-18, W. B. Sanders (1980); Kohl, S., et al., *Immunology*, 48: 187 (1983)); while the variable region determines the antigen with which it will react. Light chains are classified as either

κ (kappa) or λ (lambda). Each heavy chain class can be prepared with either kappa or lambda light chain. The light and heavy chains are covalently bonded to each other, and the "tail" portions of the two heavy chains are bonded to each other by covalent disulfide linkages when the immunoglobulins are generated either by hybridomas or by B cells.

The expression "variable region" or "VR" refers to the domains within each pair of light and heavy chains in an antibody that are involved directly in binding the antibody to the antigen. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain (V_L) at one end and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

The expressions "complementarity determining region," "hypervariable region," or "CDR" refer to one or more of the hyper-variable or complementarity determining regions (CDRs) found in the variable regions of light or heavy chains of an antibody (See Kabat, E. A. et al., *Sequences of Proteins of Immunological Interest*, National Institutes of Health, Bethesda, Md., (1987)). These expressions include the hypervariable regions as defined by Kabat et al. ("Sequences of Proteins of Immunological Interest," Kabat E., et al., US Dept. of Health and Human Services, 1983) or the hypervariable loops in 3-dimensional structures of antibodies (Chothia and Lesk, *J Mol. Biol.* 196 901-917 (1987)). The CDRs in each chain are held in close proximity by framework regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site. Within the CDRs there are select amino acids that have been described as the selectivity determining regions (SDRs) which represent the critical contact residues used by the CDR in the antibody-antigen interaction (Kashmiri, S., Methods, 36:25-34 (2005)). In the present invention when specific antibody amino acid or nucleic acid residues are referenced by number this generally refers to its position within a specified amino acid or nucleic acid sequence (i.e., particular sequence identifier) and/or in accordance with Kabat et al numbering.

The expressions "framework region" or "FR" refer to one or more of the framework regions within the variable regions of the light and heavy chains of an antibody (See Kabat, E. A. et al., *Sequences of Proteins of Immunological Interest*, National Institutes of Health, Bethesda, Md., (1987)). These expressions include those amino acid sequence regions interposed between the CDRs within the variable regions of the light and heavy chains of an antibody.

"Cmax" refers to the maximum (or peak) concentration that an antibody or other compound achieves in tested area (e.g., in the serum or another compartment such as cerebrospinal fluid) after the drug has been administered. For example, serum Cmax may be measured from serum, e.g., prepared by collecting a blood sample, allowing it to clot and separating solid components by centrifugation or other means to yield serum (blood containing neither blood cells nor clotting factors), and then detecting the concentration of the analyte in the serum by ELISA or other means known in the art.

"AUC" refers to the area under the concentration-time curve which is expressed in units of mg/mL*hr (or equivalently mg*hr/ml) unless otherwise specified. "AUC_{0-t}" refers to the area under the concentration-time curve from

time=0 to last quantifiable concentration. "AUC_{0-inf}" refers to the area under the concentration-time curve from time=0 extrapolated to infinity.

"I_{max}" refers to the maximal pharmacodynamic response elicited by an anti-CGRP antibody dosage, preferably a dosage of 350 mg or more, more typically at least 750 or 1000 mg, as compared to the response elicited by a lower anti-CGRP antibody doses, e.g., wherein such response may be detected by the inhibition of vasodilation after topical application of capsaicin.

Anti-CGRP Antibodies and Binding Fragments Thereof Having Binding Specificity for CGRP

The invention specifically includes the use of specific anti-CGRP antibodies and antibody fragments referred to herein as Ab1-Ab14 which comprise or consist of the CDR, VL, VH, CL, CH polypeptides sequences identified in FIGS. 1A-12. The polypeptides comprised in an especially preferred anti-CGRP antibody, Ab6 is further described below.

Antibody Ab6

In a preferred exemplary embodiment, the invention includes humanized antibodies having binding specificity to CGRP and possessing a variable light chain sequence comprising the sequence set forth below:

(SEQ ID NO: 222)
QVLTQSPSSLSASVGDRVTINQASQSVYHNTYLAWYQQKPGKVPKQLIY
DASTLASGVPSRFSGSQSGTDFTLTISSLQPEDVATYYCLGSYDCTNGDC
FVFGGGTKVEIKR.

The invention also includes humanized antibodies having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below:

(SEQ ID NO: 221)
QVLTQSPSSLSASVGDRVTINQASQSVYHNTYLAWYQQKPGKVPKQLIY
DASTLASGVPSRFSGSQSGTDFTLTISSLQPEDVATYYCLGSYDCTNGDC
FVFGGGTKVEIKRTVAAPSVFIPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLKADYEHKVYACE
VTHQGLSSPVTKSFNRGEC.

The invention further includes humanized antibodies having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 202)
EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYMMNWRQAPGKGLEWVG
IGINGATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDI
WGQGTLTVSS.

The invention also includes humanized antibodies having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 201)
EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYMMNWRQAPGKGLEWVG
IGINGATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDI
WGQGTLTVSSASTKGPSVFLAPSSKSTSGGTAALGCLVKDYFPEPVTW

-continued

SWNSGALTSGVHTFPAVLQSSGLYSLSVVTPSSSLGTQTYICNVNHKP
SNTKVDARVEPKSCDKTHTCPCPAPELLGGPSVFLFPPKPDKTLMISRT
5 PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNNAKTKPREEQYASTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL
10 YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK.

Alternatively, the heavy chain of Ab6 may lack the C-terminal lysine of SEQ ID NO: 201, i.e., a heavy chain sequence comprising the sequence set forth below:

15 (SEQ ID NO: 566)
EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYMMNWRQAPGKGLEWVG
IGINGATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDI
WGQGTLTVSSASTKGPSVFLAPSSKSTSGGTAALGCLVKDYFPEPVTW
SWNSGALTSGVHTFPAVLQSSGLYSLSVVTPSSSLGTQTYICNVNHKP
SNTKVDARVEPKSCDKTHTCPCPAPELLGGPSVFLFPPKPDKTLMISRT
25 PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNNAKTKPREEQYASTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL
30 YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG.

The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221, and/or one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

55 The invention also contemplates fragments of the antibody having binding specificity to CGRP. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 222 or SEQ ID NO: 221. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 202 or SEQ ID NO: 201 or SEQ ID NO: 566.

60 In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221.

29

In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566.

The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 222; the variable heavy chain region of SEQ ID NO: 202; the complementarity-determining regions (SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228) of the variable light chain region of SEQ ID NO: 222; and the complementarity-determining regions (SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208) of the variable heavy chain region of SEQ ID NO: 202.

In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody is Ab6, comprising, or alternatively consisting of, SEQ ID NO: 221 and SEQ ID NO: 201 or SEQ ID NO: 566, and having at least one of the biological activities set forth herein.

In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab6, the Fab fragment includes the variable light chain sequence of SEQ ID NO: 222 and the variable heavy chain sequence of SEQ ID NO: 202. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 222 and/or SEQ ID NO: 202 in said Fab while retaining binding specificity for CGRP.

In another particularly preferred embodiment of the invention, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, e.g., human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells.

In another particularly preferred embodiment of the invention, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions.

In another particularly preferred embodiment of the invention, any of the aforementioned anti-CGRP antibodies or antibody fragments may be optionally comprised in a formulation as disclosed herein, e.g., comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg

30

L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8.

In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab6. In another embodiment of the invention, anti-CGRP antibodies such as Ab6 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

In another embodiment, antibody fragments may be present in one or more of the following non-limiting forms: Fab, Fab', F(ab')₂, Fv and single chain Fv antibody forms. In a preferred embodiment, the anti-CGRP antibodies described herein further comprises the kappa constant light chain sequence comprising the sequence set forth below:

(SEQ ID NO: 563)

TVAAPSVFIFPPSDEQLKSGTASVVCNNYFREAKVQWVKVDNALQSGN
SQESVTQEVDKDTSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC.

In another preferred embodiment, the anti-CGRP antibodies described herein further comprises the gamma-1 constant heavy chain polypeptide sequence comprising the sequence set forth below or the same sequence lacking the carboxy terminal lysine residue (SEQ ID NO: 564 and SEQ ID NO: 565, respectively)

(SEQ ID NO: 564)

ASTKGPSVFPLAPSSKSTSGGTAAALGCLVKDYPFPEPVTVSWNSGALTSGV
HTFPAAVLQSSGLYSLSSVTVPSLGTQTYICNVNHKPSNTKVDKRVEP
KSCDKTHCTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
40 HEDPEVKPNWYVGVEVHNAAKTKPREEQYASTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTIASKAGQPREPVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRW
45 QQGNVFSCVMHEALHNHYTQKSLSLSPKG.

(SEQ ID NO: 565)

ASTKGPSVFPLAPSSKSTSGGTAAALGCLVKDYPFPEPVTVSWNSGALTSGV
HTFPAAVLQSSGLYSLSSVTVPSLGTQTYICNVNHKPSNTKVDKRVEP
KSCDKTHCTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
40 HEDPEVKPNWYVGVEVHNAAKTKPREEQYASTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTIASKAGQPREPVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRW
55 QQGNVFSCVMHEALHNHYTQKSLSLSPKG.

For clarity, any antibody disclosed herein is intended to include any variant of the disclosed constant region variant sequences, e.g., Ab6 may comprise the constant region of SEQ ID NO: 564 containing the C-terminal lysine or may comprise the constant region of SEQ ID NO: 565 lacking the C-terminal lysine. Thus, every disclosure herein of the heavy chain of SEQ ID NO: 201 also includes a variant lacking the C-terminal lysine residue thereof, i.e., having the heavy chain variable region sequence of Ab6 (SEQ ID NO:

31

202) and the constant region sequence of SEQ ID NO: 565. For example, the sequence encoding an antibody comprising a C-terminal lysine in the heavy chain may, when expressed in cell lines such as CHO cells, produce an antibody lacking said C-terminal lysine due to proteolysis, or a mixture of heavy chains containing or lacking said C-terminal lysine.

In another embodiment, the invention contemplates use of an isolated anti-CGRP antibody comprising a V_H polypeptide sequence selected from: SEQ ID NO: 2, SEQ ID NO: 42, SEQ ID NO: 82, SEQ ID NO: 122, SEQ ID NO: 162, SEQ ID NO: 202, SEQ ID NO: 242, SEQ ID NO: 282, SEQ ID NO: 322, SEQ ID NO: 362, SEQ ID NO: 402, SEQ ID NO: 442, SEQ ID NO: 482, or SEQ ID NO: 522, or a variant thereof; and further comprising a V_L polypeptide sequence selected from: SEQ ID NO: 22, SEQ ID NO: 62, SEQ ID NO: 102, SEQ ID NO: 142, SEQ ID NO: 182, SEQ ID NO: 222, SEQ ID NO: 262, SEQ ID NO: 302, SEQ ID NO: 342, SEQ ID NO: 382, SEQ ID NO: 422, SEQ ID NO: 462, SEQ ID NO: 502, or SEQ ID NO: 542, or a variant thereof, wherein one or more of the framework residues (FR residues) in said V_H or V_L polypeptide has been substituted with another amino acid residue resulting in an anti-CGRP antibody that specifically binds CGRP. The invention contemplates humanized and chimeric forms of these antibodies. The chimeric antibodies may include an Fc derived from IgG1, IgG2, IgG3, or IgG4 constant regions.

In one embodiment of the invention, the antibodies or V_H or V_L polypeptides originate or are selected from one or more rabbit B cell populations prior to initiation of the humanization process referenced herein.

In another embodiment of the invention, the anti-CGRP antibodies and fragments thereof do not have binding specificity for CGRP-R. In a further embodiment of the invention, the anti-CGRP antibodies and fragments thereof inhibit the association of CGRP with CGRP-R. In another embodiment of the invention, the anti-CGRP antibodies and fragments thereof inhibit the association of CGRP with CGRP-R and/or additional proteins and/or multimers thereof, and/or antagonizes the biological effects thereof.

As stated herein, antibodies and fragments thereof may be modified post-translationally to add effector moieties such as chemical linkers, detectable moieties such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, and chemiluminescent moieties, or functional moieties such as for example streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, and radioactive materials.

Antibodies or fragments thereof may also be chemically modified to provide additional advantages such as increased solubility, stability and circulating time (in vivo half-life) of the polypeptide, or decreased immunogenicity (See U.S. Pat. No. 4,179,337). The chemical moieties for derivatization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The antibodies and fragments thereof may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained

32

release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa. Branched polyethylene glycols are described, for example, in U.S. Pat. No. 5,643,575; Morpurgo et al., Appl. Biochem. Biotechnol. 56:59-72 (1996); Vorobjev et al., Nucleosides Nucleotides 18:2745-2750 (1999); and Caliceti et al., Bioconjug. Chem. 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

There are a number of attachment methods available to those skilled in the art. See e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF). See also Malik et al., *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to polypeptides via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof).

Alternatively, antibodies or fragments thereof may have increased in vivo half-lives via fusion with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (See, e.g., U.S. Pat. No. 5,876,969, issued Mar. 2, 1999, EP Patent 0 413 622, and U.S. Pat. No. 5,766,883, issued Jun. 16, 1998, herein incorporated by reference in their entirety)) or other circulating blood proteins such as transferrin or ferritin. In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1-585 of human serum albumin as shown in FIGS. 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

Regarding detectable moieties, further exemplary enzymes include, but are not limited to, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, beta-galac-

tosidase and luciferase. Further exemplary fluorescent materials include, but are not limited to, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycocerythrin and dansyl chloride. Further exemplary chemiluminescent moieties include, but are not limited to, luminol. Further exemplary bioluminescent materials include, but are not limited to, luciferin and aequorin. Further exemplary radioactive materials include, but are not limited to, Iodine 125 (^{125}I), Carbon 14 (^{14}C), Sulfur 35 (^{35}S), Tritium (^3H) and Phosphorus 32 (^{32}P).

Regarding functional moieties, exemplary cytotoxic agents include, but are not limited to, methotrexate, amiopterin, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil, decarbazine; alkylating agents such as mechlorethamine, thioepa, chlorambucil, melphalan, carbustine (BSNU), mitomycin C, lomustine (CCNU), 1-methylnitrosourea, cyclophosphamide, mechlorethamine, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II) (DDP) cisplatin and carboplatin (paraplatin); anthracyclines include daunorubicin (formerly daunomycin), doxorubicin (adriamycin), detorubicin, carminomycin, idarubicin, epirubicin, mitoxantrone and bisantrene; antibiotics include dactinomycin (actinomycin D), bleomycin, calicheamicin, mithramycin, and anthramycin (AMC); and antimyotic agents such as the *vinca* alkaloids, vincristine and vinblastine. Other cytotoxic agents include paclitaxel (taxol), ricin, *pseudomonas* exotoxin, gemcitabine, cytochalasin B, gramicidin D, ethidium bromide, emetine, etoposide, tenoposide, colchicine, dihydroxyanthracin dione, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, procarbazine, hydroxyurea, asparaginase, corticosteroids, mytotox (O,P⁻(DDD)), interferons, and mixtures of these cytotoxic agents.

Further cytotoxic agents include, but are not limited to, chemotherapeutic agents such as carboplatin, cisplatin, paclitaxel, gemcitabine, calicheamicin, doxorubicin, 5-fluorouracil, mitomycin C, actinomycin D, cyclophosphamide, vincristine and bleomycin. Toxic enzymes from plants and bacteria such as ricin, diphtheria toxin and *Pseudomonas* toxin may be conjugated to the humanized or chimeric antibodies, or binding fragments thereof, to generate cell-type-specific-killing reagents (Youle, et al., Proc. Nat'l Acad. Sci. USA 77:5483 (1980); Gilliland, et al., Proc. Nat'l Acad. Sci. USA 77:4539 (1980); Krolick, et al., Proc. Nat'l Acad. Sci. USA 77:5419 (1980)).

Other cytotoxic agents include cytotoxic ribonucleases as described by Goldenberg in U.S. Pat. No. 6,653,104. Embodiments of the invention also relate to radioimmunoconjugates where a radionuclide that emits alpha or beta particles is stably coupled to the antibody, or binding fragments thereof, with or without the use of a complex-forming agent. Such radionuclides include beta-emitters such as Phosphorus-32 (^{32}P), Scandium-47 (^{47}Sc), Copper-67 (^{67}Cu), Gallium-67 (^{67}Ga), Yttrium-88 (^{88}Y), Yttrium-90 (^{90}Y), Iodine-125 (^{125}I), Iodine-131 (^{131}I), Samarium-153 (^{153}Sm), Lutetium-177 (^{177}Lu), Rhenium-186 (^{186}Re) or Rhenium-188 (^{188}Re), and alpha-emitters such as Astatine-211 (^{211}At), Lead-212 (^{212}Pb), Bismuth-212 (^{212}Bi) or -213 (^{213}Bi) or Actinium-225 (^{225}Ac).

Methods are known in the art for conjugating an antibody or binding fragment thereof to a detectable moiety and the like, such as for example those methods described by Hunter et al, *Nature* 144:945 (1962); David et al, *Biochemistry* 13:1014 (1974); Pain et al, *J. Immunol. Meth.* 40:219 (1981); and Nygren, J., *Histochem. and Cytochem.* 30:407 (1982).

Embodiments described herein further include variants and equivalents that are substantially homologous to the antibodies, antibody fragments, diabodies, SMIPs, camel-bodies, nanobodies, IgNAR, polypeptides, variable regions and CDRs set forth herein. These may contain, e.g., conservative substitution mutations, (i.e., the substitution of one or more amino acids by similar amino acids). For example, conservative substitution refers to the substitution of an amino acid with another within the same general class, e.g., one acidic amino acid with another acidic amino acid, one basic amino acid with another basic amino acid, or one neutral amino acid by another neutral amino acid. What is intended by a conservative amino acid substitution is well known in the art.

In another embodiment, the invention contemplates polypeptide sequences having at least 90% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. More preferably, the invention contemplates polypeptide sequences having at least 95% or greater sequence homology, even more preferably at least 98% or greater sequence homology, and still more preferably at least 99% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. Methods for determining homology between nucleic acid and amino acid sequences are well known to those of ordinary skill in the art.

In another embodiment, the invention further contemplates the above-recited polypeptide homologs of the antibody fragments, variable regions and CDRs set forth herein further having anti-CGRP activity. Non-limiting examples of anti-CGRP activity are set forth herein.

The present invention also contemplates anti-CGRP antibodies comprising any of the polypeptide or polynucleotide sequences described herein substituted for any of the other polynucleotide sequences described herein. For example, without limitation thereto, the present invention contemplates antibodies comprising the combination of any of the variable light chain and variable heavy chain sequences described herein, and further contemplates antibodies resulting from substitution of any of the CDR sequences described herein for any of the other CDR sequences described herein. Additional Exemplary Embodiments of the Invention

In another embodiment, the invention contemplates treatment methods using one or more anti-human CGRP antibodies or antibody fragments thereof which specifically bind to the same overlapping linear or conformational epitope(s) and/or competes for binding to the same overlapping linear or conformational epitope(s) on an intact human CGRP polypeptide or fragment thereof as an anti-human CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, or Ab14. In a preferred embodiment, the anti-human CGRP antibody or fragment thereof specifically binds to the same overlapping linear or conformational epitope(s) and/or competes for binding to the same overlapping linear or conformational epitope(s) on an intact human CGRP polypeptide or a fragment thereof as Ab3, Ab6, Ab13, or Ab14.

A preferred embodiment of the invention is directed to treatment methods using chimeric or humanized antibodies and fragments thereof (including Fab fragments) having binding specificity for CGRP and inhibiting biological activities mediated by the binding of CGRP to the CGRP receptor. In a particularly preferred embodiment of the invention, the chimeric or humanized anti-CGRP antibodies are selected from Ab3, Ab6, Ab13, or Ab14.

In another embodiment of the invention, the anti-human CGRP antibody used in the described treatment methods is an antibody which specifically binds to the same overlapping linear or conformational epitopes on an intact CGRP polypeptide or fragment thereof that is (are) specifically bound by Ab3, Ab6, Ab13, or Ab14 as ascertained by epitope mapping using overlapping linear peptide fragments which span the full length of the native human CGRP polypeptide.

The invention is also directed to treatment methods using an anti-CGRP antibody that binds with the same CGRP epitope and/or competes with an anti-CGRP antibody for binding to CGRP as an antibody or antibody fragment disclosed herein, including but not limited to an anti-CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, 15 Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, or Ab14.

In another embodiment, the invention is also directed to treatment methods using an isolated anti-CGRP antibody or antibody fragment comprising one or more of the CDRs contained in the V_H polypeptide sequences selected from: 3, 13, 23, 33, 43, 53, 63, 73, 83, 93, 103, 113, 123, or 133, or a variant thereof, and/or one or more of the CDRs contained in the V_L polypeptide sequences selected from: 1, 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, or 131, or a variant thereof.

In one embodiment of the invention, the anti-human CGRP antibody discussed in the two prior paragraphs comprises at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in an anti-human CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, or Ab14.

In a preferred embodiment, the anti-human CGRP antibody used in the described treatment methods comprises at least 2 complementarity determining regions (CDRs) in each the variable light and the variable heavy regions which are identical to those contained in Ab3 or Ab6. In another embodiment, all of the CDRs of the anti-human CGRP antibody discussed above are identical to the CDRs contained in an anti-human CGRP antibody selected from Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, Ab13, or Ab14. In a preferred embodiment of the invention, all of the CDRs of the anti-human CGRP antibody discussed above are identical to the CDRs contained in an anti-human CGRP antibody selected from Ab3 or Ab6.

The invention further contemplates treatment methods wherein the one or more anti-human CGRP antibodies discussed above are glycosylated or if glycosylated are only mannosylated; that contain an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation; are human, humanized, single chain or chimeric; and are a humanized antibody derived from a rabbit (parent) anti-human CGRP antibody. An exemplary mutation which impairs glycosylation comprises the mutation of the Asn residue at position 297 of an IgG heavy chain constant region such as IgG1 to another amino acid, such as Ala as described in U.S. Pat. No. 5,624,821, which is incorporated by reference in its entirety.

The invention further contemplates one or more anti-human CGRP antibodies wherein the framework regions (FRs) in the variable light region and the variable heavy regions of said antibody respectively are human FRs which are unmodified or which have been modified by the substitution of one or more human FR residues in the variable light or heavy chain region with the corresponding FR residues of the parent rabbit antibody, and wherein said human FRs

have been derived from human variable heavy and light chain antibody sequences which have been selected from a library of human germline antibody sequences based on their high level of homology to the corresponding rabbit 5 variable heavy or light chain regions relative to other human germline antibody sequences contained in the library.

The invention also contemplates a method of treating or preventing medication overuse headache, e.g., associated with the overuse of anti-migraine drugs and/or associated 10 with triptan and/or ergot and/or analgesic overuse, comprising administering to a patient exhibiting medication overuse headache or at risk of developing medication overuse headache a therapeutically effective amount of at least one anti-human CGRP antibody or fragment described herein. The invention also contemplates that the treatment method 15 may involve the administration of two or more anti-CGRP antibodies or fragments thereof and disclosed herein. If more than one antibody is administered to the patient, the multiple antibodies may be administered simultaneously or concurrently, 20 or may be staggered in their administration. The anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, may also be described by their strength of binding or their affinity for CGRP. In one embodiment of 25 the invention, the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to CGRP with a dissociation constant (K_D) of less than or equal to 5×10^{-7} M, 10^{-8} M, 5×10^{-8} M, 10^{-9} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, or 10^{-13} M. Preferably, 30 the anti-CGRP antibodies and fragments thereof bind CGRP with a dissociation constant of less than or equal to 10^{-11} M, 5×10^{-2} M, or 10^{-12} M. In another embodiment of the invention, the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to a linear or conformational CGRP epitope.

In another embodiment of the invention, the anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to CGRP with an off-rate of less than or equal 40 to 10^{-4} S⁻¹, 5×10^{-5} S⁻¹, 10^{-5} S⁻¹, 5×10^{-6} S⁻¹, 10^{-6} S⁻¹, 5×10^{-7} S⁻¹, or 10^{-7} S⁻¹.

In a further embodiment of the invention, the anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, exhibit anti-CGRP activity by preventing, ameliorating or reducing the symptoms of, or alternatively treating, diseases and disorders associated with CGRP. Non-limiting examples of diseases and disorders associated with CGRP are set forth herein and include headache and migraine disorders.

Polynucleotides Encoding Anti-CGRP Antibody Polypeptides

As aforementioned the invention specifically includes the 55 use of specific anti-CGRP antibodies and antibody fragments referred to herein as Ab1-Ab14 which comprise or consist of the CDR, VL, VH, CL, and CH polypeptides having the sequences identified in FIGS. 1A-12. The nucleic acid sequences encoding the foregoing VL, VH, CL, and CH 60 polypeptides comprised in Ab1-Ab14 are also comprised in FIGS. 1A-12. The nucleic acid sequences which encode the CDR, VL, VH, CL, and CH polypeptides of an especially preferred anti-CGRP antibody, Ab6, are further described below.

Antibody Ab6

The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity

to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 222:

(SEQ ID NO: 232)
 CAAGTGCTGaccaggatctccatcctccctgtcatctgttaggagacag
 agtcaccatcATTgcCAGGCCAGTCAGAGTGTATCATAACACCTACC
 TGGCCtggtatcagcagaaaccaggaaagtccataagCAActgtctat
 GATGCATCCACTCTGGCATCTgggtccatctcgttcagtggcagtgg
 atctggacagattcactctaccatcagcgcgtcagccgtaaagatg
 ttgcaacttattactgtCTGGCAGTTATGATTGACTAATGGTATTGT
 TTGTTttcggggaggaaaccaggtaatcaaacgt.

In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 221:

(SEQ ID NO: 231)
 CAAGTGCTGaccaggatctccatcctccctgtcatctgttaggagacag
 agtcaccatcATTgcCAGGCCAGTCAGAGTGTATCATAACACCTACC
 TGGCCtggtatcagcagaaaccaggaaagtccataagCAActgtctat
 GATGCATCCACTCTGGCATCTgggtccatctcgttcagtggcagtgg
 atctggacagattcactctaccatcagcgcgtcagccgtaaagatg
 ttgcaacttattactgtCTGGCAGTTATGATTGACTAATGGTATTGT
 TTGTTttcggggaggaaaccaggtaatcaaacgtACGGTGGCTGC
 ACCATCTGTCTCATCTCCGCCATCTGATGAGCAGTTGAATCTGGAA
 CTGCCTCTGTTGTGCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA
 GTACAGTGGAAAGGTGGATAACCCCTCCAATCGGTAACTCCAGGAGAG
 TGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCC
 TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCCTGCGAA
 GTCACCCCATCAGGGCCTGAGCTGCCGTACAAGAGCTTCAACAGGGG
 AGAGTGTAG.

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 202:

(SEQ ID NO: 212)
 gaggtgcagctTgtggagtctggggaggcttggccagcgtgggggtc
 cctgagactctctgtcaGTctgtggaaATCGACCTCagtgGCTACTACA
 TGAAActgggtccgtcaggccaggaaagggtggagtggtcGGAGTC
 ATTGGTATTAATGGTGCCACATACGCGAGCTGGCGAAAGGGCcgatt
 caccatctccagagacaattcaagACCACGGTGtatcttcaaata
 gcctgagactgaggacactgtgttatTCtgtGCTAGAGGGACATC
 tggggccaaggggaccctcgtaaccgtTCGAGC.

In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the

following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 201:

5 (SEQ ID NO: 211)
 gaggtgcagctTgtggagtctggggaggcttggccagcgtgggggtc
 cctgagactctctgtcaGTctgtggaaATCGACCTCagtgGCTACTACA
 TGAAActgggtccgtcaggccaggaaagggtggagtggtcGGAGTC
 ATTGGTATTAATGGTGCCACATACGCGAGCTGGCGAAAGGGCcgatt
 caccatctccagagacaattcaagACCACGGTGtatcttcaaata
 gcctgagactgaggacactgtgttatTCtgtGCTAGAGGGACATC
 10 tggggccaaggggaccctcgtaaccgtTCGAGCCTCCACCAAGGGCCC
 ATCGGTCTTCCCCCTGGCACCTCCCTCCAGACCTCTGGGGCACAG
 CGGCGCTGGCTGCCCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTG
 15 TCGTGGAACTCAGGCGCCCTGACCAGCGCGTGCACACCTCCGGCTGT
 CCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTACCGTGCCT
 CCAGCAGCTTGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCC
 20 AGCAACACCAAGGTGGACCGAGAGTTGAGCCAAATCTGTGACAAAAC
 TCACACATGCCAACCGTGCCTGGCAGCACCTGAACCTGGGGGACCGTCAG
 TCTTCCCTTCCCCCAAAACCAAGGACACCTCATGATCTCCCgGACC
 25 CCTGAGGTACATGCGTGGTGGACGTGAGCCACGAAGACCCCTGAGGT
 CAAGTCAACTGGTACGTGGACGGCGTGGAGGTGATAATGCCAAGACAA
 AGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTACCGTGCCTC
 30 ACCGTCCTGCACCAGGACTGGCTGAATGCCAAGGAGTACAAGTGAAGGT
 CTCCAACAAAGGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAAGCCA
 AAGGGCAGCCCCGAGAACACAGGTGTACACCCTGCCCATCCGGAG
 GAGATGACCAAGAACCGGTACGCCCTGGCTGGTACCGTGTGGTACCGTGCCT
 35 TCCCAGCGACATGCCCTGGAGTGGAGAGCAATGGCAGCCGGAGAACAA
 ACTACAAAGACCGCCTCCCGTGTGGACTCCGACGGCTCTTCTCC
 TACAGCAAGCTACCCTGGACAAGAGCAGGTGGCAGCAGGGAACGTCTT
 40 45 CTCATGCTCCGTATGCACTGGCTCTGCACAACCAACTACACGCAGAAGA
 GGCTCTCCCTGTCTCCGGTAAATGA.

In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 566:

55 (SEQ ID NO: 567)
 gaggtgcagctTgtggagtctggggaggcttggccagcgtgggggtc
 cctgagactctctgtcaGTctgtggaaATCGACCTCagtgGCTACTACA
 TGAAActgggtccgtcaggccaggaaagggtggagtggtcGGAGTC
 60 ATTGGTATTAATGGTGCCACATACGCGAGCTGGCGAAAGGGCcgatt
 caccatctccagagacaattcaagACCACGGTGtatcttcaaata
 gcctgagactgaggacactgtgttatTCtgtGCTAGAGGGACATC
 tggggccaaggggaccctcgtaaccgtTCGAGCCTCCACCAAGGGCCC
 65

- continued

```

ATCGGTCTTCCCCCTGGCcCCTCCTCAAGGCACCTCTGGGGCACAG
CGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTG
TCGTGGAACTCAGGCGCCTGACCAGGGCGTGCACACCTTCCCGCTGT
CCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGAACGTGCCCT
CCAGCAGCTTGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCC
AGCAACACCAAAAGGTGGACGCGAGAGTTGAGCCAAATCTTGTGACAAAAC
TCACACATGCCACCTGTGCCCAGCACCTGAACTCCTGGGGGACCGTCAG
TCTTCCTCTTCCCCCAAAACCCAAGGACACCCTCATGaTCTCCCgGACC
CCTGAGGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCTGAGGT
CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAA
AGCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTC
ACCGTCCTGCACCAAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGT
CTCCAACAAAGCCTCCCAGCCCCATCGAGAAAACCTCTCAAAGCCA
AAGGGCAGCCCCGAGAACCAACAGGTTACACCCTGCCCCATCCGGGAG
GAGATGACCAAGAACCCAGGTCAGCCTGACCTGGCTGGTCAAGGCTTCTA
TCCCAGCGACATCGCCTGGAGTGGGAGAGCAATGGGAGCGGGAGAACAA
ACTACAAGACCACGCCTCCCGTGGACTCCGACGGCTCCTTCTCCTC
TACAGCAAGCTACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTT
CTCATGCTCCTGATGCTGAGGCTCTGCACAAACCACTACACCGCAGAAGA
GCCTCTCCTGTCTCCGGTTGA.

```

In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221.

In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566.

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 232 encoding the light chain variable sequence of SEQ ID NO: 222; the polynucleotide SEQ ID NO: 231 encoding the light chain sequence of SEQ ID NO: 221; the polynucleotide SEQ ID NO: 212 encoding the heavy chain variable sequence of SEQ ID NO: 202; the polynucleotide SEQ ID NO: 211 encoding the heavy chain sequence of SEQ ID NO: 201; the polynucleotide SEQ ID NO: 567 encoding the heavy chain sequence of SEQ ID NO: 566; polynucleotides encoding the

complementarity-determining regions (SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238) of the light chain variable sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218) of the heavy chain variable sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566.

In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab6, the polynucleotides encoding the full length Ab6 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 231 encoding the light chain sequence of SEQ ID NO: 221 and the polynucleotide SEQ ID NO: 211 encoding the heavy chain sequence of SEQ ID NO: 201 or the polynucleotide SEQ ID NO: 567 encoding the heavy chain sequence of SEQ ID NO: 566.

Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast *Pichia*. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab6 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab6 or Fab fragments thereof may be produced via expression of Ab6 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

In one embodiment, the invention is directed to an isolated polynucleotide comprising a polynucleotide encoding an anti-CGRP V_H antibody amino acid sequence selected from SEQ ID NO: 2, SEQ ID NO: 42, SEQ ID NO: 82, SEQ ID NO: 122, SEQ ID NO: 162, SEQ ID NO: 202, SEQ ID NO: 242, SEQ ID NO: 282, SEQ ID NO: 322, SEQ ID NO: 362, SEQ ID NO: 402, SEQ ID NO: 442, SEQ ID NO: 482, or SEQ ID NO: 522 or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-CGRP antibody V_H polypeptide or a conservative amino acid substitution.

In another embodiment, the invention is directed to an isolated polynucleotide comprising the polynucleotide sequence encoding an anti-CGRP V_L antibody amino acid sequence of SEQ ID NO: 22, SEQ ID NO: 62, SEQ ID NO: 102, SEQ ID NO: 142, SEQ ID NO: 182, SEQ ID NO: 222, SEQ ID NO: 262, SEQ ID NO: 302, SEQ ID NO: 342, SEQ ID NO: 382, SEQ ID NO: 422, SEQ ID NO: 462, SEQ ID NO: 502, or SEQ ID NO: 542, or encoding a variant thereof wherein at least one framework residue (FR residue) has been substituted with an amino acid present at the corresponding position in a rabbit anti-CGRP antibody V_L polypeptide or a conservative amino acid substitution.

In yet another embodiment, the invention is directed to one or more heterologous polynucleotides comprising a sequence encoding the polypeptides contained in SEQ ID NO: 22 and SEQ ID NO: 2; SEQ ID NO: 62 and SEQ ID NO: 42; SEQ ID NO: 102 and SEQ ID NO: 82; SEQ ID NO: 142 and SEQ ID NO: 122; SEQ ID NO: 182 and SEQ ID NO: 162; SEQ ID NO: 222 and SEQ ID NO: 202; SEQ ID

NO: 262 and SEQ ID NO: 242; SEQ ID NO: 302 and SEQ ID NO: 282; SEQ ID NO: 342 and SEQ ID NO: 322; SEQ ID NO: 382 and SEQ ID NO: 362; SEQ ID NO: 422 and SEQ ID NO: 402; SEQ ID NO: 462 and SEQ ID NO: 442; SEQ ID NO: 502 and SEQ ID NO: 482; or SEQ ID NO: 542 and SEQ ID NO: 522.

In another embodiment, the invention is directed to an isolated polynucleotide that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-CGRP antibody wherein said expressed polypeptide alone specifically binds CGRP or specifically binds CGRP when expressed in association with another polynucleotide sequence that expresses a polypeptide containing at least one CDR polypeptide derived from an anti-CGRP antibody wherein said at least one CDR is selected from those contained in the V_L or V_H polypeptides of SEQ ID NO: 22, SEQ ID NO: 2, SEQ ID NO: 62, SEQ ID NO: 42, SEQ ID NO: 102, SEQ ID NO: 82, SEQ ID NO: 142, SEQ ID NO: 122, SEQ ID NO: 182, SEQ ID NO: 162, SEQ ID NO: 222, SEQ ID NO: 202, SEQ ID NO: 262, SEQ ID NO: 242, SEQ ID NO: 302, SEQ ID NO: 282, SEQ ID NO: 342, SEQ ID NO: 322, SEQ ID NO: 382, SEQ ID NO: 362, SEQ ID NO: 422, SEQ ID NO: 402, SEQ ID NO: 462, SEQ ID NO: 442, SEQ ID NO: 502, SEQ ID NO: 482, SEQ ID NO: 542, or SEQ ID NO: 522.

Host cells and vectors comprising said polynucleotides are also contemplated.

The invention further contemplates vectors comprising the polynucleotide sequences encoding the variable heavy and light chain polypeptide sequences, as well as the individual complementarity-determining regions (CDRs, or hypervariable regions), as set forth herein, as well as host cells comprising said vector sequences. In one embodiment of the invention, the host cell is a yeast cell. In another embodiment of the invention, the yeast host cell belongs to the genus *Pichia*.

Methods of Producing Antibodies and Fragments Thereof

In another embodiment, the present invention contemplates methods for producing anti-CGRP antibodies and fragments thereof. Methods for producing antibodies and fragments thereof secreted from polyploidal, preferably diploid or tetraploid strains of mating competent yeast are taught, for example, in U.S. patent application publication no. US 2009/0022659 to Olson et al., and in U.S. Pat. No. 7,935,340 to Garcia-Martinez et al., the disclosures of each of which are herein incorporated by reference in their entireties. Methods for producing antibodies and fragments thereof in mammalian cells, e.g., CHO cells are further well known in the art.

Other methods of producing antibodies are also well known to those of ordinary skill in the art. For example, methods of producing chimeric antibodies are now well known in the art (See, for example, U.S. Pat. No. 4,816,567 to Cabilly et al.; Morrison et al., *P.N.A.S. USA*, 81:8651-55 (1984); Neuberger, M. S. et al., *Nature*, 314:268-270 (1985); Boulianne, G. L. et al., *Nature*, 312:643-46 (1984), the disclosures of each of which are herein incorporated by reference in their entireties).

Likewise, other methods of producing humanized antibodies are now well known in the art (See, for example, U.S. Pat. Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370 to Queen et al.; U.S. Pat. Nos. 5,225,539 and 6,548,640 to Winter; U.S. Pat. Nos. 6,054,297, 6,407,213 and 6,639,055 to Carter et al.; U.S. Pat. No. 6,632,927 to Adair; Jones, P. T. et al., *Nature*, 321:522-525 (1986); Reichmann, L., et al., *Nature*, 332:323-327 (1988); Verhoeyen, M. et al., *Science*,

239:1534-36 (1988), the disclosures of each of which are herein incorporated by reference in their entireties).

The term "opioid analgesic" herein refers to all drugs, natural or synthetic, with morphine-like actions. The synthetic and semi-synthetic opioid analgesics are derivatives of five chemical classes of compound: phenanthrenes; phenylheptamines; phenylpiperidines; morphinans; and benzomorphans, all of which are within the scope of the term. Exemplary opioid analgesics include codeine, dihydrocodeine, 10 diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine or pharmaceutically acceptable salts thereof.

The term "NSAID" refers to a non-steroidal anti-inflammatory compound. NSAIDs are categorized by virtue of their ability to inhibit cyclooxygenase. Cyclooxygenase 1 and cyclooxygenase 2 are two major isoforms of cyclooxygenase and most standard NSAIDs are mixed inhibitors of 15 the two isoforms. Most standard NSAIDs fall within one of the following five structural categories: (1) propionic acid derivatives, such as ibuprofen, naproxen, naprosyn, diclofenac, and ketoprofen; (2) acetic acid derivatives, such as tolmetin and slindac; (3) fenamic acid derivatives, such as mefenamic acid and meclofenamic acid; (4) biphenylcarboxylic acid derivatives, such as diflunisal and flufenisal; and (5) oxicams, such as piroxim, sudoxicam, and isoxicam. Another class of NSAID has been described which selectively inhibit cyclooxygenase 2. Cox-2 inhibitors have been 20 described, e.g., in U.S. Pat. Nos. 5,616,601; 5,604,260; 5,593,994; 5,550,142; 5,536,752; 5,521,213; 5,475,995; 5,639,780; 5,604,253; 5,552,422; 5,510,368; 5,436,265; 5,409,944; and 5,130,311, all of which are hereby incorporated by reference. Certain exemplary COX-2 inhibitors include celecoxib (SC-58635), DUP-697, flosulide (CGP-28238), meloxicam, 6-methoxy-2 naphthylacetic acid (6-MNA), rofecoxib, MK-966, nabumetone (prodrug for 6-MNA), nimesulide, NS-398, SC-5766, SC-58215, T-614; or combinations thereof.

In some embodiments, aspirin and/or acetaminophen may be taken in conjunction with the subject CGRP antibody or fragment. Aspirin is another type of non-steroidal anti-inflammatory compound.

The subject to which the pharmaceutical formulation is administered can be, e.g., any human or non-human animal that is in need of such treatment, prevention and/or amelioration, or who would otherwise benefit from the inhibition or attenuation of medication overuse headache. For example, the subject can be an individual that is diagnosed with, or 45 who is deemed to be at risk of being afflicted by medication overuse headache. The present invention further includes the use of any of the pharmaceutical formulations disclosed herein in the manufacture of a medicament for the treatment, prevention and/or amelioration of medication overuse headache.

Administration

In one embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject at a concentration of between about 0.1 and 100.0 mg/kg of body weight of recipient subject. In a preferred embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of 60 said antibodies or antibody fragments, are administered to a subject at a concentration of about 0.4 mg/kg of body weight of recipient subject and/or at a dosage of 100 or 300 mg. In

a preferred embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a recipient subject with a frequency of once every twenty-six weeks or six months or less, such as once every sixteen weeks or four months or less, once every eight weeks or two months or less, once every four weeks or monthly or less, once every two weeks or bimonthly or less, once every week or less, or once daily or less. In general the administration of sequential doses may vary by plus or minus a few days from the aforementioned schedule, e.g., administration every 3 months or every 12 weeks includes administration of a dose varying from the schedule day by plus or minus 1, 2, 3, 4, 5, 5, or 7 days.

Fab fragments may be administered every two weeks or less, every week or less, once daily or less, multiple times per day, and/or every few hours. In one embodiment of the invention, a patient receives Fab fragments of 0.1 mg/kg to 40 mg/kg per day given in divided doses of 1 to 6 times a day, or in a sustained release form, effective to obtain desired results.

It is to be understood that the concentration of the antibody or Fab administered to a given patient may be greater or lower than the exemplary administration concentrations set forth above.

A person of skill in the art would be able to determine an effective dosage and frequency of administration through routine experimentation, for example guided by the disclosure herein and the teachings in Goodman, L. S., Gilman, A., Brunton, L. L., Lazo, J. S., & Parker, K. L. (2006). *Goodman & Gilman's the pharmacological basis of therapeutics*. New York: McGraw-Hill; Howland, R. D., Mycek, M. J., Harvey, R. A., Champe, P. C., & Mycek, M. J. (2006). *Pharmacology*. Lippincott's illustrated reviews. Philadelphia: Lippincott Williams & Wilkins; and Golan, D. E. (2008). *Principles of pharmacology: the pathophysiologic basis of drug therapy*. Philadelphia, Pa., [etc.]: Lippincott Williams & Wilkins.

In another embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject in a pharmaceutical formulation.

A "pharmaceutical composition" refers to a chemical or biological composition suitable for administration to a mammal. Such compositions may be specifically formulated for administration via one or more of a number of routes, including but not limited to buccal, epicutaneous, epidural, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal, preferably intravenous. In addition, administration can occur by means of injection, powder, liquid, gel, drops, or other means of administration.

A "pharmaceutical excipient" or a "pharmaceutically acceptable excipient" is a carrier, usually a liquid, in which an active therapeutic agent is formulated. In one embodiment of the invention, the active therapeutic agent is a humanized antibody described herein, or one or more fragments thereof. The excipient generally does not provide any pharmacological activity to the formulation, though it may provide chemical and/or biological stability, and release characteristics. Exemplary formulations can be found, for example, in Remington's Pharmaceutical Sciences, 19th Ed., Grennaro, A., Ed., 1995 which is incorporated by reference.

As used herein "pharmaceutically acceptable carrier" or "excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, or sublingual administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders 10 for the extemporaneous preparation of sterile injectable solutions or dispersions. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Pharmaceutical compositions typically must be sterile and stable under the conditions of manufacture and storage. The 20 invention contemplates that the pharmaceutical composition is present in lyophilized form. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The invention further contemplates the inclusion of a stabilizer in the pharmaceutical composition. The proper fluidity can be maintained, for example, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged 35 absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the alkaline polypeptide can be formulated in a time release formulation, for example in a composition which includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers 40 can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

An exemplary composition comprises, consists essentially of, or consists of an anti-CGRP antibody or fragment thereof (e.g., Ab6), an excipient such as histidine, an isotonic agent such as sorbitol, and a surfactant such as polysorbate 80 in an aqueous solution. For example, the composition 50 may comprise, consist essentially of, or consist of histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody (e.g., Ab6), about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8, or approximately that constitution, e.g., within 10% of those values, within 5% of those values, within 1% of those values, within 0.5% of those values, or within 0.10% of those values, and water. For example, the pH value may be within 10% of 5.8, i.e., between 5.22 and 6.38. The Ab6 antibody may comprise or consist of the variable light and heavy chain polypeptides of SEQ ID NO: 222 and SEQ ID NO: 202 respectively, or the light and heavy chain polypep-

tides of SEQ ID NO: 221 and SEQ ID NO: 201 respectively, or the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 566 respectively. The composition may be in the form of an aqueous solution, or a concentrate (e.g., lyophilized) which when reconstituted, e.g., by addition of water, yields the aforementioned constitution. An exemplary composition consists of, per mL, 100 mg of the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 201 respectively, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, and water Q.S., or approximately that constitution, e.g., within 10% of those quantities, within 5% of those quantities, within 1% of those quantities, within 0.5% of those quantities, or within 0.1% of those quantities. Another exemplary composition consists of, per mL, 100 mg of the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 566 respectively, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, and water Q.S., or approximately that constitution, e.g., within 10% of those quantities, within 5% of those quantities, within 1% of those quantities, within 0.5% of those quantities, or within 0.1% of those quantities. The composition may be suitable for intravenous or subcutaneous administration, preferably intravenous administration. For example, the composition may be suitable for mixing with an intravenous solution (such as 0.9% sodium chloride) at an amount of between about 100 mg and about 300 mg antibody added to 100 mL of intravenous solution. Preferably the composition may be shelf-stable for at least 1, 3, 6, 12, 18, or 24 months, e.g., showing formation of aggregates of no more than 5% or no more than 10% of the antibody or fragment after storage at room temperature or when refrigerated at 4° C. for the specified duration, or in an accelerated aging test that simulates storage for that duration.

For each of the recited embodiments, the compounds can be administered by a variety of dosage forms. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, powders, granules, particles, microparticles, dispersible granules, cachets, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, injectables (including subcutaneous, intramuscular, intravenous, and intradermal, preferably intravenous), infusions, and combinations thereof.

The above description of various illustrated embodiments of the invention is not intended to be exhaustive or to limit the invention to the precise form disclosed. While specific embodiments of, and examples for, the invention are described herein for illustrative purposes, various equivalent modifications are possible within the scope of the invention, as those skilled in the relevant art will recognize. The teachings provided herein of the invention can be applied to other purposes, other than the examples described above.

These and other changes can be made to the invention in light of the above detailed description. In general, in the following claims, the terms used should not be construed to limit the invention to the specific embodiments disclosed in the specification and the claims. Accordingly, the invention is not limited by the disclosure, but instead the scope of the invention is to be determined entirely by the following claims.

The invention may be practiced in ways other than those particularly described in the foregoing description and examples. Numerous modifications and variations of the

invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

Certain CGRP antibody polynucleotides and polypeptides are disclosed in the sequence listing accompanying this patent application filing, and the disclosure of said sequence listing is herein incorporated by reference in its entirety.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is herein incorporated by reference in their entireties.

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the subject invention, and are not intended to limit the scope of what is regarded as the invention. Efforts have been made to ensure accuracy with respect to the numbers used (e.g. amounts, temperature, concentrations, etc.) but some experimental errors and deviations should be allowed for. Unless otherwise indicated, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees centigrade; and pressure is at or near atmospheric.

ADDITIONAL EXEMPLARY EMBODIMENTS

Additional exemplary embodiments of the invention are provided as follows:

S1. Use of an anti-CGRP antibody for the manufacturing of a medicament for treating acute migraine, comprising administering to a patient an anti-CGRP antibody while the patient has a headache and within 30 hours of headache onset, preferably within 24 hours of headache onset.

S2. Use of the anti-CGRP antibody of embodiment 1, wherein the medicament is for administration within 18 hours, within 12 hours, within 6 hours, within 5 hours, within 4 hours, within 3 hours, within 2 hours, or within 1 hour of headache onset, such as between 1-6 hours from headache onset.

S3. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is for intravenous or subcutaneous infusion.

S4. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is for intravenous infusion.

S5. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient is headache free 2 hours post-completion of administration or infusion.

S6. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient is free from the most bothersome symptom (MBS) at 2 hours post-completion of administration or infusion.

S7. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the administration of said medicament improves one or more of the following: time to pain relief; time to pain freedom; headache pain freedom at 2 hours with sustained headache pain freedom for 24 and 48 hours post completion of infusion; use of rescue medication by 24 hours and by 48 hours post completion of infusion; absence of photophobia at 2 hours post completion of infusion; absence of phonophobia at 2 hours post completion of infusion; absence of nausea at 2 hours post completion of infusion; change from baseline in Headache Impact Test (HIT-6) at Week 4; or change from baseline in Migraine Treatment Optimization Questionnaire-6 (MTOQ-6) at Week 4.

47

S8. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises any one of Ab1-Ab14.

S9. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises Ab6.

S10. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively.

S11. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively.

S12. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

S13. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

S14. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

S15. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

S16. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

S17. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

S18. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

S19. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

S20. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

S21. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

48

S22. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

S23. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

S24. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

S25. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

S26. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

S27. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

S28. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is between about 100 mg and about 300 mg, or is about 100 mg, or is about 300 mg.

S29. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is 100 mg.

S30. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is for intravenous administration in a dosage of 100 mg of said anti-CGRP antibody every 10^{-14} weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

S31. Use of the anti-CGRP antibody of any one of the foregoing embodiments S1-S29, wherein said medicament is for intravenous administration in a dosage of 300 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

S32. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient suffers from medication overuse headache.

S33. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits between 1-10 migraine attacks per month in the month or in the 3 months prior to administration.

S34. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits between 2-8 migraine attacks per month in the month or in the 3 months prior to administration.

S35. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits between 3-7 migraine attacks per month in the month or in the 3 months prior to administration.

S36. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits less than 25 headache days per month in the month or in the 3 months prior to administration.

S37. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of

said medicament, the patient exhibits less than 20 headache days per month in the month or in the 3 months prior to administration.

S38. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits less than 15 headache days per month in the month or in the 3 months prior to administration.

S39. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits less than 10 headache days per month in the month or in the 3 months prior to administration.

S40. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 10 years prior to administration of said medicament.

S41. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 15 years prior to administration of said medicament.

S42. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to administration of said medicament.

S43. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

S44. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

S45. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

S46. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

S47. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

S48. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

S49. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is further for administration in a second dose of said anti-CGRP antibody about 10-14 weeks, preferably 11-13 weeks, more preferably about 12 weeks or about 3 months after administration of said medicament.

S50. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament comprises about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

S51. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody is aglycosylated or if glycosylated only contains only mannose residues.

S52. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

S53. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

S54. Use of the anti-CGRP antibody of any one of the embodiments S7-S53, wherein said rescue medication comprises one or more of a triptan, non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic), a combination of two or more drug classes, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone, and/or wherein said combination of two or more drug class optionally comprises two drugs with analgesic effects (for example, paracetamol and codeine) or acting as adjuvants (for example, caffeine), optionally wherein said combination-analgesics combine non-opioid analgesic includes at least one opioid (such as tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital and/or caffeine.

S55. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said headache or said migraine is diagnosed according to the third edition of the International Classification of Headache Disorders.

S56. Use of the anti-CGRP antibody of any of any one of the foregoing embodiments, wherein said anti-CGRP antibody is expressed in or obtained by expression in *Pichia pastoris*.

S57. Use of the anti-CGRP antibody of any of any one of the embodiments S1-S55, wherein said anti-CGRP antibody is expressed in or obtained by expression in CHO cells.

S58. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

S59. Use of the anti-CGRP antibody of embodiment S58, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-10% of said values, and having a pH of 5.8 or within +/-10% of said value.

S60. Use of the anti-CGRP antibody of embodiment S58, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-5% of said values, and/or having a pH of 5.8 or within +/-5% of said value.

51

S61. Use of the anti-CGRP antibody of embodiment S58, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-1% of said values, and/or having a pH of 5.8 or within +/-1% of said value.

S62. Use of the anti-CGRP antibody of embodiment S58, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-0.5% of said values, and/or having a pH of 5.8 or within +/-0.5% of said value.

S63. Use of the anti-CGRP antibody of embodiment S58, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-0.1% of said values, and/or having a pH of 5.8 or within +/-0.1% of said value.

S64. Use of an anti-CGRP antibody for the manufacture of a medicament for treating chronic migraine, wherein said medicament is for intravenous administration in a first dosage comprising between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein in the first 24 hours after administration of said first dosage the patient exhibits at least a 50% reduction in migraine prevalence.

S65. Use of an anti-CGRP antibody for the manufacture of a medicament for treating chronic migraine, wherein said medicament is for intravenous administration in a first dosage comprising between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein on the first day following the day of administration the patient exhibits at least a 50% reduction in migraine prevalence.

S66. Use of the anti-CGRP antibody of embodiment S64 or embodiment S65, wherein the first dosage of said anti-CGRP antibody is 100 mg.

S67. Use of the anti-CGRP antibody of embodiment S64 or embodiment S65, wherein the first dosage of said anti-CGRP antibody is 300 mg.

S68. Use of the anti-CGRP antibody of embodiment S64, S65, or S66, wherein said medicament is for intravenous administration in a dosage of 100 mg of said anti-CGRP antibody every 10-14 weeks, preferably 11-13 weeks, more preferably every 12 weeks.

S69. Use of the anti-CGRP antibody of embodiment S64, S65, or S67, wherein said medicament is for intravenous administration in a dosage of 300 mg of said anti-CGRP antibody every 10-14 weeks, preferably 11-13 weeks, more preferably every 12 weeks.

S70. Use of the anti-CGRP antibody of any one of embodiments S64-S69 wherein, prior to said first dosage, the patient exhibits between about 10 and about 22 migraine days per month.

S71. Use of the anti-CGRP antibody of any one of embodiments S64-S70 wherein, prior to said first dosage, the patient exhibits between about 13 and about 19 migraine days per month.

S72. Use of the anti-CGRP antibody of any one of embodiments S64-S71 wherein, prior to said first dosage, the patient exhibits about 16 migraine days per month.

52

S73. Use of the anti-CGRP antibody of any one of embodiments S64-S72 wherein, prior to said first dosage, the patient exhibits between about 14 and about 27 headache days per month.

S74. Use of the anti-CGRP antibody of any one of embodiments S64-S73 wherein, prior to said first dosage, the patient exhibits between about 17 and about 24 headache days per month.

S75. Use of the anti-CGRP antibody of any one of embodiments S64-S74 wherein, prior to said first dosage, the patient exhibits about 20 or about 21 headache days per month.

S76. Use of the anti-CGRP antibody of any one of embodiments S64-S75 wherein said patient was diagnosed with migraine at least 10 years prior to said first dosage.

S77. Use of the anti-CGRP antibody of any one of embodiments S64-S76 wherein said patient was diagnosed with migraine at least 15 years prior to said first dosage.

S78. Use of the anti-CGRP antibody of any one of embodiments S64-S77 wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to said first dosage.

S79. Use of the anti-CGRP antibody of any one of embodiments S64-S78 wherein said patient was diagnosed with chronic migraine at least 5 years prior to said first dosage.

S80. Use of the anti-CGRP antibody of any one of embodiments S64-S79 wherein said patient was diagnosed with chronic migraine at least 8 years prior to said first dosage.

S81. Use of the anti-CGRP antibody of any one of embodiments S64-S80 wherein said patient was diagnosed with chronic migraine at least 11 or at least 12 years prior to said first dosage.

S82. Use of the anti-CGRP antibody of any one of embodiments S64-S81 wherein said medicament is for administration of said first dosage when the patient has a headache.

S83. Use of the anti-CGRP antibody of any one of embodiments S64-S82 wherein said medicament is for administration of said first dosage when the patient has a migraine.

S84. Use of the anti-CGRP antibody of any one of embodiments S64-S83 wherein said medicament is for administration of said first dosage when the patient has a migraine with aura.

S85. Use of the anti-CGRP antibody of any one of embodiments S64-S84, wherein said patient has a reduction in the number of migraine days by at least 50% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

S86. Use of the anti-CGRP antibody of any one of embodiments S64-S85, wherein said patient has a reduction in the number of migraine days by at least 75% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

S87. Use of the anti-CGRP antibody of any one of embodiments S64-S86, wherein said patient has a reduction in the number of migraine days by 100% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

S88. Use of the anti-CGRP antibody of any one of embodiments S64-S87, wherein said patient has a reduction in the number of migraine days by at least 50% in the 12

week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

S89. Use of the anti-CGRP antibody of any one of embodiments S64-S88, wherein said patient has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

S90. Use of the anti-CGRP antibody of any one of embodiments S64-S89, wherein said patient has a reduction in the number of migraine days by 100% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

S91. Use of the anti-CGRP antibody of any one of embodiments S64-S90, further comprising administering a second dose of said anti-CGRP antibody to said patient about 12 weeks or about 3 months after said first dose.

S92. Use of the anti-CGRP antibody of any one of embodiments S64-S91, wherein said first dose comprises about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

S93. Use of the anti-CGRP antibody of any one of embodiments S64-S92, wherein said anti-CGRP antibody or antibody fragment is aglycosylated or if glycosylated only contains only mannose residues.

S94. Use of the anti-CGRP antibody of any one of embodiments S64-S93, wherein said anti-CGRP antibody consists of the light chain polypeptide of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

S95. Use of the anti-CGRP antibody of any of any one of embodiments S64-S94, wherein said anti-CGRP antibody is expressed in or obtained by expression in *Pichia pastoris*.

S96. Use of the anti-CGRP antibody of any of any one of embodiments S64-S94, wherein said anti-CGRP antibody is expressed in or obtained by expression in CHO cells.

S97. Use of the anti-CGRP antibody of any one of embodiments S64-S96, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

S98. Use of the anti-CGRP antibody of embodiment S97, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-10% of said values, and having a pH of 5.8 or within +/-10% of said value.

S99. Use of the anti-CGRP antibody of embodiment S97, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-5% of said values, and/or having a pH of 5.8 or within +/-5% of said value.

S100. Use of the anti-CGRP antibody of embodiment S97, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-1% of said values, and/or having a pH of 5.8 or within +/-1% of said value.

S101. Use of the anti-CGRP antibody of embodiment S97, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or

having amounts of each constituent within +/-0.5% of said values, and/or having a pH of 5.8 or within +/-0.5% of said value.

S102. Use of the anti-CGRP antibody of embodiment S97, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-0.1% of said values, and/or having a pH of 5.8 or within +/-0.1% of said value.

FURTHER EXEMPLARY EMBODIMENTS

Further exemplary embodiments of the invention are provided as follows:

E1. An anti-CGRP antibody for use in treating acute migraine while the patient has a headache and within 30 hours of headache onset, preferably within 24 hours of headache onset.

E2. The anti-CGRP antibody for use of embodiment E1, wherein the anti-CGRP antibody is for administration within 18 hours, within 12 hours, within 6 hours, within 5 hours, within 4 hours, within 3 hours, within 2 hours, or within 1 hour of headache onset, such as between 1-6 hours from headache onset.

E3. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody is for intravenous or subcutaneous infusion.

E4. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody is for intravenous infusion.

E5. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient is headache free 2 hours post-completion of administration or infusion.

E6. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient is free from the most bothersome symptom (MBS) at 2 hours post-completion of administration or infusion.

E7. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein the administration of said anti-CGRP antibody improves one or more of the following: time to pain relief, time to pain freedom; headache pain freedom at 2 hours with sustained headache pain freedom for 24 and 48 hours post completion of infusion; use of rescue medication by 24 hours and by 48 hours post completion of infusion; absence of photophobia at 2 hours post completion of infusion; absence of phonophobia at 2 hours post completion of infusion; absence of nausea at 2 hours post completion of infusion; change from baseline in Headache Impact Test (HIT-6) at Week 4; or change from baseline in Migraine Treatment Optimization Questionnaire-6 (MTOQ-6) at Week 4.

E8. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises any one of Ab1-Ab14.

E9. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises Ab6.

E10. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively.

E11. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide

sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively.

E12. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

E13. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

E14. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

E15. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

E16. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

E17. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

E18. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

E19. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

E20. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

E21. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

E22. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

E23. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

E24. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

E25. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

E26. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

E27. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

E28. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is between about 100 mg and about 300 mg, or is about 100 mg, or is about 300 mg.

E29. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is 100 mg.

E30. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody is for intravenous administration in a dosage of 100 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

E31. The anti-CGRP antibody for use of any one of the embodiments E1-E29, wherein said anti-CGRP antibody is for intravenous administration in a dosage of administering 300 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

E32. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient suffers from medication overuse headache.

E33. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits between 1-10 migraine attacks per month in the month or in the 3 months prior to administration.

E34. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits between 2-8 migraine attacks per month in the month or in the 3 months prior to administration.

E35. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits between 3-7 migraine attacks per month in the month or in the 3 months prior to administration.

E36. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits less than 25 headache days per month in the month or in the 3 months prior to administration.

E37. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits less than 20 headache days per month in the month or in the 3 months prior to administration.

E38. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits less than 15 headache days per month in the month or in the 3 months prior to administration.

E39. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits less than 10 headache days per month in the month or in the 3 months prior to administration.

E40. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 10 years prior to the administration of said anti-CGRP antibody.

E41. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 15 years prior to the administration of said anti-CGRP antibody.

E42. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to the administration of said anti-CGRP antibody.

E43. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

E44. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

E45. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

E46. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

E47. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

E48. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

E49. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said use comprises administering a second dose of said anti-CGRP antibody to said patient about 10-14 weeks, preferably 11-13 weeks, more preferably about 12 weeks or about 3 months after the administration of said anti-CGRP antibody.

E50. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said use comprises administering about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

E51. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody is aglycosylated or if glycosylated only contains only mannose residues.

E52. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

E53. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

E54. The anti-CGRP antibody for use of any one of the foregoing embodiments E7-E53, wherein said rescue medication comprises one or more of a triptan, non-opioid analgesics (such as paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic), a combination of two or more drug classes, wherein said triptan use optionally comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, and/or wherein said opioid use optionally comprises use of one or more of oxycodone,

tramadol, butorphanol, morphine, codeine, and hydrocodone, and/or wherein said combination of two or more drug class optionally comprises two drugs with analgesic effects (for example, paracetamol and codeine) or acting as adjuvants (for example, caffeine), optionally wherein said combination-analgesics combine non-opioid analgesic includes at least one opioid (such as tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital and/or caffeine.

E55. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said headache or said migraine is diagnosed according to the third edition of the International Classification of Headache Disorders.

E56. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody is expressed in or obtained by expression in *Pichia pastoris*.

E57. The anti-CGRP antibody for use of any one of the foregoing embodiments E1-E55, wherein said anti-CGRP antibody is expressed in or obtained by expression in CHO cells.

E58. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

E59. The anti-CGRP antibody for use of embodiment E58, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-10% of said values, and having a pH of 5.8 or within +/-10% of said value.

E60. The anti-CGRP antibody for use of embodiment E58, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-5% of said values, and/or having a pH of 5.8 or within +/-5% of said value.

E61. The anti-CGRP antibody for use of embodiment E58, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or

59

having amounts of each constituent within +/-1% of said values, and/or having a pH of 5.8 or within +/-1% of said value.

E62. The anti-CGRP antibody for use of embodiment E58, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-0.5% of said values, and/or having a pH of 5.8 or within +/-0.5% of said value.

E63. The anti-CGRP antibody for use of embodiment E58, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-0.1% of said values, and/or having a pH of 5.8 or within +/-0.1% of said value.

E64. An anti-CGRP antibody for use in treating chronic migraine, wherein said antibody is for intravenous administration in a first dosage comprising between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein in the first 24 hours after administration of said first dosage the patient exhibits at least a 50% reduction in migraine prevalence.

E65. An anti-CGRP antibody for use in treating chronic migraine, wherein said antibody is for intravenous administration in a first dosage comprising between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein on the first day following the day of administration the patient exhibits at least a 50% reduction in migraine prevalence.

E66. The anti-CGRP antibody for use of embodiment E64 or embodiment E65, wherein the first dosage of said anti-CGRP antibody is 100 mg.

E67. The anti-CGRP antibody for use of embodiment E64 or embodiment E65, wherein the first dosage of said anti-CGRP antibody is 300 mg.

E68. The anti-CGRP antibody for use of embodiment E64, E65, or E66, wherein said anti-CGRP antibody is for intravenous administration in a dosage of 100 mg of said anti-CGRP antibody every 10-14 weeks, preferably 11-13 weeks, more preferably every 12 weeks.

E69. The anti-CGRP antibody for use of embodiment E64, E65, or E67, wherein said anti-CGRP antibody is for intravenous administration in a dosage of 300 mg of said anti-CGRP antibody every 10-14 weeks, preferably 11-13 weeks, more preferably every 12 weeks.

E70. The anti-CGRP antibody for use of any one of embodiments E64-E69 wherein, prior to said first dosage, the patient exhibits between about 10 and about 22 migraine days per month.

E71. The anti-CGRP antibody for use of any one of embodiments E64-E70 wherein, prior to said first dosage, the patient exhibits between about 13 and about 19 migraine days per month.

E72. The anti-CGRP antibody for use of any one of embodiments E64-E71 wherein, prior to said first dosage, the patient exhibits about 16 migraine days per month.

E73. The anti-CGRP antibody for use of any one of embodiments E64-E72 wherein, prior to said first dosage, the patient exhibits between about 14 and about 27 headache days per month.

60

E74. The anti-CGRP antibody for use of any one of embodiments E64-E73 wherein, prior to said first dosage, the patient exhibits between about 17 and about 24 headache days per month.

E75. The anti-CGRP antibody for use of any one of embodiments E64-E74 wherein, prior to said first dosage, the patient exhibits about 20 or about 21 headache days per month.

E76. The anti-CGRP antibody for use of any one of embodiments E64-E75 wherein said patient was diagnosed with migraine at least 10 years prior to said first dosage.

E77. The anti-CGRP antibody for use of any one of embodiments E64-E76 wherein said patient was diagnosed with migraine at least 15 years prior to said first dosage.

E78. The anti-CGRP antibody for use of any one of embodiments E64-E77 wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to said first dosage.

E79. The anti-CGRP antibody for use of any one of embodiments E64-E78 wherein said patient was diagnosed with chronic migraine at least 5 years prior to said first dosage.

E80. The anti-CGRP antibody for use of any one of embodiments E64-E79 wherein said patient was diagnosed with chronic migraine at least 8 years prior to said first dosage.

E81. The anti-CGRP antibody for use of any one of embodiments E64-E80 wherein said patient was diagnosed with chronic migraine at least 11 or at least 12 years prior to said first dosage.

E82. The anti-CGRP antibody for use of any one of embodiments E64-E81 wherein said anti-CGRP antibody is for administration of said first dosage when the patient has a headache.

E83. The anti-CGRP antibody for use of any one of embodiments E64-E82 wherein said anti-CGRP antibody is for administration of said first dosage when the patient has a migraine.

E84. The anti-CGRP antibody for use of any one of embodiments E64-E83 wherein said anti-CGRP antibody is for administration of said first dosage when the patient has a migraine with aura.

E85. The anti-CGRP antibody for use of any one of embodiments E64-E84, wherein said patient has a reduction in the number of migraine days by at least 50% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

E86. The anti-CGRP antibody for use of any one of embodiments E64-E85, wherein said patient has a reduction in the number of migraine days by at least 75% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

E87. The anti-CGRP antibody for use of any one of embodiments E64-E86, wherein said patient has a reduction in the number of migraine days by 100% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

E88. The anti-CGRP antibody for use of any one of embodiments E64-E87, wherein said patient has a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

61

E89. The anti-CGRP antibody for use of any one of embodiments E64-E88, wherein said patient has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

E90. The anti-CGRP antibody for use of any one of embodiments E64-E89, wherein said patient has a reduction in the number of migraine days by 100% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

E91. The anti-CGRP antibody for use of any one of embodiments E64-E90, further comprising administering a second dose of said anti-CGRP antibody to said patient about 12 weeks or about 3 months after said first dose.

E92. The anti-CGRP antibody for use of any one of embodiments E64-E91, wherein said first dose comprises about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

E93. The anti-CGRP antibody for use of any one of embodiments E64-E92, wherein said anti-CGRP antibody or antibody fragment is glycosylated or if glycosylated only contains only mannose residues.

E94. The anti-CGRP antibody for use of any one of embodiments E64-E93, wherein said anti-CGRP antibody consists of the light chain polypeptide of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

E95. The anti-CGRP antibody for use of any one of embodiments E64-E94, wherein said anti-CGRP antibody is expressed in or obtained by expression in *Pichia pastoris*.

E96. The anti-CGRP antibody for use of any one of embodiments E64-E94, wherein said anti-CGRP antibody is expressed in or obtained by expression in CHO cells.

E97. The anti-CGRP antibody for use of any one of embodiments E64-E96, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

E98. The anti-CGRP antibody for use of embodiment E97, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-10% of said values, and having a pH of 5.8 or within +/-10% of said value.

E99. The anti-CGRP antibody for use of embodiment E97, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-5% of said values, and/or having a pH of 5.8 or within +/-5% of said value.

E100. The anti-CGRP antibody for use of embodiment E97, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-1% of said values, and/or having a pH of 5.8 or within +/-1% of said value.

E101. The anti-CGRP antibody for use of embodiment E97, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or

62

having amounts of each constituent within +/-0.5% of said values, and/or having a pH of 5.8 or within +/-0.5% of said value.

E102. The anti-CGRP antibody for use of embodiment E97, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-0.1% of said values, and/or having a pH of 5.8 or within +/-0.1% of said value.

EXAMPLES

The following examples are provided in order to illustrate the invention, but are not to be construed as limiting the scope of the claims in any way.

Example 1

Preparation of Antibodies that Bind CGRP

The preparation of exemplary anti-CGRP antibodies Ab1-Ab14 having the sequences in FIGS. 1A-12 is disclosed in commonly owned PCT Application WO/2012/162243, published on Nov. 29, 2012, the contents of which are incorporated by reference herein. This application exemplifies synthesis of these antibodies in *Pichia pastoris* cells. The present Applicant further contemplates synthesis of anti-CGRP antibodies Ab1-Ab14, and Ab6 in particular in CHO cells.

Example 2

Human Clinical Study Evaluating the Safety and Efficacy of an Anti-CGRP Antibody According to the Invention Clinical Treatment Protocol

The humanized anti-CGRP IgG1 antibody identified herein as Ab6 was assessed in human subjects for its ability to inhibit, alleviate or prevent the number of, duration, and/or the intensity of migraine episodes. The Ab6 antibody contains the V_L and light chain polypeptides respectively in SEQ ID NO: 222 and SEQ ID NO: 221, and contains the V_H and heavy chain polypeptides respectively in SEQ ID NO: 202 and SEQ ID NO: 201. This antibody comprises an IgG1 constant region that contains a mutation in the heavy chain constant region (replacement of asparagine residue at position 297 with an alanine residue which substantially eliminates glycosylation and lytic activity (see U.S. Pat. No. 5,624,821).

Specifically, the clinical efficacy of the Ab6 antibody was tested in a placebo controlled double-blind, randomized study. The individuals in the study were all selected based on specific criteria. Particularly all were diagnosed as migraine sufferers at ≤ 50 years of age (ICHD-II, 2004 Section 1), and further had a history of migraine ≥ 12 months with ≥ 5 and ≤ 14 migraine days in each 28 day period in the 3 months prior to screening.

Further, all of the individuals in the study used acute migraine medications ≤ 14 days per 28 day period and, within those days, ≤ 10 days of triptan use per 28 day period in the 3 months prior to screening and the 28 day period of completion of eDiary prior to randomization.

Table 1 summarizes the demographic characteristics of the study population.

TABLE 1

Characteristic	Placebo iv (n = 82)	Ab6 1000 mg iv (n = 81)
Mean ± SD Age (years)	39.0 (9.6)	38.6 (10.8)
Mean ± SD Weight (kg)	75.4 (14.4)	75.0 (16.5)
Female Gender	66 (80%)	67 (83%)
Race:		
Caucasian	66 (80.5%)	66 (81.5%)
African American	9 (11.0%)	10 (12.4%)
Asian	3 (3.7%)	4 (5.0%)
Other	4 (4.8%)	1 (1.1%)
Baseline (per 28 days):		
Mean ± SD Migraine Days	8.8 (2.7)	8.4 (2.1)
Mean ± SD Migraine Episodes	6.7 (2.4)	6.0 (2.2)
Mean ± SD Headache Frequency	9.6 (2.8)	9.2 (2.6)
Mean ± SD Migraine Hours	72.2 (51.0)	80.1 (49.1)
Mean ± SD HIT-6 Score	64.5 (4.44)	63.8 (5.21)
Mean ± SD MSQ RFP Score	49.0 (17.9)	49.5 (21.2)
Mean ± SD MSQ RFR Score	61.9 (22.7)	63.9 (24.0)
Mean ± SD MSQ EF Score	59.5 (22.9)	59.8 (27.0)

Throughout the study all of the individuals were required to record their migraine status daily using an e-diary. In the e-diary the subjects in the study were required to record the number of migraine days/month, migraine episodes/month, migraine hours/month, migraine severity, and the use of any abortive medicine such as triptans.

In addition, the study participants were required to use the e-diary to record their migraine status in the 28 day period prior to treatment with antibody or placebo in order to establish a migraine day/hour/episode baseline per month. Also, this allowed the subjects in the study to become familiar with the use of the e-diary.

After the 28-day run-in the subjects in the study were broken into two groups, each including 80 subjects (FIG. 17). In the first group, i.e., the antibody treatment group, (n=80) each subject in the group was administered intravenously a single 1000 mg dose of Ab6. In the second group (n=80), i.e., the placebo group, each of the subjects was given an intravenous injection containing only the aqueous antibody carrier solution.

The individuals in the treated and placebo groups were assessed in the 24 weeks post-dose administration. Initially, a 12 week interim analysis was conducted. Subsequent to the 12 week interim analysis, a refined analysis was conducted. This refined analysis potentially included, for example, addition or removal of patient data in accord with the study protocol, e.g., updating data that had not been fully loaded from the e-diaries. This refinement resulted in slight changes but did not alter the overall conclusions.

The efficacy of the antibody versus the placebo was assessed in part based on the recorded data in the e-diary entries. For example, this analysis included a comparison of the number of recorded migraine days/month, migraine episodes/month, migraine hours/month in the subjects in the treated versus the placebo group. The percentage of responders in each group (i.e., the subjects with 50%, 75%, and 100% reduction in migraine days) in both groups was also compared.

In addition, the responses of the Ab6- and placebo-treated subjects in both groups to MSQ and HIT-6 questionnaires are to be evaluated and compared. MSQ is a frequently utilized disease-specific tool to assess the impact of migraine on health-related quality of life (HRQL). MSQ comprises a 16-item Migraine-Specific Quality-of-Life Questionnaire

(Version 1.0), which was developed by Glaxo Wellcome Inc. MSQ is hypothesized to measure 3 parameters: (i) Role Function-Restrictive; (ii) Role Function-Preventive; and (iii) Emotional Function.

The HIT-6 or functional impact (also called the Headache Impact Test or HIT-6) similarly is a well known tool for assessing migraine intensity. This test uses six questions to capture the impact of headache and its treatment on an individual's functional health and well-being.

Also, the pharmacokinetic (PK) properties of the CGRP antibody and immunogenicity are to be assessed in the Ab6 antibody treated subjects.

Clinical Results and Analysis

The results of this human clinical trial and analysis through week 12 in the treated subjects are summarized in the Table 2 below.

TABLE 2

Time period	% reduction migraine days	Responder analysis for migraine days		P value
		Placebo iv	Ab6 1000 mg iv	
Week 1-4	n = 80	n = 75		
	50	40 (50.0)	58 (77.3)	p = 0.0005
	75	19 (23.8)	39 (52.0)	p = 0.0005
Week 5-8	100	4 (5.0)	21 (28.0)	p = 0.0001
	n = 80	n = 78		
	50	43 (53.8)	59 (75.6)	p = 0.0048
Week 9-12	75	28 (35.0)	35 (44.9)	p = 0.2555
	100	12 (15.0)	21 (26.9)	p = 0.0791
	n = 77	n = 72		
	50	51 (66.2)	54 (75.0)	p = 0.2827
	75	24 (31.2)	38 (52.8)	p = 0.0083
	100	13 (16.9)	29 (40.3)	p = 0.0019

In addition, the results of the clinical study were compared based on the number of responders in the treatment and placebo groups. As shown in FIG. 13 the number of subjects who showed a 50, 75 or 100% reduction in migraine days for each month of the interim period were compared in the treatment and placebo groups. As shown in the figure, 60% of the Ab6-treated group had at least 50% reduction in headache days, 310% of the Ab6-treated group had at least 75% reduction in headache days and 15% of the Ab6 treated group had 100% reduction in headache days.

By contrast, 33% of the placebo-treated group had at least 50% reduction in headache days, 9% of the placebo-treated group had at least 75% reduction in headache days, and 0% (none) of the placebo-treated group had 100% reduction in headache days.

These results clearly show that the reduction in the number of migraine days was much greater in the Ab6-treated group. But for the significant placebo effect, the difference in these numbers would have been more pronounced. (Elevated placebo effect is not surprising as the phenomenon is often very high for migraine and other neurological drugs).

In addition, the % change from baseline in the number of migraine days per month in the placebo and Ab6-treated group was compared. As shown in FIG. 14, the median (\pm QR) % change from baseline in the number of migraine days per month in the placebo and Ab6-treated group was compared for the 2 groups during the 12 weeks post-treatment. These results which are statistically significant (p=0.0078) clearly show the Ab6-treated group had a much greater reduction in the number of headache days per month compared to baseline than the placebo-treated group.

Also, the % change from baseline in the number of migraine episodes per month in the placebo and Ab6-treated group was compared. As shown in FIG. 15 the median (\pm QR) % change from baseline in the number of migraine episodes per month in the placebo and Ab6-treated group was compared during the 12 weeks post-treatment. These results indicate that the Ab6-treated group had a significantly greater reduction in the number of migraine episodes per month compared to baseline than the placebo-treated group.

Further, the % change from baseline in the number of migraine hours per month in the placebo and Ab6-treated group was compared. As shown in FIG. 16, the median (\pm QR) % change from baseline in the number of migraine hours per month in the placebo and Ab6-treated group was compared for the 2 groups during the 12 weeks post-treatment. These results clearly show the Ab6-treated group had a greater reduction in the number of migraine hours per month compared to baseline than the placebo-treated group.

In addition, the HIT-6 results were compared for both groups. As noted, this questionnaire finds well accepted usage in assessing the migraine status of individuals with frequent/chronic migraine. FIG. 18 compares the HIT-6 responder analysis for the Ab6-treated and placebo groups at baseline, week 4 after treatment, week 8 after treatment and week 12 after treatment. The results at each time point reveal that the Ab6-treated group had a statistically significant improvement in the HIT-6 scores relative to the placebo group, i.e., 54.4% for the Ab6-treated compared to 30% for the placebo at week 4 ($p=0.0023$), 51.3% for the Ab6-treated compared to 38.0% for the placebo at week 8 ($p=0.1094$) and 61.1% for the Ab6-treated compared to 33.3% for the placebo at week 12 ($p=0.0007$). FIG. 19 shows the percentage of patients having a HIG-6 score of some or little/none over time in the placebo and Ab6 treatment groups (statistical significance a shown).

In addition, FIG. 20 contains the pharmacokinetic (PK) profile for Ab6 administered intravenously at a single dosage of 1000 mg in mg/mL over the 24 week period following Ab6 administration.

FIG. 21 contains plasma-free pharmacokinetic (PK) parameters N (number of patients), mean, and standard deviation (SD) for a single 1000 mg intravenous dosage of Ab6. The parameters shown in the table and the units are C_{max} (μ g/mL), $AUC_{0-\infty}$ (mg*hr/mL), half-life (days), V_z (L) and C_L (mL/hr).

Further analysis was conducted for patient data between 12-weeks and 24-weeks. The treatment group continued to exhibit decreased migraine days relative to the control group, however, the magnitude of the difference decreased over time. Additionally, the control group exhibited fewer migraine days per month than at baseline. This was thought to result at least in part from “diary fatigue” wherein patients potentially report no migraine on a day in which a migraine actually occurred, in order to avoid the time and effort of answering further queries about the migraine that would result from giving an affirmative answer to the question of whether they had a migraine on a given day.

Further analysis of the study results are shown in FIGS. 22-33. These result include analysis of the change (mean/ \pm SEM) from baseline in migraine days per month for Ab6 (1000 mg i.v.) versus placebo (FIG. 22), change in average migraine days ($+/-$ SD) over time for the full analysis population (FIG. 23). Additionally, shown are the distribution of migraine days actual and change for the Ab6 treatment group during weeks 1-4 (FIG. 24), distribution of migraine days actual and change for the placebo group during weeks 1-4 (FIG. 25), distribution of migraine days

actual and change for the Ab6 treatment group during weeks 5-8 (FIG. 26), distribution of migraine days actual and change for the placebo group during weeks 5-8 (FIG. 27), distribution of migraine days actual and change for the Ab6 treatment group during weeks 9-12 (FIG. 28), and distribution of migraine days actual and change for the placebo group during weeks 9-12 (FIG. 29).

Responder rate analysis was also performed (FIGS. 30-32). These figures respectively show the 50%, 75%, and 100% responder rate for the Ab6 and placebo treatment groups. Subjects with $\geq 50\%$ reduction in migraine frequency were considered to be a 50% responder. Subjects with $\geq 75\%$ reduction in migraine frequency were considered to be a 75% responder. Likewise, subjects with 100% reduction in migraine frequency were considered to be a 100% responder.

In FIGS. 22 and 30-32, normalization was applied to visit intervals where eDiaries were completed for 21-27 days by multiplying the observed frequency by the inverse of the completion rate.

Migraine severity was also analyzed. FIG. 33 shows the mean migraine severity over time for the full analysis population. On the scale used, a mean migraine score of 3 represents “moderate pain.”

FIG. 34 summarizes the change from baseline in migraine days, migraine episodes, average migraine severity, headache frequency, and outcome measures including the HIT-6 score, MSQ (Migraine Specific Quality of Life Questionnaire) RFP (Role Function-Preventative), MSQ RFR (Role Function-Restrictive), and MSQ EF (Emotional Function).

Example 3

35 Human Clinical Study Evaluating the Safety and Efficacy of an Anti-CGRP Antibody in Chronic Migraine Patients

This example describes a randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of Ab6 for chronic migraine prevention. In the study, 40 1,072 patients were randomized to receive Ab6 (300 mg or 100 mg), or placebo administered by infusion once every 12 weeks. To be eligible for the trial, patients must have experienced at least 15 headache days per month, of which at least eight met criteria for migraine. Patients that participated in the trial had an average of 16.1 migraine days per month at baseline. Study endpoints included the mean change from baseline in monthly migraine days, reduction in migraine prevalence at day 1 and over days 1-28, and reduction of at least 50%, 75%, and 100% from baseline in mean monthly migraine days, change from baseline in mean monthly acute migraine-specific medication days, and reductions from baseline in patient-reported impact scores on the Headache Impact Test (HIT-6). The administered antibody, Ab6, is an anti-CGRP antibody consisting of the light chain polypeptide of SEQ ID NO: 221 and heavy chain polypeptide of SEQ ID NO: 201.

Patient characteristics are summarized in FIG. 39, with separate columns for patients receiving placebo, 100 mg of the antibody, or 300 mg of the antibody. Patients had a mean number of years from migraine diagnosis of between 17.0 and 19.0 years, a mean duration of suffering from chronic migraine of between 11.5 and 12.4 years, and between 44.3% and 45.2% of patients utilized at least one prophylactic medication. At baseline, in both antibody treatment groups the mean number of migraine days per month was 16.1, while for the placebo group, the mean number of migraine days per month was 16.2.

The reduction in a specified percentage (50%, 75%, or 100%) from baseline in mean monthly migraine days refers to the number or percentage of patients in a treatment group that exhibited the given percentage reduction in the number of migraine days per month. For example, a patient exhibiting 16 migraine days per month at baseline would be a 75% responder if the number of migraine days per month was decreased by at least 12 days per month over specified period.

The results are shown in FIGS. 35-39. FIG. 35 shows the percentages of patients with migraine in the 300 mg, 100 mg, and placebo treatment groups at days 1, 7, 14, 21, and 28. The uppermost line shows results for placebo, the lowest line shows results for the 300 mg dosage, and the middle line shows results for the 100 mg dosage.

As shown in FIG. 35, at day 1 the percentage reduction in migraine prevalence was 52% for the 300 mg dosage, 50% at the 100 mg dosage, and 27% for placebo. The decrease was statistically significant compared to the placebo group for both the 100 mg and 300 mg treatment groups.

FIGS. 36-38 show the percentage of patients in the 300 mg and 100 mg treatment groups achieving, respectively, 50%, 75%, and 100% reduction in migraine days in month 1, over months 1-3 (after the 1st infusion), and over months 4-5 (after the 2nd infusion). In each graph, the data bars, from left to right, show results for the 100 mg, 300 mg, and placebo groups. Statistical significance is as shown. ++ indicates a statistically significant difference from placebo; + indicates a statistically significant difference from placebo (unadjusted); and § indicates a statistically significant difference from placebo (post hoc).

Example 4

Baseline Subgroup Analysis for Human Clinical Studies Evaluating the Safety and Efficacy of an Anti-CGRP Antibody in Chronic or Episodic Migraine Patients

In the study of Chronic Migraine described in Example 3, at intake, each patient was assessed for potential medication overuse headache (MOH). MOH was present in 39.9% (139 patients) in the 100 mg treatment group, 42.0% (147 patients) in the 300 mg treatment group, and 39.6% (145 patients) in the placebo group. Assessment of the treatment outcomes in this patient subset indicated that treatment with the anti-CGRP antibody was efficacious for MOH (FIG. 41). Specifically, in the 100 mg treatment group, mean migraine days per month changed by -3.0 days (95% CI, -4.56 to -1.52 days) in the patients having MOH at baseline, compared to MOH patients receiving placebo. Similarly, in the 300 mg treatment group, mean migraine days per month changed by -3.2 days (95% CI, -4.66 to -1.78 days) in the patients having MOH at baseline, compared to MOH patients receiving placebo. By contrast, for patients without MOH at baseline, in the 100 mg treatment group, mean migraine days per month changed by -1.3 days (95% CI, -2.43 to -0.16 days), compared to patients without MOH at baseline receiving placebo. Likewise, for patients without MOH at baseline in the 300 mg treatment group, mean migraine days per month changed by -2.1 days (95% CI, -3.24 to -0.88 days), compared to patients without MOH at baseline receiving placebo. Efficacy for other subgroups was shown as well, including efficacy for patients with mean migraine day (MMD) frequency less than 17 days or greater than or equal to 17 days, patients with an age at diagnosis of less than or equal to 21 years or greater than 21 years, patients having a duration of migraine of less than or equal to 15 year or greater than 15 years, patients suffering from

migraine with aura or migraine with no aura, patients with prior prophylactic medication use or no prior prophylactic medication use, patients with concomitant prophylactic medication use or no concomitant prophylactic medication use, and patients with triptan use on greater than or equal to 33% of days, or less than 33% of days. In each case, efficacy for each subgroup was shown (FIG. 41).

In another human clinical trial of patients with episodic migraine, patients were randomized to receive Ab6 100 mg (n=221), 300 mg (n=222), or placebo (n=222) in a double blind, parallel study. After a 28 day screening period, patients were administered the drug or placebo intravenously every 3 months for 4 total infusions (FIG. 40). Efficacy was shown over months 1-3 for both the 100 mg and 300 mg treatment groups, with a mean change in migraine days of -3.9 for the 100 mg treatment group and -4.3 days for the 300 mg treatment group, compared to -3.2 days for the placebo group. Efficacy for subgroups of patients was also shown, including efficacy for patients with mean migraine day (MMD) frequency less than or equal to 9 days or greater than 9 days, patients with an age at diagnosis of less than or equal to 21 years or greater than 21 years, patients having a duration of migraine of less than or equal to 15 year or greater than 15 years, and patients suffering from migraine with aura or migraine with no aura.

Example 5

Effects of Ab6 Treatment on Medication Use in Chronic and Episodic Migraine Patients

During the studies of chronic migraine patients described in Example 3 and episodic migraine patients described in Example 4, patients also recorded use of acute medication in a daily eDiary and were allowed to use acute medication at their own discretion. Acute medications for migraine included ergots, triptans, and analgesics (e.g., NSAIDS, opioids, and caffeine-containing combination analgesics).

For further analysis, patients were stratified by the number of days with acute medication use during the 28-day screening period (1-9 or ≥ 10 days; "baseline"). Acute medication days were calculated for individual types of acute medications and combined, meaning that if 2 or more types medications were used on the same calendar days, they were counted as separate medication use days. For example, if a patient took an opioid and a triptan on the same day, it counted as 2 days of acute medication use. These analyses included patients with at least 1 acute medication use day during the 28-day baseline screening period.

In both chronic migraine and episodic migraine patients who used acute medication during the 28-day baseline period, Ab6 treatment resulted in greater average reductions in monthly migraine days and acute medication days than placebo as early as Month 1 after dosing, with similar results across 2 dose intervals over 6 months.

Ab6 consistently demonstrated greater reductions in mean monthly migraine days over 6 months of treatment than placebo in chronic migraine patients taking ≥ 1 day of acute medication use during baseline (FIG. 42). Chronic migraine patients who had at least one day of acute medication use per month during baseline demonstrated greater decreases in acute medication use than placebo as early as month 1 after treatment and across the entire 6 month treatment period (FIG. 43). In the subgroup of chronic migraine patients who were taking 1-9 days of acute medication during baseline, the change from baseline in days of acute medication use was greater in the 300 mg Ab6 group than placebo across 6 months of treatment (FIG. 44). A clear decrease in medica-

tion days per month was observed for patients with at least 10 days of medication use per month at baseline for both Ab6 treatment group compared to placebo over the entire 6 month period. FIG. 45 shows the changes in medication use days at Month 1 and Month 6 in the subgroups of chronic migraine patients with ≥ 1 , 1-9, and >10 days of acute medication use at baseline. With the exception of Ab6 100 mg at month 6 in patients with 1-9 days/month of use at baseline, Ab6 demonstrated a greater treatment effect in reducing acute medication use than placebo.

Similarly, across 2 dose intervals over 6 months, episodic migraine patients with one or more days of acute medication use during baseline experienced greater reductions in mean monthly migraine days with Ab6 than Placebo (FIG. 46). Episodic migraine patients who had at least one day of acute medication use per month during baseline demonstrated greater decreases in acute medication use than placebo as early as month 1 after treatment and across the entire 6 month treatment period (FIG. 47). In the subgroup of episodic migraine patients who were taking 1-9 days of acute medication during baseline, the change from baseline in days of acute medication use was greater with Ab6 than placebo across 6 months of treatment (FIG. 48). A similar pattern was observed in the subgroup of patients who were taking ≥ 10 days of acute medication during baseline, though smaller sample sizes may have contributed to the less consistent pattern over time. FIG. 49 shows the changes in medication use days at Month 1 and Month 6 in the subgroups of episodic migraine patients with ≥ 1 , 1-9, and >10 days of acute medication use at baseline. With the exception of Ab6 100 mg at Month 6 in patients with ≥ 10 days/month of use at baseline, the reduction in acute medication use was greater in the Ab6 treatment groups than placebo.

The results show that both episodic migraine and chronic migraine patients who were at risk for medication-overuse headache (≥ 10 days/month of acute medication use) demonstrated the greatest reductions in acute medication use, with Ab6 treatment generally resulting in larger decreases in medication use days than placebo.

The most frequently reported acute headache medications in $>10\%$ of subjects included Thomapyrin N (44.5%) (a combination of paracetamol, aspirin, and caffeine), ibuprofen (40.6%), sumatriptan (33.6%), paracetamol (acetaminophen) (20.3%), and naproxen sodium (10.2%). The most frequently reported preventive headache medication in $>10\%$ of subjects was topiramate (12.5%).

Example 6

Efficacy of anti-CGRP Antibodies in Subjects Experiencing an Acute Attack of Migraine

This example describes a randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of Ab6 for the acute treatment of migraine. In the study, approximately 450 patients are randomized 1:1 to receive either 100 mg Ab6 or placebo. During a screening period (approx. 1-8 weeks) patients are assessed for migraine frequency and medication use frequency. Eligible patients have a migraine attack frequency of about 4-15 migraine days per month in the 3 months prior to screening. By history, the subject's typical migraine attack, if untreated, would be associated with headache pain of moderate to severe intensity and a most bothersome symptom of nausea, photophobia, or phonophobia. Subjects must be headache free for at least 24 hours prior to onset of a qualifying migraine in order to participate in the trial. On the day of

treatment, the patient will travel to the study site and intravenous infusion of 100 mg Ab6 or placebo will commence between about 1-6 hours from the start of the attack. Patients will not have received any other monoclonal antibody (e.g., any CGRP antagonist antibody) within the 6 month period prior to screening.

Co-Primary Endpoints are time to headache pain freedom and time to absence of most bothersome symptom. Co-Key secondary are headache pain freedom at 2 hours and absence of most bothersome symptom at 2 hours. Secondary endpoints are time to headache pain relief, headache pain freedom at 2 hours with sustained headache pain freedom for 24 and 48 hours, use of rescue medication by 24 hours and by 48 hours, absence of photophobia at 2 hours, absence of phonophobia at 2 hours, absence of nausea at 2 hours, change from Baseline in Headache Impact Test (HIT 6) at Week 4, and change from Baseline in Migraine Treatment Optimization Questionnaire-6 (mTOQ-6) at Week 4. Exploratory Endpoints are absence of headache pain at all timepoints other than 2 hours, absence of photophobia at all timepoints other than 2 hours, absence of phonophobia at all timepoints other than 2 hours, absence of nausea at all timepoints other than 2 hours, pain relapse when the subject was headache pain-free at 2 hours, patient Global Impression of Change (PGIC) at Week 4, and time to next migraine. Headache pain is collected on a 4-point scale with 3 being severe, 2 being moderate, 1 being mild, and 0 being no pain. Pain freedom is no pain (0) with the absence of rescue medication (note that in the trial rescue medication is not to be used for 2 hours post completion of infusion in order to separate the effects of the antibody from the rescue medication, however, in the course of normal use, rescue medication optionally may be used; any use of rescue medication is collected as data).

Statistical analysis is performed to determine significance of the difference in endpoints between patients receiving Ab6 or placebo, including the time to pain freedom and time to absence of most bothersome symptom, and each of the other aforementioned endpoints.

Use of rescue medication refers to any intervention (medical or device) provided to the subject to provide relief of migraine. In the study this should not be provided sooner than 2 hours following completion of the study drug administration in order to separate the effects of the antibody from the effects of said rescue medication; however, rescue medication is not contraindicated. The proportion of subjects requiring rescue medication use is summarized in the study.

Acute rescue medication includes any medication to treat migraine or migraine associated symptoms, e.g., triptans, analgesics such as non-opioids or opioids/narcotics, acetaminophen, NSAIDS, combination medications such as EXCEDRIN® or EXCEDRIN MIGRAINE®, antiemetic medications, ergotamines, ergot derivatives, etc.

Absence of Migraine-Associated Symptoms (Photophobia, Phonophobia and Nausea) refers to the absence or presence of each of the aforementioned migraine-associated symptoms, as reported by the subject. The proportion of subjects absent the symptoms, with no administration of rescue medication, is summarized in the study.

Headache Impact Test (HIT-6) is assessed as the change from baseline of the total score, and is summarized and compared between treatment groups in the study.

Migraine Treatment Optimization Questionnaire-6 (mTOQ-6) is assessed as the change from baseline of the

71

total score and is summarized and compared between the treatment groups in the study.

Time to Headache Pain Relief is assessed as the first time point post completion of infusion at which the subject reports relief of pain meaning their headache pain has gone from moderate or severe (2 or 3) to mild or no pain (1 or 0) with no administration of rescue medication.

72

Pain Relapse is assessed as the occurrence of headache of any severity within 48 hours of drug administration for a patient who has no headache pain (0) at 2 hours. The proportion of subjects with recurrence of headache pain of any severity is summarized in the study.

The study shows that Ab6 is effective and safe for acute migraine treatment.

SEQUENCE LISTING

```

Sequence total quantity: 567
SEQ ID NO: 1      moltype = AA length = 439
FEATURE          Location/Qualifiers
REGION           1..439
source            note = Engineered antibody sequence
                  1..439
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 1
QSLEESGGRL VTPGTPLTLT CTVSGLDLSS YYMQWVRQAP GKGLEWIGVI GINDNTYYAS 60
WAKGRFTISR ASSTTVDLKM TSLTTEDAT YFCARGDIWG PGTLVTVSSA STKGPSVFPL 120
APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV 180
PSSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCP CPAPELLGGP SVFLFPPKPK 240
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VGVEVHNIAK TKPREEQYAS TYRVVSVLTV 300
LHQDWLNGKE YKCKVSNKAL PAPIEKTIK AKGQPREPQV YTLPPSREEM TKNQVSLTCL 360
VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM 420
HEALHNHYTQ KSLSLSPGK                                         439

SEQ ID NO: 2      moltype = AA length = 109
FEATURE          Location/Qualifiers
REGION           1..109
source            note = Engineered antibody sequence
                  1..109
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 2
QSLEESGGRL VTPGTPLTLT CTVSGLDLSS YYMQWVRQAP GKGLEWIGVI GINDNTYYAS 60
WAKGRFTISR ASSTTVDLKM TSLTTEDAT YFCARGDIWG PGTLVTVSS             109

SEQ ID NO: 3      moltype = AA length = 29
FEATURE          Location/Qualifiers
REGION           1..29
source            note = Engineered antibody sequence
                  1..29
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 3
QSLEESGGRL VTPGTPLTLT CTVSGLDLSS                                         29
WAKGRFTISR ASSTTVDLKM TSLTTEDAT YFCARGDIWG PGTLVTVSS

SEQ ID NO: 4      moltype = AA length = 5
FEATURE          Location/Qualifiers
REGION           1..5
source            note = Engineered antibody sequence
                  1..5
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 4
SYYMQ                                         5

SEQ ID NO: 5      moltype = AA length = 14
FEATURE          Location/Qualifiers
REGION           1..14
source            note = Engineered antibody sequence
                  1..14
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 5
WVRQAPGKGL EWIG                                         14

SEQ ID NO: 6      moltype = AA length = 16
FEATURE          Location/Qualifiers
REGION           1..16
source            note = Engineered antibody sequence
                  1..16
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 6
VIGINDNTYY ASWAKG                                         16

```

-continued

```

SEQ ID NO: 7          moltype = AA length = 31
FEATURE           Location/Qualifiers
REGION            1..31
note = Engineered antibody sequence
source             1..31
mol_type = protein
organism = synthetic construct
SEQUENCE: 7          RFTISRASST TVDLKMTSLT TEDTATYFCA R
                                         31

SEQ ID NO: 8          moltype = length =
SEQUENCE: 8          000

SEQ ID NO: 9          moltype = AA length = 11
FEATURE           Location/Qualifiers
REGION            1..11
note = Engineered antibody sequence
source             1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 9          WGPGTTLTVS S
                                         11

SEQ ID NO: 10         moltype = AA length = 330
FEATURE           Location/Qualifiers
REGION            1..330
note = Engineered antibody sequence
source             1..330
mol_type = protein
organism = synthetic construct
SEQUENCE: 10          ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICNVNHPKS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKPK KDLMISRTP EVTCVVVDVS HEDPEVKFPN YVDGVEVHNA KTKPREEQYA 180
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 11          moltype = DNA length = 1320
FEATURE           Location/Qualifiers
misc_feature      1..1320
note = Engineered antibody sequence
source             1..1320
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 11          cagtcgtgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccc gacactcacc 60
tgcacagtct ctggactcg cctcgttagt tactacatgc aatgggtccg ccaggctcca 120
ggaaaggggc tggaaatggat cggacttatt ggttataatg ataaacacata ctacgcgagc 180
tgggcgaaag gocgattcac catctccaga gcctcgtcgaa ccacgggtga tctgaaaatg 240
accagtctga caaccggagga cacggccacc tatttctgtg ccagagggga catctggggc 300
ccaggccacc tcgtcaccgtt ctcgagcccccc tccaccaagg gcccatcggt cttecccctg 360
gcaccctctt ccaagggac ctctggggcc acagccggcc tgggtcgct ggtcaaggac 420
tacttccccc aaccggtgac ggttcgtgg aactcaggccg ccctgaccag cggcgctgac 480
accttccccc ctgtcttaca gtcctcgaa ctctactccc tcagcagcgt ggtgaccgt 540
ccctccagca gtttgggcac ccagacctac atctgcaacag tgaatcacaa gcccagcaac 600
accaaagggtgg acaagggaggt tgagaaaaaa tcttgtgaca aaactcacac atgcccacccg 660
tgcccgac ctgaactctt ggggggaccc tcagtttcc ttttcccccc aaaacccaaag 720
gacaccctca tgatctcccg gacccttgat gtcacatgcg ttgttgtgga cgtgagccac 780
gaagacccctg aggtcaaggta caactggat gtggacggccg tggagggtgca taatgccaag 840
acaacccgcg gggaggagca gtacggccagc acgttaccgtg tggtcagcgt cctcaccgtc 900
ctgcaccagg actggctaa tggcaaggag tacaatgtca aggtctccaa caaaggccctc 960
ccagccccca tcgagaaaaac catctccaaa gccaaaggccg agccccgaga accacagggt 1020
tacaccctgc ccccatccccgggaggagatg accaagaacc aggtcagcgt gacctgctg 1080
gtcaaaggct tctatcccg cgacatgcg tggagggtgg agagcaatgg gcagccggag 1140
aacaactaca agaccacgccc tccctggatg gactccggacg gtccttctt cctctacagc 1200
aaagctcaaccg tggacaagag cagggtggcag caggggaaacg tcttctcatg ctccctgtatg 1260
catgaggcgc tgcacaacca ctacacgcg aagagccctc ctctgttotcc gggtaatga 1320

SEQ ID NO: 12          moltype = DNA length = 327
FEATURE           Location/Qualifiers
misc_feature      1..327
note = Engineered antibody sequence
source             1..327
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 12

```

-continued

cagtgcgtgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60
tgcacagtct ctggactcga cctcagtago tactacatgc aatgggtccg ccaggctcca 120
ggaaaggggc tggaatggat cgagtcatt ggttataatg ataacacata ctacgcgagc 180
tggcgaaag gccgattcac catctccaga gcctcgtaa ccacgggtga tctgaaaatg 240
accagtctga caacccgagga cacggccacc tatttctgtg ccagaggggc catctgggc 300
ccaggcaccc tcgtcaccgt ctcgagc 327

SEQ ID NO: 13 moltype = DNA length = 87
FEATURE Location/Qualifiers
misc_feature 1..87
note = Engineered antibody sequence
source 1..87
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 13
cagtgcgtgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60
tgcacagtct ctggactcga cctcagtagt 87

SEQ ID NO: 14 moltype = DNA length = 15
FEATURE Location/Qualifiers
misc_feature 1..15
note = Engineered antibody sequence
source 1..15
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 14
agctactaca tgcaa 15

SEQ ID NO: 15 moltype = DNA length = 42
FEATURE Location/Qualifiers
misc_feature 1..42
note = Engineered antibody sequence
source 1..42
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 15
tgggtccgcc aggctccagg gaaggggtcg gaatggatcg ga 42

SEQ ID NO: 16 moltype = DNA length = 48
FEATURE Location/Qualifiers
misc_feature 1..48
note = Engineered antibody sequence
source 1..48
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 16
gtcattggta ttaatgataa cacatactac gcgagctggg cgaaaggc 48

SEQ ID NO: 17 moltype = DNA length = 93
FEATURE Location/Qualifiers
misc_feature 1..93
note = Engineered antibody sequence
source 1..93
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 17
cgattcacca tctccagagc ctcgtcgacc acgggtggatc tgaaaatgac cagtctgaca 60
accgaggaca cggccaccta tttctgtgcc aga 93

SEQ ID NO: 18 moltype = length =
SEQUENCE: 18
000

SEQ ID NO: 19 moltype = DNA length = 33
FEATURE Location/Qualifiers
misc_feature 1..33
note = Engineered antibody sequence
source 1..33
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 19
tggggcccaag gcaccctcgat caccgtctcg agc 33

SEQ ID NO: 20 moltype = DNA length = 993
FEATURE Location/Qualifiers
misc_feature 1..993
note = Engineered antibody sequence
source 1..993
mol_type = other DNA

-continued

organism = synthetic construct

SEQUENCE: 20

```
gcctccacca agggcccatc ggtcttcccc ctggcaccc cctccaagag cacctctggg 60
ggcacagcg ggctgggctg cctggtaag gactactcc cggaaagggt gacgggttcg 120
tggaaactcg gogccctgac cagccggctg cacacccctcc cggctgtct acagtcccta 180
ggactctact ccctcagcag cgtgggtgacc gtgccttcca gcagcttggg caccagacc 240
tacatctgca acgtgaatca caagcccago aacaccaagg tggacaagg agttgagccc 300
aaatcttg acaaactca cacatgccca cctgtccca cactgaact cctgggggga 360
cctgtcaatc tctcttcccc cccaaaaccc aaggacacc ctcgtatctc cccggaccct 420
gagggtcacat gctgtgggtt ggacgttggcggc cagaagaccc ctgggttcaa gttcaactgg 480
tacgtggacg gctgtggaggc gcataatggc aagacaaacg cccggggggc gcagtacgcc 540
agcacgtacc gtgtggtag cgttccacc gtctgtcc accgtactggt gaatggcaag 600
gagtacaatg gcaagggtctc caaacaaggc cttccacccc ccattggaaa aaccatctcc 660
aaaggccaaag ggcagggcccg agaaccacag gtgtacacc tgcccccattt cccgggggg 720
atgaccaaga accagggtcag cttgtacccctc ctgtcaaaat gtttctatcc cagcgtacatc 780
gccgtggagt gggagagcaa tggcagccg gagaacaact acaagaccac gcctccctg 840
ctggactccg acggcttccctt ctccctctac agcaagtcac ccgtggacaa gagcagggtgg 900
cagcaggggc acgttccatc atgtccgtg atgcgtatggg ctctgcacaa ccactacacg 960
cagaagggc ttccctgtt tccgggtaaa tga 993
```

SEQ ID NO: 21 moltype = AA length = 219
FEATURE Location/Qualifiers
REGION 1..219
note = Engineered antibody sequence
source 1..219
mol_type = protein
organism = synthetic construct

SEQUENCE: 21

```
QVLTQTASPV SAAVGSTVTI NCQASQSVYD NNYLAWYQQK PGQPPKQLIY STSTLASGVS 60
SRFKGSQSGT QFTLTISDLE CADAATYYCL GSYDCSSGDC FVFGGGTEVV VKRTVAAPSV 120
FIPPPSDEQL KSGTASVVCN LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 219
```

SEQ ID NO: 22 moltype = AA length = 113
FEATURE Location/Qualifiers
REGION 1..113
note = Engineered antibody sequence
source 1..113
mol_type = protein
organism = synthetic construct

SEQUENCE: 22

```
QVLTQTASPV SAAVGSTVTI NCQASQSVYD NNYLAWYQQK PGQPPKQLIY STSTLASGVS 60
SRFKGSQSGT QFTLTISDLE CADAATYYCL GSYDCSSGDC FVFGGGTEVV VKR 113
```

SEQ ID NO: 23 moltype = AA length = 22
FEATURE Location/Qualifiers
REGION 1..22
note = Engineered antibody sequence
source 1..22
mol_type = protein
organism = synthetic construct

SEQUENCE: 23

```
QVLTQTASPV SAAVGSTVTI NC 22
```

SEQ ID NO: 24 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
note = Engineered antibody sequence
source 1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 24

```
QASQSVYDNN YLA 13
```

SEQ ID NO: 25 moltype = AA length = 15
FEATURE Location/Qualifiers
REGION 1..15
note = Engineered antibody sequence
source 1..15
mol_type = protein
organism = synthetic construct

SEQUENCE: 25

```
WYQQKPGQPP KQLIY 15
```

SEQ ID NO: 26 moltype = AA length = 7
FEATURE Location/Qualifiers
REGION 1..7
note = Engineered antibody sequence
source 1..7

-continued

```

mol_type = protein
organism = synthetic construct

SEQUENCE: 26
STSTLAS                                              7

SEQ ID NO: 27      moltype = AA length = 32
FEATURE          Location/Qualifiers
REGION           1..32
note = Engineered antibody sequence
source            1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 27
GVSSRFKGSG SGTQFTLTIS DLECADAATY YC               32

SEQ ID NO: 28      moltype = AA length = 13
FEATURE          Location/Qualifiers
REGION           1..13
note = Engineered antibody sequence
source            1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 28
LGSYDCSSGD CFV                                         13

SEQ ID NO: 29      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Engineered antibody sequence
source            1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 29
FGGGTEVVVK R                                           11

SEQ ID NO: 30      moltype = AA length = 106
FEATURE          Location/Qualifiers
REGION          1..106
note = Engineered antibody sequence
source            1..106
mol_type = protein
organism = synthetic construct

SEQUENCE: 30
TVAAPSVFIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC                106

SEQ ID NO: 31      moltype = DNA length = 660
FEATURE          Location/Qualifiers
misc_feature     1..660
note = Engineered antibody sequence
source            1..660
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 31
caagtgcgtg cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
aattgccagg ccagtcagag tgtttatgt aacaactacc tagcctggta tcagcagaaa 120
ccagggcagc ctcccaagca actgatctat tctacatcca ctctggcatc tggggctca 180
tgcgcgttca aaggcagttg atctgggaca cagttcactc tcaccatcg cgacctggag 240
tgtgcccgtat ctgcactta ctactgtcta ggcagttatg attgttagtag tggtgatgt 300
tttgttttcg gggggggac cgagggttgc gtcaaactgta cggtggtc accatctgtc 360
ttcatcttcc cgccatctga tgacgagttg aaatctggaa ctgcctctgt tggtgctgc 420
ctgaataact tctatcccaag agaggccaaa gtacagtgg aagggtggataa cgcctccaa 480
tcgggttaact cccaggactat tgtcacagag caggacagcac ctacagcctc 540
agcagcaccc tgacgctgtgc caaaaggacat tgcggaaa acaaagtctca cgcctcgaa 600
gtcacccatc agggccttag ctcggccgtc acaaaggatc tcaacagggg agagtgttag 660

SEQ ID NO: 32      moltype = DNA length = 339
FEATURE          Location/Qualifiers
misc_feature     1..339
note = Engineered antibody sequence
source            1..339
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 32
caagtgcgtg cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
aattgccagg ccagtcagag tgtttatgt aacaactacc tagcctggta tcagcagaaa 120
ccagggcagc ctcccaagca actgatctat tctacatcca ctctggcatc tggggctca 180
tgcgcgttca aaggcagttg atctgggaca cagttcactc tcaccatcg cgacctggag 240
tgtgcccgtat ctgcactta ctactgtcta ggcagttatg attgttagtag tggtgatgt 300

```

-continued

tttggtttcg gcgaggggac cgaggtggtg gtcaaacgt	339
SEQ ID NO: 33	moltype = DNA length = 66
FEATURE	Location/Qualifiers
misc_feature	1..66
	note = Engineered antibody sequence
source	1..66
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 33	
caagtgtga cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc	60
aattgc	66
SEQ ID NO: 34	moltype = DNA length = 39
FEATURE	Location/Qualifiers
misc_feature	1..39
	note = Engineered antibody sequence
source	1..39
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 34	
caggccagtc agagtgttta tgataacaac tacctagcc	39
SEQ ID NO: 35	moltype = DNA length = 45
FEATURE	Location/Qualifiers
misc_feature	1..45
	note = Engineered antibody sequence
source	1..45
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 35	
tggtatcagc agaaaaccagg gcagcctccc aagcaactga tctat	45
SEQ ID NO: 36	moltype = DNA length = 21
FEATURE	Location/Qualifiers
misc_feature	1..21
	note = Engineered antibody sequence
source	1..21
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 36	
tctacatcca ctctggcatc t	21
SEQ ID NO: 37	moltype = DNA length = 96
FEATURE	Location/Qualifiers
misc_feature	1..96
	note = Engineered antibody sequence
source	1..96
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 37	
gggggtctcat cgccgttcaa aggcaagtggaa tctgggacac agttcactct caccatcagc	60
gacactggagt gtgccgatgc tgccacttac tactgt	96
SEQ ID NO: 38	moltype = DNA length = 39
FEATURE	Location/Qualifiers
misc_feature	1..39
	note = Engineered antibody sequence
source	1..39
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 38	
ctaggcagtt atgattttag tagtggtgat tgttttgtt	39
SEQ ID NO: 39	moltype = DNA length = 33
FEATURE	Location/Qualifiers
misc_feature	1..33
	note = Engineered antibody sequence
source	1..33
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 39	
ttcggcggag ggaccgaggt ggtggtcaaa cgt	33
SEQ ID NO: 40	moltype = DNA length = 321
FEATURE	Location/Qualifiers
misc_feature	1..321
	note = Engineered antibody sequence
source	1..321

-continued

```

mol_type = other DNA
organism = synthetic construct

SEQUENCE: 40
acggtgtggctg caccatctgt ctcatcttc ccgcgcattgt atgagcaggaaatcttga 60
actgcctctg ttgtgtgcct gctataaac ttttatccca gagaggccaa agtacatgtgg 120
aagggtggata acggccttcca atcggttaac tcccaggaga gtgtcacaga gcaggacagc 180
aaggacacca octacagcct cagcagcacc ctgacgcgtga gcaaaacgaca ctacgagaaa 240
cacaaggatct acgcctgcga agtcacccat cagggcctga gtcgcggcgt cacaaggagc 300
ttcaacaggagagttt g 321

SEQ ID NO: 41      moltype = AA length = 441
FEATURE           Location/Qualifiers
REGION            1..441
note = Engineered antibody sequence
source             1..441
mol_type = protein
organism = synthetic construct

SEQUENCE: 41
EVOLVESGGG LVQPGGSLRL SCAVSGLDLS SYYMQWVRQA PGKGLEWVGIGINDNTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
PLAPSSSKTS CGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
TVPSSSLGTQ TYICNVNHPK SNTKVDKRPE PKSCDKTHTC PPCPAPELLG GPSVFLPPK 240
PKDTLMSRT PEVTCVVDV SHEDPEVKFN WYDGVEVHN AKTKPREEQY ASTYRVSVL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
CLVKGFYPSD IAVEWESNGQ PENNYKTPPP VLDSDGSPFL YSKLTVDKSR WQQGNVFSCS 420
VMHEALHNHY TQKSLSLSPG K 441

SEQ ID NO: 42      moltype = AA length = 111
FEATURE           Location/Qualifiers
REGION            1..111
note = Engineered antibody sequence
source             1..111
mol_type = protein
organism = synthetic construct

SEQUENCE: 42
EVOLVESGGG LVQPGGSLRL SCAVSGLDLS SYYMQWVRQA PGKGLEWVGIGINDNTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS S 111

SEQ ID NO: 43      moltype = AA length = 30
FEATURE           Location/Qualifiers
REGION            1..30
note = Engineered antibody sequence
source             1..30
mol_type = protein
organism = synthetic construct

SEQUENCE: 43
EVQLVESGGG LVQPGGSLRL SCAVSGLDLS 30

SEQ ID NO: 44      moltype = AA length = 5
FEATURE           Location/Qualifiers
REGION            1..5
note = Engineered antibody sequence
source             1..5
mol_type = protein
organism = synthetic construct

SEQUENCE: 44
SYYMQ 5

SEQ ID NO: 45      moltype = AA length = 14
FEATURE           Location/Qualifiers
REGION            1..14
note = Engineered antibody sequence
source             1..14
mol_type = protein
organism = synthetic construct

SEQUENCE: 45
WVRQAPGKGL EWVG 14

SEQ ID NO: 46      moltype = AA length = 16
FEATURE           Location/Qualifiers
REGION            1..16
note = Engineered antibody sequence
source             1..16
mol_type = protein
organism = synthetic construct

SEQUENCE: 46
VIGINDNTYY ASWAKG 16

SEQ ID NO: 47      moltype = AA length = 32

```

-continued

FEATURE Location/Qualifiers
REGION 1..32
note = Engineered antibody sequence
source 1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 47
RFTISRDNSK TTVYLQMNSL RAEDTAVYFC AR 32

SEQ ID NO: 48 moltype = length =
SEQUENCE: 48
000

SEQ ID NO: 49 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Engineered antibody sequence
source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 49
WGQGTLVTVS S 11

SEQ ID NO: 50 moltype = AA length = 330
FEATURE Location/Qualifiers
REGION 1..330
note = Engineered antibody sequence
source 1..330
mol_type = protein
organism = synthetic construct

SEQUENCE: 50
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPPKP KDTLMISGVS EVTCKVFKNV YDGVVEVHNA KTKPREEQVA 180
STYRVRVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPSSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 51 moltype = DNA length = 1326
FEATURE Location/Qualifiers
misc_feature 1..1326
note = Engineered antibody sequence
source 1..1326
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 51
gaggtcagc ttgtggagtc tgggggaggc ttgttccagc ctggggggtc ccttagactc 60
tccctgtcag tctctggact cgacctcgat agctactaca tgcaatgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggtcgaggatc attggatata atgataaacac atactacgcg 180
agctggggca aaggccgatt caccatctcc agagacaatcca ccaagaccac ggttatctt 240
caaatacgaca gcctcgagac tgaggacact gctgttatc tctgtgttag aggggacatc 300
tggggccaag ggacctctgt cacccgtctcg agccgcctcca ccaaggcccc atccggcttc 360
cccctggcac cccctccaa gacccatctcg gggggccacag cggccctggg ctgcctggtc 420
aaggactact tcccccgaacc ggtacggctg tcgttggact cagggccctt gaccagccgc 480
gtgcacaccc tcccggtctgt cctacagtcc tcaggactact ccccttcacatc cagcgtggc 540
accgtgcctt ccacgacgtt gggccacccatcg acctacatcc gcaacgtgaa tcacaagccc 600
agcaacacca aggtggacaa gagagtttag cccaaatctt gtgacaaaac tcacacatgc 660
ccaccgtgcc cagcacctgt actccctgggg ggaccgtcaag tttccctt ccccccaaaa 720
cccaaggaca ccctcatgtat ctcggggacc cctgagggtca catgcgttgt ggtggacgtg 780
agccacaaag accctggaggt caagtcaac ttgttacgtgg acggcgtgga ggtgcataat 840
gccaagacaa agccgggga ggacgactac gccacgttcc accgtgttgtt cagcgtcctc 900
accgtccgtc accggactgt gctaatggc aaggactacca agtgcacggt ctccaaacaaa 960
gcccctcccg ccccccattgtc gaaaaggccca tccaaaggccca aaggccggacc cccgagaacca 1020
cagggtgtaca ccctggccccc atccggggag gagatggccca agaaccaggat cagccgtacc 1080
tgcctggta aaggcttcta tcccgacgtatc atccgggtgg agtggggagag caatggggcag 1140
ccggagaaca actacaagac cacgcctccc gtgtggact ccggacggctc cttcttcctc 1200
tacagcaacg tcacccgtgga caagagcagg tggcagcagg ggaacgttcc ctcatgtcc 1260
gtgtatgcatg aggctctgtca caaccactac acgcagaaga gctctccct gtctccgggt 1320
aaatga 1326

SEQ ID NO: 52 moltype = DNA length = 333
FEATURE Location/Qualifiers
misc_feature 1..333
note = Engineered antibody sequence
source 1..333
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 52
gaggtcagc ttgtggagtc tgggggaggc ttgttccagc ctggggggtc ccttagactc 60

-continued

tcctgtgcag tctctggact cgacctcagt agctactaca tgcaatgggt ccgtcaggct 120
 ccaggaaagg ggctggagtg ggtcgaggatc attggatatac atgataaac acatacgcg 180
 agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
 caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgttag aggggacatc 300
 tggggccaag ggaccctcgta caccgtctcg agc 333

SEQ ID NO: 53 moltype = DNA length = 90
 FEATURE Location/Qualifiers
 misc_feature 1..90
 note = Engineered antibody sequence
 source 1..90
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 53 gaggtgcagc ttgtggagtc tgggggaggc ttgttccagc ctggggggc cctgagactc 60
 tcctgtgcag tctctggact cgacctcagt 90

SEQ ID NO: 54 moltype = DNA length = 15
 FEATURE Location/Qualifiers
 misc_feature 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 54 agctactaca tgcaa 15

SEQ ID NO: 55 moltype = DNA length = 42
 FEATURE Location/Qualifiers
 misc_feature 1..42
 note = Engineered antibody sequence
 source 1..42
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 55 tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga 42

SEQ ID NO: 56 moltype = DNA length = 48
 FEATURE Location/Qualifiers
 misc_feature 1..48
 note = Engineered antibody sequence
 source 1..48
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 56 gtcattggta tcaatgataa cacatactac gcgagctggc cgaaaggc 48

SEQ ID NO: 57 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 57 cgattcacca tctccagaga caattccaag accacgggt atcttcaa at gaacagcctg 60
 agagctgagg acactgctgt gtatttctgt gctaga 96

SEQ ID NO: 58 moltype = length =

SEQUENCE: 58 000

SEQ ID NO: 59 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33
 note = Engineered antibody sequence
 source 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 59 tggggccaag ggaccctcgta caccgtctcg agc 33

SEQ ID NO: 60 moltype = DNA length = 993
 FEATURE Location/Qualifiers
 misc_feature 1..993
 note = Engineered antibody sequence
 source 1..993
 mol_type = other DNA
 organism = synthetic construct

-continued

SEQUENCE: 60
 gcctccacca agggcccata ggtttcccc ctggcaccc cctccaagag cacctctggg 60
 ggcacagcgg ccctgggctg cctggtaaq gactacttc cccaaagggt gacgggtcg 120
 tggaaactcg ggcggctgac cagcggctgtg cacaccttc cggctgtct acagtctca 180
 ggactctact ccctcagtag cgtgttgacc gtggccctcca gcaagttggg caccctgg 240
 tacatctgca acgtgaatca caacccaga aacaccaagg tggacaagag agttgagccc 300
 aaatcttgtc aaaaaactca cacatgcca cccgtccccag caccctgact cctgggggga 360
 cccgtcgtct tccttcccc cccaaaaccc aaggacaccc tcatgtatcc cccggaccct 420
 gaggtcacat ggtgtgggtt ggacgtgago cacaagacc ctgaggtaaa gtcaactgg 480
 tacgtggacg ggtgtgggtt gcatatggcc aagacaaagg cccggggaga gcaatggcc 540
 agcacgtacc gtgtggttag cgtcttcacc gtcctgcacc aggactgggt gaatggcaag 600
 gagtacaagt gcaaggatctc caacaaagcc ctcccaagcc ccatcgagaa aaccatctcc 660
 aaaggccaaag ggcaccccg agaaccacag gtgtacacc tgcccccattt cccggggag 720
 atgaccaaga accaggatcg cctgacttc cttgtcaaa gttttatcc cccggggatcc 780
 gccgtggagt gggagagcaa tggcagccg gagaacaact acaagaccac gcctccctgt 840
 ctggactccg acggctctt cttctctac agcaagctca ccgtggacaa gaggcagggtt 900
 cagcagggggaa acgtttctc atgtccctgt atgtcatggg ctctgcacaa ccactacacg 960
 cagaagaccc tctccctgtc tccgggtaaa tga 993

SEQ ID NO: 61 moltype = AA length = 219
 FEATURE Location/Qualifiers
 REGION 1..219
 note = Engineered antibody sequence
 source 1..219
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 61
 QVLTQSPSSL SASVGDRVTI NCQASQSYVD NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFGSGSGGT DFTLTISSLQ PEDVATYYCL GSYDCSSGDC FVFGGGTKVE IKRTVAAPSV 120
 FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
 STSTLTLKAD YEKHKVYACE VTHQGLSSPV TKSFNRRGEC 219

SEQ ID NO: 62 moltype = AA length = 113
 FEATURE Location/Qualifiers
 REGION 1..113
 note = Engineered antibody sequence
 source 1..113
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 62
 QVLTQSPSSL SASVGDRVTI NCQASQSYVD NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFGSGSGGT DFTLTISSLQ PEDVATYYCL GSYDCSSGDC FVFGGGTKVE IKR 113

SEQ ID NO: 63 moltype = AA length = 22
 FEATURE Location/Qualifiers
 REGION 1..22
 note = Engineered antibody sequence
 source 1..22
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 63
 QVLTQSPSSL SASVGDRVTI NC 22

SEQ ID NO: 64 moltype = AA length = 13
 FEATURE Location/Qualifiers
 REGION 1..13
 note = Engineered antibody sequence
 source 1..13
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 64
 QASQSYDNN YLA 13

SEQ ID NO: 65 moltype = AA length = 15
 FEATURE Location/Qualifiers
 REGION 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 65
 WYQQKPGKVP KQLIY 15

SEQ ID NO: 66 moltype = AA length = 7
 FEATURE Location/Qualifiers
 REGION 1..7
 note = Engineered antibody sequence
 source 1..7
 mol_type = protein

-continued

organism = synthetic construct

SEQUENCE: 66
STSTLAS 7

SEQ ID NO: 67 moltype = AA length = 32
FEATURE Location/Qualifiers
REGION 1..32
note = Engineered antibody sequence
source 1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 67 GPVSRFSGSG SGTDFTLTIS SLQPEDVATY YC 32

SEQ ID NO: 68 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
note = Engineered antibody sequence
source 1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 68 LGSYDCSSGD CFV 13

SEQ ID NO: 69 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Engineered antibody sequence
source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 69 FGGGTTKVEIK R 11

SEQ ID NO: 70 moltype = AA length = 106
FEATURE Location/Qualifiers
REGION 1..106
note = Engineered antibody sequence
source 1..106
mol_type = protein
organism = synthetic construct

SEQUENCE: 70 TVAAPSVIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSS LTLSKADYEK HKVYACEVT QGLSSPVTKS FNRGEC 106

SEQ ID NO: 71 moltype = DNA length = 660
FEATURE Location/Qualifiers
misc_feature 1..660
note = Engineered antibody sequence
source 1..660
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 71 caagtgtcga cccagtcctcc atcctccctg tctgcacatctg taggagacag agtcaccatc 60
aattggcagg ccagtcaagag tgtttatgtt aacaactacc tagcctggta tcagcagaaaa 120
ccaggaaag ttccctaagca actgatctat tctacatcca ctctggcatc tggggtccca 180
tctcgtttca gtggcagtgg atctgggaca gatttcactc tcacccatcag cagcctgcag 240
cctgaagatg ttgcactta ttactgtctt ggcagttatg attgttagtag tggtgatgt 300
tttggtttccg gcgaggaaac caagggtggaa atcaaacgtca cgggtggctc accatctgtc 360
ttcatcttcc cgccatctga tgacgatgtt aatctggaa ctgcctctgt tggtgctcg 420
ctgaataact tctatcccag agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcgggttaact cccaggagag tgtcacagag caggacacgca aggacacgac ctacagcctc 540
agcagcaccc tgacgtctgag caaaggcagac tacggagaaac acaaagtcta cgcctgcgaa 600
gtcacccatc agggccttagt acaaaaggact tcaacagggg agagtgttag 660

SEQ ID NO: 72 moltype = DNA length = 339
FEATURE Location/Qualifiers
misc_feature 1..339
note = Engineered antibody sequence
source 1..339
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 72 caagtgtcga cccagtcctcc atcctccctg tctgcacatctg taggagacag agtcaccatc 60
aattggcagg ccagtcaagag tgtttatgtt aacaactacc tagcctggta tcagcagaaaa 120
ccaggaaag ttccctaagca actgatctat tctacatcca ctctggcatc tggggtccca 180
tctcgtttca gtggcagtgg atctgggaca gatttcactc tcacccatcag cagcctgcag 240
cctgaagatg ttgcactta ttactgtctt ggcagttatg attgttagtag tggtgatgt 300
tttggtttccg gcgaggaaac caagggtggaa atcaaacgtca cgcctgcgaa 339

-continued

```

SEQ ID NO: 73      moltype = DNA length = 66
FEATURE          Location/Qualifiers
misc_feature     1..66
source           note = Engineered antibody sequence
                 1..66
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 73
caagtgcgtga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgc                                     66

SEQ ID NO: 74      moltype = DNA length = 39
FEATURE          Location/Qualifiers
misc_feature     1..39
source           note = Engineered antibody sequence
                 1..39
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 74
caggccagtc agagtgttta tgataacaac taccttagcc                                39

SEQ ID NO: 75      moltype = DNA length = 45
FEATURE          Location/Qualifiers
misc_feature     1..45
source           note = Engineered antibody sequence
                 1..45
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 75
tggttatcagc agaaaaccagg gaaagttcct aagcaactga tctat                                45

SEQ ID NO: 76      moltype = DNA length = 21
FEATURE          Location/Qualifiers
misc_feature     1..21
source           note = Engineered antibody sequence
                 1..21
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 76
tctacatcca ctctggcatc t                                         21

SEQ ID NO: 77      moltype = DNA length = 96
FEATURE          Location/Qualifiers
misc_feature     1..96
source           note = Engineered antibody sequence
                 1..96
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 77
gggggtcccat ctgcgttcag tggcagtggaa tctggggacag atttcactct caccatcagc 60
agcctgcagc ctgaagatgt tgcaacttat tactgt                               96

SEQ ID NO: 78      moltype = DNA length = 39
FEATURE          Location/Qualifiers
misc_feature     1..39
source           note = Engineered antibody sequence
                 1..39
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 78
ctaggcagtt atgattgttag tagtggtagt tgttttgtt                                39

SEQ ID NO: 79      moltype = DNA length = 33
FEATURE          Location/Qualifiers
misc_feature     1..33
source           note = Engineered antibody sequence
                 1..33
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 79
ttcggcggag gaaccaaggt ggaaatcaaa cgt                                33

SEQ ID NO: 80      moltype = DNA length = 321
FEATURE          Location/Qualifiers
misc_feature     1..321
source           note = Engineered antibody sequence
                 1..321
mol_type = other DNA

```

-continued

organism = synthetic construct

SEQUENCE: 80

```
acgggtggctg caccatctgt cttcatcttc ccgcctctg atgagcaggta gaaatcttga 60
actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
aagggtggata acggccctcca atcggttaac tcccaggaga gtgtcacaga gcaggacagc 180
aaggacagca ctacagcc cagcagcacc ctgacgctga gcaaagcaga ctacgaaaa 240
cacaatgtt acggctgcga agtacccat caggccctga gctcgccctg cacaagagc 300
ttcaacaggg gagagtgtta g 321
```

SEQ ID NO: 81 moltype = AA length = 441
FEATURE Location/Qualifiers
REGION 1..441
note = Engineered antibody sequence
source 1..441
mol_type = protein
organism = synthetic construct

SEQUENCE: 81

```
EVQLVESGGGVQPGGSLRL SCAVSGLDLS SYYMQWVRQA PGKGLEWVGIGINDNTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
PLAPSSKSTS GGTAAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
TVPSSSLGQ TYICCNVNHKP SNTKVDARVE PKSCDKTHTC PPCPAPELLG GPSVFLPPK 240
PKDTLMISRT PEVTCVVVDW SHEDPEVKFN YVVDGVEVHN AKTKPREEQY ASTYRVVSVL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSSFL YSKLTVDKSR WQQGNVFSCS 420
VMHEALHNHY TQKSLSLSPG K 441
```

SEQ ID NO: 82 moltype = AA length = 111
FEATURE Location/Qualifiers
REGION 1..111
note = Engineered antibody sequence
source 1..111
mol_type = protein
organism = synthetic construct

SEQUENCE: 82

```
EVQLVESGGGVQPGGSLRL SCAVSGLDLS SYYMQWVRQA PGKGLEWVGIGINDNTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS S 111
```

SEQ ID NO: 83 moltype = AA length = 30
FEATURE Location/Qualifiers
REGION 1..30
note = Engineered antibody sequence
source 1..30
mol_type = protein
organism = synthetic construct

SEQUENCE: 83

```
EVQLVESGGGVQPGGSLRL SCAVSGLDLS 30
```

SEQ ID NO: 84 moltype = AA length = 5
FEATURE Location/Qualifiers
REGION 1..5
note = Engineered antibody sequence
source 1..5
mol_type = protein
organism = synthetic construct

SEQUENCE: 84

```
SYMMQ 5
```

SEQ ID NO: 85 moltype = AA length = 14
FEATURE Location/Qualifiers
REGION 1..14
note = Engineered antibody sequence
source 1..14
mol_type = protein
organism = synthetic construct

SEQUENCE: 85

```
WVRQAPGKGL EWVG 14
```

SEQ ID NO: 86 moltype = AA length = 16
FEATURE Location/Qualifiers
REGION 1..16
note = Engineered antibody sequence
source 1..16
mol_type = protein
organism = synthetic construct

SEQUENCE: 86

```
VGINDNTYY ASWAKG 16
```

SEQ ID NO: 87 moltype = AA length = 32
FEATURE Location/Qualifiers

-continued

REGION 1..32
note = Engineered antibody sequence

source 1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 87
RFTISRDNSK TTVYLQMNSL RAEDTAVYFC AR 32

SEQ ID NO: 88 moltype = length =
SEQUENCE: 88
000

SEQ ID NO: 89 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Engineered antibody sequence
source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 89
WGQGTLVTVS S 11

SEQ ID NO: 90 moltype = AA length = 330
FEATURE Location/Qualifiers
REGION 1..330
note = Engineered antibody sequence
source 1..330
mol_type = protein
organism = synthetic construct

SEQUENCE: 90
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDARVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKP KDTLMSRTP EVTCVVVDVS HEDPEVKPNW YVDGVEVHNA KTKPREEQYA 180
STYRVVSVLT VLHQDWLNGK EYKCKVSNSKA LPAPIEKTIIS KAKGQPREPQ VYTLPSSREE 240
MTKNQVSLTC AVWEWSNGQP ENNYKTPPPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 91 moltype = DNA length = 1326
FEATURE Location/Qualifiers
misc_feature 1..1326
note = Engineered antibody sequence
source 1..1326
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 91
gggtgcgcg ttgtggagtc tgggggaggc ttgtgtccagc ctggggggtc cctgagactc 60
tcttgtgcag tctctggact cgacacctcg agtactaca tgcaatgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggtcgaggc atttggatca atgataaacat atactacgcg 180
agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
caaatacaca gaactggagac tgaggacact gctgtgtatt tctgtgttag aggggacatc 300
tggggcacaag ggacccctcg caccgtctcg agccgcctcca ccaaggccc atcggtcttc 360
ccccctggcac cctcttccaa gagacctctt gggggcacac eggccttggg ctgcctggc 420
aaggactact tccccgaacc ggtgacgggt tcgtgaaact caggcgcctt gaccagccgc 480
gtgcacacact tcccggtctt cctcagactt tcaggactact ctcgccttcc cagcgtggg 540
accgtgcctcc ccaggcactt gggccaccc acctacatctt gcaacgtgaa tcacaagccc 600
agaacacacca aggtggacgc gagagtttag cccaaatctt gtgacaaaac tcacacatgc 660
ccaccgtgcc cagcacctga actctctgggg ggaccgtcaq tttcccttt ccccccaaaa 720
cccaaggaca ccctcatgtat ctcggggacc cctgagggtca catgcgtgtt ggtggacgtg 780
agccacacag accctggatg caagttaac tggtagctgg acggcgtggaa ggtgcataat 840
gccaagacaa accgcgggaa ggacgactac gccagcactt acgtgttggg cagcgtctc 900
accgtcttc accaggactg gctgaatggc aaggagttaca agtgcacggt ctccaaacaaa 960
ggccctcccg ccccatcgaa gaaaaccatccaaaggccca aaggccggccc ccggagaacca 1020
cagggtgtaca ccctgttccca atccggggat gagatggacc cttttttttt cggccgtgg 1080
tgccctgttca aaggcttcttcccaaggccca atccggggat gttggggatggg caatggccag 1140
ccggagaaca actacaagac cacgcctccc gtgtgttggact ccggacggctc ctttttctc 1200
tacagcaagc tcaccgtggaa caagagcagg tggcagcagg ggaacgttccctt ctcatgtcc 1260
gtgtatgtcatg aggctctgca caaccactac acgcagaaga gctctccctt gtctccgggt 1320
aatatga 1326

SEQ ID NO: 92 moltype = DNA length = 333
FEATURE Location/Qualifiers
misc_feature 1..333
note = Engineered antibody sequence
source 1..333
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 92
gagggtgcgcg ttgtggagtc tgggggaggc ttgtgtccagc ctggggggtc cctgagactc 60
tcttgtgcag tctctggact cgacacctcg agtactaca tgcaatgggt ccgtcaggct 120

US 12,391,749 B2

99**100**

-continued

ccagggaaagg ggctggagtg ggctggagtc attggtatca atgataaacac atactacgct agctggcgta aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgttag aggggacatc tggggccaag ggaccctcgta caccgtctcg agc	180 240 300 333
 SEQ ID NO: 93 moltype = DNA length = 90 FEATURE Location/Qualifiers misc_feature 1..90 note = Engineered antibody sequence source 1..90 mol_type = other DNA organism = synthetic construct	
 SEQUENCE: 93 ggaggtcagtc ttgtggagtc tggggggaggc ttgggtccagg ctggggggtc cctgagactc tcctgtcag tctctggact cgacctcagt	60 90
 SEQ ID NO: 94 moltype = DNA length = 15 FEATURE Location/Qualifiers misc_feature 1..15 note = Engineered antibody sequence source 1..15 mol_type = other DNA organism = synthetic construct	
 SEQUENCE: 94 agctactaca tgcaa	15
 SEQ ID NO: 95 moltype = DNA length = 42 FEATURE Location/Qualifiers misc_feature 1..42 note = Engineered antibody sequence source 1..42 mol_type = other DNA organism = synthetic construct	
 SEQUENCE: 95 tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga	42
 SEQ ID NO: 96 moltype = DNA length = 48 FEATURE Location/Qualifiers misc_feature 1..48 note = Engineered antibody sequence source 1..48 mol_type = other DNA organism = synthetic construct	
 SEQUENCE: 96 gtcattggta tcaatgataa cacatactac gcgagctggg cgaaaggc	48
 SEQ ID NO: 97 moltype = DNA length = 96 FEATURE Location/Qualifiers misc_feature 1..96 note = Engineered antibody sequence source 1..96 mol_type = other DNA organism = synthetic construct	
 SEQUENCE: 97 cgattccacca tctccagaga caattccaaag accacggtgt atcttcaat gaacagcctg agagctgagg acactgctgt gtatttctgt gctaga	60 96
 SEQ ID NO: 98 moltype = length = SEQUENCE: 98 000	
 SEQ ID NO: 99 moltype = DNA length = 33 FEATURE Location/Qualifiers misc_feature 1..33 note = Engineered antibody sequence source 1..33 mol_type = other DNA organism = synthetic construct	
 SEQUENCE: 99 tggggccaag ggaccctcgta caccgtctcg agc	33
 SEQ ID NO: 100 moltype = DNA length = 993 FEATURE Location/Qualifiers misc_feature 1..993 note = Engineered antibody sequence source 1..993 mol_type = other DNA organism = synthetic construct	
 SEQUENCE: 100	

-continued

```

gcctccacca agggcccatc ggtttcccc ctggcacccct cctccaagag cacctctggg 60
ggcacagcg gcccggctg cctggtaag gactacttc ccgaaccgg gacgggtcg 120
tggaaactcg ggcgcctgac cagcggcggtg cacacccctc cggctgtct acagtccctca 180
ggactctact ccctcagcag cgtggtgacc gtgcctccca gcagctggg caccaggacc 240
tacatctgca acgtgaatca caagcccgao aacccaagg tggacggcgag agttgagccc 300
aaatcttgg aaaaaactca cacaatggca cctgtccca caccgtgaact ccttgggggaa 360
ccgtcagtct tccttctccc cccaaaaccc aaggacacc tcatgatctc ccggaccct 420
gagggtcacat gctgtgggt ggacgtgago cacgaagacc ctgaggtaa gttcaactgg 480
taacgtggacg gctgtggggat gcataatggc aagacaaacg egcggggagga gcagtgaccc 540
agcacgtacc ttgtggtcag cgttctcacc gtcctgcacc aggactggct gaatggcaag 600
gagttacaatg gcaagggtctc caacaagcc cttccagccccc ecategagaa aaccatctcc 660
aaagccaaag ggcagcccc agaaccacag gtgtacacc tgccccatc ccggggaggag 720
atgaccaaga accagggtca gctgtggctc ctgtcaaaagg gtttctatcc cagcgacatc 780
gcccgtggagt gggagggca gggacggcc gagaacaact acaagaccac gcctccctgg 840
cttgactccg acgggtctt cttcttctac agcaagtc a cctgtggacaa gagcagggtgg 900
cagcagggggaa acgttcttc atgtccgtg atgtcatgagg ctctgcacaa ccactacacg 960
cagaagagcc tttccctgtc tccgggtaaa tga 993

```

SEQ ID NO: 101 moltype = AA length = 219
 FEATURE Location/Qualifiers
 REGION 1..219
 note = Engineered antibody sequence
 source 1..219
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 101
 QVLTQSPSSL SASVGDRVTI NCQASQSVYD NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSSSGDC FVFGGGTKVE IKRTVAAPSV 120
 FIRPPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
 STSTTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 219

SEQ ID NO: 102 moltype = AA length = 113
 FEATURE Location/Qualifiers
 REGION 1..113
 note = Engineered antibody sequence
 source 1..113
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 102
 QVLTQSPSSL SASVGDRVTI NCQASQSVYD NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSSSGDC FVFGGGTKVE IKR 113

SEQ ID NO: 103 moltype = AA length = 22
 FEATURE Location/Qualifiers
 REGION 1..22
 note = Engineered antibody sequence
 source 1..22
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 103
 QVLTQSPSSL SASVGDRVTI NC 22

SEQ ID NO: 104 moltype = AA length = 13
 FEATURE Location/Qualifiers
 REGION 1..13
 note = Engineered antibody sequence
 source 1..13
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 104
 QASQSVYDNN YLA 13

SEQ ID NO: 105 moltype = AA length = 15
 FEATURE Location/Qualifiers
 REGION 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 105
 WYQQKPGKVP KQLIY 15

SEQ ID NO: 106 moltype = AA length = 7
 FEATURE Location/Qualifiers
 REGION 1..7
 note = Engineered antibody sequence
 source 1..7
 mol_type = protein
 organism = synthetic construct

-continued

SEQUENCE: 106
STSTLAS

SEQ ID NO: 107 moltype = AA length = 32
FEATURE Location/Qualifiers
REGION 1..32
note = Engineered antibody sequence
source 1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 107
GVPSRFSGSG SGTDFTLTIS SLQPEDVATY YC 32

SEQ ID NO: 108 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
note = Engineered antibody sequence
source 1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 108
LGSYDCSSGD CFV 13

SEQ ID NO: 109 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Engineered antibody sequence
source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 109
FGGGTKVEIK R 11

SEQ ID NO: 110 moltype = AA length = 106
FEATURE Location/Qualifiers
REGION 1..106
note = Engineered antibody sequence
source 1..106
mol_type = protein
organism = synthetic construct

SEQUENCE: 110
TVAAPSVFIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC 106

SEQ ID NO: 111 moltype = DNA length = 660
FEATURE Location/Qualifiers
misc_feature 1..660
note = Engineered antibody sequence
source 1..660
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 111
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattggcagg ccagtccatcg tggttatcat aacaactacc tagcctggta tcagcagaaa 120
ccagggaaag ttccataagca actgtatcatat tctacatccca ctctggcatc tggggtccca 180
tctcgtttca gtggcagtgg atctgggaca gatttcacttc tcaccatcag cagcctgcag 240
cctgaagatg ttgcaactta ttactgtcta ggcagttatg attgttagtg tggtgatgt 300
tttgttttcg gggggggaaac caagggtggaa atcaaacatcg cgggtggctgc accatctgtc 360
ttcatcttcc cgccatctgtca tgacgtgg aaatctggaa ctgcctctgt tggtgctgt 420
ctgataataact ttatccccag agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcgggtaact cccaggagag tgcacatcg caggacacaa aggacacac ctacagcctc 540
agcagcaccc tgacgtcgag caaaggcagac tacgagaaac acaaagtcta cgcctgcga 600
gtcacccatc agggcctcgat ctcgcggcgtc acaaagggcgt tcaacagggg agagtgttag 660

SEQ ID NO: 112 moltype = DNA length = 339
FEATURE Location/Qualifiers
misc_feature 1..339
note = Engineered antibody sequence
source 1..339
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 112
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattggcagg ccagtccatcg tggttatcat aacaactacc tagcctggta tcagcagaaa 120
ccagggaaag ttccataagca actgtatcatat tctacatccca ctctggcatc tggggtccca 180
tctcgtttca gtggcagtgg atctgggaca gatttcacttc tcaccatcag cagcctgcag 240
cctgaagatg ttgcaactta ttactgtcta ggcagttatg attgttagtg tggtgatgt 300
tttgttttcg gggggggaaac caagggtggaa atcaaacatcg cgggtggctgc accatctgtc 339

-continued

```

SEQ ID NO: 113      moltype = DNA  length = 66
FEATURE
misc_feature        Location/Qualifiers
1..66
note = Engineered antibody sequence
source
1..66
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 113
caagtgtga cccagtcctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60
aattgc                                         66

SEQ ID NO: 114      moltype = DNA  length = 39
FEATURE
misc_feature        Location/Qualifiers
1..39
note = Engineered antibody sequence
source
1..39
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 114
caggccagtc agagtgttta tgataacaac tacctagcc                                39

SEQ ID NO: 115      moltype = DNA  length = 45
FEATURE
misc_feature        Location/Qualifiers
1..45
note = Engineered antibody sequence
source
1..45
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 115
tggtatcagc agaaaccagg gaaaattctt aagcaactga tctat                                45

SEQ ID NO: 116      moltype = DNA  length = 21
FEATURE
misc_feature        Location/Qualifiers
1..21
note = Engineered antibody sequence
source
1..21
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 116
tctacatcca ctctggcatc t                                         21

SEQ ID NO: 117      moltype = DNA  length = 96
FEATURE
misc_feature        Location/Qualifiers
1..96
note = Engineered antibody sequence
source
1..96
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 117
ggggtccccat ctcgttttag tggcagtgg a tttcactct caccatcagc 60
agcctgcagc ctgaagatgt tgcaacttat tactgt                                         96

SEQ ID NO: 118      moltype = DNA  length = 39
FEATURE
misc_feature        Location/Qualifiers
1..39
note = Engineered antibody sequence
source
1..39
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 118
ctaggcagtt atgattttag tagtggtat tttttgtt                                39

SEQ ID NO: 119      moltype = DNA  length = 33
FEATURE
misc_feature        Location/Qualifiers
1..33
note = Engineered antibody sequence
source
1..33
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 119
ttcggcgagg gaaccaaggat ggaaatcaaa cgt                                33

SEQ ID NO: 120      moltype = DNA  length = 321
FEATURE
misc_feature        Location/Qualifiers
1..321
note = Engineered antibody sequence
source
1..321
mol_type = other DNA
organism = synthetic construct

```

-continued

SEQUENCE: 120
 acgggtggctg caccatctgt cttcatcttc ccgcacatctg atgaggcgtt gaaatcttgg 60
 actgcctctg ttgtgtgcct gctgataac ttcataccca gagaggccaa agtacagtgg 120
 aagggtggata acgcctcca atcgggttaac tcccaggaga gtgtcacaga gcaggacagc 180
 aaggacacga octacagctc cagcagcacc ctgacgcgtg gcaaaggaga ctacgagaaa 240
 cacaaggctc acgcctgcga agtcacccat caggcctgta gtcgcggcgt cacaaggagc 300
 ttcaacagg gagagtgtta g 321

SEQ ID NO: 121 moltype = AA length = 439
 FEATURE Location/Qualifiers
 REGION 1..439
 note = Engineered antibody sequence
 source 1..439
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 121
 QSLLEESGGLR VTPGTPLTLT CSVSGIDLSG YYMNWVRQAP GKGLEWIGVI GINGATYYAS 60
 WAKGRFTISK TSSTTVDLKM TSLTTEDTAT YFCARGDIWG PGTLVTVSSA STKGPSVFPL 120
 APSSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TPPAVLQSSG LYSLSSVTV 180
 PSSSLGTQTY ICNVNHPKSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 240
 DTMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAAK TKPREEQYAS TYRVVSVLTV 300
 LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREEPVY YTLPPSREEM TKNQVSLTCL 360
 VIKGFYPSDIA VEWESENQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM 420
 HEALHNHYTQ KSLSLSPGK 439

SEQ ID NO: 122 moltype = AA length = 109
 FEATURE Location/Qualifiers
 REGION 1..109
 note = Engineered antibody sequence
 source 1..109
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 122
 QSLLEESGGGLR VTPGTPLTLT CSVSGIDLSG YYMNWVRQAP GKGLEWIGVI GINGATYYAS 60
 WAKGRFTISK TSSTTVDLKM TSLTTEDTAT YFCARGDIWG PGTLVTVSS 109

SEQ ID NO: 123 moltype = AA length = 29
 FEATURE Location/Qualifiers
 REGION 1..29
 note = Engineered antibody sequence
 source 1..29
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 123
 QSLLEESGGGLR VTPGTPLTLT CSVSGIDLS 29

SEQ ID NO: 124 moltype = AA length = 5
 FEATURE Location/Qualifiers
 REGION 1..5
 note = Engineered antibody sequence
 source 1..5
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 124
 GYYMN 5

SEQ ID NO: 125 moltype = AA length = 14
 FEATURE Location/Qualifiers
 REGION 1..14
 note = Engineered antibody sequence
 source 1..14
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 125
 WVRQAPGKGL EWIG 14

SEQ ID NO: 126 moltype = AA length = 16
 FEATURE Location/Qualifiers
 REGION 1..16
 note = Engineered antibody sequence
 source 1..16
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 126
 VIGINGATYY ASWAKG 16

SEQ ID NO: 127 moltype = AA length = 31
 FEATURE Location/Qualifiers
 REGION 1..31

-continued

```

source          note = Engineered antibody sequence
               1..31
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 127
RFTISKTSST TVDLKMTSLT TEDTATYFCA R                         31

SEQ ID NO: 128      moltype = length =
SEQUENCE: 128
000

SEQ ID NO: 129      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Engineered antibody sequence
source            1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 129
WGPGLTVS S                                         11

SEQ ID NO: 130      moltype = AA length = 330
FEATURE          Location/Qualifiers
REGION           1..330
note = Engineered antibody sequence
source            1..330
mol_type = protein
organism = synthetic construct
SEQUENCE: 130
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYPPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
STYRVSLSVT VLHQDWLNGK EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPSSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPKG                         330

SEQ ID NO: 131      moltype = DNA length = 1320
FEATURE          Location/Qualifiers
misc_feature     1..1320
note = Engineered antibody sequence
source            1..1320
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 131
cagtcgtgg aggagtccgg gggtcgcctg gtcacgcctg ggacaccct gacactcacc 60
tggccgtct ctggcatcg  cctcagtgg tactacatga actgggtccg ccaggctcca 120
ggaaaggggc tggaatggat cggagttatgg gtgattatgg gtgcacata ctacgcgagc 180
tgggcgaaag gocgattcac catctccaaa acctcgtcg  ccacgggtga tctgaaaatg 240
accagtcgtca caaccgagga cacggccacc tatttctgtg ccagaggggcatctggggc 300
ccggccaccc tcgtcaccgt ctcgagccg  tccacaaccg gcccacatcggt ctccccctg 360
geaccctcc  caaaggagcac ctctggggc acagcggccc tgggctgcgt ggtcaaggac 420
taacctcccg aaccggtgac ggtgcgtgg aactcaggcg ccctgaccag cggcggtcac 480
accttcccg  ctgtcctaca gtcctcgg  ctctactccc tcagcagcgt ggtgaccgtg 540
ccctccagca gttggggcac ccagacaccat atctgcaacg tgaatcacac gcccaccaac 600
accaaaggaggc acaagaggat tgagggccaaa tcttggtgaca aaactcacac atgcccacccg 660
tgcccaaggcc ctgaaactctt gggggggaccg tcagtcttcc ttttcccccc aaaacccaaag 720
gacaccctca tgatctcccg gacccttgag gtcacatgcg tgggtggta cgtgagccac 780
gaagaccctcg aggtcaaggct caactggtagt gtggacggcg tgggggtgca taatgccaag 840
acaaaaggccg gggaggagca gtacccgacg acgttaccgtg tggtcagcgt cctcaccgtc 900
ctgcaccagg actggctaa tggcaaggag tacaaggcg  aggtctccaa caaaggccctc 960
ccagccccca tcgagaaaaac catctccaaa gccaaagggc accccccgaga accacagggt 1020
tacaccctgc ccccatcccg ggaggaggat accaagaacc aggtcaaggct gacccgtctg 1080
gtcaaaggctc tctatggccg cgacatcgcc gtggagtgccc agagcaatgg gcagccggag 1140
aacaactaca accacacgccc tccctgtcg gactccgacg gtccttctt cctctacacg 1200
aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgtatg 1260
catgagggtc tgcacaacca ctacacgcac aagagcctctt ccctgtctcc gggtaatga 1320

SEQ ID NO: 132      moltype = DNA length = 327
FEATURE          Location/Qualifiers
misc_feature     1..327
note = Engineered antibody sequence
source            1..327
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 132
cagtcgtgg aggagtccgg gggtcgcctg gtcacgcctg ggacaccct gacactcacc 60
tggccgtct ctggcatcg  cctcagtgg tactacatga actgggtccg ccaggctcca 120
ggaaaggggc tggaatggat cggagttatgg gtgattatgg gtgcacata ctacgcgagc 180
tgggcgaaag gocgattcac catctccaaa acctcgtcg  ccacgggtga tctgaaaatg 240

```

-continued

```

accagtctga caaccgagga cacggccacc tatttctgtg ccagagggga catctgggc 300
cgggcaccc tcgtcaccgt ctcgagc 327

SEQ ID NO: 133      moltype = DNA length = 87
FEATURE             Location/Qualifiers
misc_feature        1..87
note = Engineered antibody sequence
source              1..87
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 133
cagtcgtgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60
tgtccgtct ctggcatcga cctcagt 87

SEQ ID NO: 134      moltype = DNA length = 15
FEATURE             Location/Qualifiers
misc_feature        1..15
note = Engineered antibody sequence
source              1..15
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 134
ggctactaca tgaac 15

SEQ ID NO: 135      moltype = DNA length = 42
FEATURE             Location/Qualifiers
misc_feature        1..42
note = Engineered antibody sequence
source              1..42
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 135
tgggtccgcc aggctccagg gaaggggatcg gaatggatcg ga 42

SEQ ID NO: 136      moltype = DNA length = 48
FEATURE             Location/Qualifiers
misc_feature        1..48
note = Engineered antibody sequence
source              1..48
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 136
gtcattggta ttaatggtgc cacatactac gcgagctggg cgaaaggc 48

SEQ ID NO: 137      moltype = DNA length = 93
FEATURE             Location/Qualifiers
misc_feature        1..93
note = Engineered antibody sequence
source              1..93
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 137
cgattcacca tctccaaaac ctcgtcgacc acgggtggatc tgaaaatgac cagtctgaca 60
acggaggaca cggccaccta tttctgtgcc aga 93

SEQ ID NO: 138      moltype = length =
SEQUENCE: 138
000

SEQ ID NO: 139      moltype = DNA length = 33
FEATURE             Location/Qualifiers
misc_feature        1..33
note = Engineered antibody sequence
source              1..33
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 139
tggggccccgg gcaccctcg caccgtctcg agc 33

SEQ ID NO: 140      moltype = DNA length = 993
FEATURE             Location/Qualifiers
misc_feature        1..993
note = Engineered antibody sequence
source              1..993
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 140
gcctccacca agggcccatc gggttcccc ctggcacccct cctccaagag cacctctggg 60
ggcacagcgg ccctgggctg cctggtcaag gactactcc cccgaaaccgt gacgggtcgg 120

```

-continued

```
tggaaactcag gcgcctgac cagggcgtg cacacccccc cggctgtctt acagtccca 180
ggactctact ccctcagcag cgtggacc gtgcctcca gcagctggg caccaggacc 240
tacatctgca acgtgaatca caagccccc aacaccaagg tggacaagg agttgagccc 300
aaatcttgta aaaaaactca cacatcccc cccgtcccc cacctgaact cctgggggga 360
ccgtcagtc tctcttcccc cccaaaaccc aaggacaccc tcattatcc ccggaccct 420
gaggtcacat gctgtgggt ggacgtggago cagaagaccc ctgaggtaaa gttcaactgg 480
tacggtggac gctgtggaggt gcataatgcc aagacaaacg cgccggggga gcagtacgcc 540
agcacgtacc gtgtggtagt cgtccctcacc gtctgcacc aggactggct gaatggcaag 600
gagtacaaatg gcaaggctcc caaacaaagg cccatcccccc ccatacgagaa aaccatctcc 660
aaaggccaaag ggcagccccg aaaggccacag tggtacaccg tgccccatcc ccggggaggag 720
atgaccaaga accaggctcag cctgacccgc ctgtcaaaatg gttctatcc cagcgacatc 780
gccgtggagt gggagagcaa tggcagccg gagaacaact acaagaccac gcctccctg 840
ctggactccg acggcccttcc ctccctctac agcaagctca ccgtggacaa gagcagggtgg 900
cagcaggggaa acgttcttc atgtccctgtt atgcatgggg ctctgcacaa ccactacacg 960
cagaagggcc tccctgtc tccggtaaa tga 993
```

```
SEQ ID NO: 141 moltype = AA length = 219
FEATURE Location/Qualifiers
REGION 1..219
note = Engineered antibody sequence
source 1..219
mol_type = protein
organism = synthetic construct
SEQUENCE: 141
QVLTQTPSPV SAAVGSTVTI NCQASQSVYH NTYLAWYQQK PGQPPKQLIY DASTLASGVP 60
SRFSGSGSGT QFTLTISGVQ CNDAAAYYCL GSYDCTNGDC FVFGGGTEVV VKRTVAAPSV 120
FIPPPSDEQL KSGTASVVCN LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STLTLASKD YEKHKVYACE VTHQGLSSPV TKSFNRRGEC 219
```

```
SEQ ID NO: 142 moltype = AA length = 113
FEATURE Location/Qualifiers
REGION 1..113
note = Engineered antibody sequence
source 1..113
mol_type = protein
organism = synthetic construct
SEQUENCE: 142
QVLTQTPSPV SAAVGSTVTI NCQASQSVYH NTYLAWYQQK PGQPPKQLIY DASTLASGVP 60
SRFSGSGSGT QFTLTISGVQ CNDAAAYYCL GSYDCTNGDC FVFGGGTEVV VKR 113
```

```
SEQ ID NO: 143 moltype = AA length = 22
FEATURE Location/Qualifiers
REGION 1..22
note = Engineered antibody sequence
source 1..22
mol_type = protein
organism = synthetic construct
SEQUENCE: 143
QVLTQTPSPV SAAVGSTVTI NC 22
```

```
SEQ ID NO: 144 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
note = Engineered antibody sequence
source 1..13
mol_type = protein
organism = synthetic construct
SEQUENCE: 144
QASQSVYHNT YLA 13
```

```
SEQ ID NO: 145 moltype = AA length = 15
FEATURE Location/Qualifiers
REGION 1..15
note = Engineered antibody sequence
source 1..15
mol_type = protein
organism = synthetic construct
SEQUENCE: 145
WYQQKPGQPP KQLIY 15
```

```
SEQ ID NO: 146 moltype = AA length = 7
FEATURE Location/Qualifiers
REGION 1..7
note = Engineered antibody sequence
source 1..7
mol_type = protein
organism = synthetic construct
SEQUENCE: 146
DASTLAS 7
```

-continued

```

SEQ ID NO: 147      moltype = AA length = 32
FEATURE          Location/Qualifiers
REGION           1..32
source            note = Engineered antibody sequence
                  1..32
mol_type = protein
organism = synthetic construct
SEQUENCE: 147
GVPSRFSGSG SGTQFTLTIS GVQCNDAAAY YC                                     32

SEQ ID NO: 148      moltype = AA length = 13
FEATURE          Location/Qualifiers
REGION           1..13
source            note = Engineered antibody sequence
                  1..13
mol_type = protein
organism = synthetic construct
SEQUENCE: 148
LGSYDCTNGD CFV                                                       13

SEQ ID NO: 149      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
source            note = Engineered antibody sequence
                  1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 149
FGGGTEVVVK R                                                       11

SEQ ID NO: 150      moltype = AA length = 106
FEATURE          Location/Qualifiers
REGION          1..106
source            note = Engineered antibody sequence
                  1..106
mol_type = protein
organism = synthetic construct
SEQUENCE: 150
TVAAPSVIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC                      106

SEQ ID NO: 151      moltype = DNA length = 660
FEATURE          Location/Qualifiers
misc_feature    1..660
source            note = Engineered antibody sequence
                  1..660
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 151
caagtgtcga cccagactcc atccccctgt tctgcagctg tgggaagcac agtcaccatc 60
aattgccagg ccagtcagag tgtttatcat aacacctacc tggcctggta tcagcagaaa 120
ccagggcagc ctcccaaaca actgatctat gatgcattca ctctggcgtc tgggtccca 180
tcgcggttca gcccggatgg atctgggaca cagttcactt caaccatcag cggcgatcag 240
tgtaacatcgatc ctgcgccta ctactgtctg ggccatgttggatggatggatggatgg 300
tttgttttcg gcccggatgg acggatggatggatggatggatggatggatggatggatgg 360
ttcatcttc cgccatctga tgacgttgg aaatctggaa ctgcctctgt tggatggatgg 420
ctgaataact ttatcccaag agggccaaa gtacatcgatc ggccatgttggatggatgg 480
tcgggttacttccatcccaag cccaggatggatggatggatggatggatggatggatgg 540
agcagcaccc tgacgttgcgatc cccaggatggatggatggatggatggatggatggatgg 600
gtcacccatc agggccatc ctcgcgttgcgatc cccaggatggatggatggatggatggatgg 660

SEQ ID NO: 152      moltype = DNA length = 339
FEATURE          Location/Qualifiers
misc_feature    1..339
source            note = Engineered antibody sequence
                  1..339
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 152
caagtgtcga cccagactcc atccccctgt tctgcagctg tgggaagcac agtcaccatc 60
aattgccagg ccagtcagag tgtttatcat aacacctacc tggcctggta tcagcagaaa 120
ccagggcagc ctcccaaaca actgatctat gatgcattca ctctggcgtc tgggtccca 180
tcgcggttca gcccggatgg atctgggaca cagttcactt caaccatcag cggcgatcag 240
tgtaacatcgatc ctgcgccta ctactgtctg ggccatgttggatggatggatggatgg 300
tttgttttcg gcccggatgg acggatggatggatggatggatggatggatggatggatgg 360
ttcatcttc cgccatctga tgacgttgg aaatctggaa ctgcctctgt tggatggatgg 420
ctgaataact ttatcccaag agggccaaa gtacatcgatc ggccatgttggatggatgg 480
tcgggttacttccatcccaag cccaggatggatggatggatggatggatggatggatgg 540
agcagcaccc tgacgttgcgatc cccaggatggatggatggatggatggatggatggatgg 600
gtcacccatc agggccatc ctcgcgttgcgatc cccaggatggatggatggatggatggatgg 660

SEQ ID NO: 153      moltype = DNA length = 66
FEATURE          Location/Qualifiers

```

-continued

```

misc_feature      1..66
                  note = Engineered antibody sequence
source           1..66
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 153
caagtgtga cccagactcc atccccgtg tctgcagctg tggaaagcac agtcaccatc  60
aattgc                                     66

SEQ ID NO: 154      moltype = DNA length = 39
FEATURE
misc_feature      1..39
                  note = Engineered antibody sequence
source           1..39
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 154
caggccagtc agagtgttta tcataaacacc tacctggcc                                39

SEQ ID NO: 155      moltype = DNA length = 45
FEATURE
misc_feature      1..45
                  note = Engineered antibody sequence
source           1..45
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 155
tggtatcagc agaaaaccagg gcagctccc aaacaactga tctat                                45

SEQ ID NO: 156      moltype = DNA length = 21
FEATURE
misc_feature      1..21
                  note = Engineered antibody sequence
source           1..21
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 156
gatgcatcca ctctggcgtc t                                         21

SEQ ID NO: 157      moltype = DNA length = 96
FEATURE
misc_feature      1..96
                  note = Engineered antibody sequence
source           1..96
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 157
gggttcccat cgcggtttag cgccagtgga tctgggacac agttcactct caccatcagc  60
ggcgtgcagt gtaacgatgc tgccgcttac tactgt                                96

SEQ ID NO: 158      moltype = DNA length = 39
FEATURE
misc_feature      1..39
                  note = Engineered antibody sequence
source           1..39
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 158
ctgggcagtt atgattgtac taatggtgat tgttttgtt                                39

SEQ ID NO: 159      moltype = DNA length = 33
FEATURE
misc_feature      1..33
                  note = Engineered antibody sequence
source           1..33
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 159
ttcggcggag ggaccgaggt ggtggtcaaa cgt                                33

SEQ ID NO: 160      moltype = DNA length = 321
FEATURE
misc_feature      1..321
                  note = Engineered antibody sequence
source           1..321
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 160
acggtgtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga  60

```

-continued

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
 aagggtggata acgcctcca atcggtaac tcccaggaga gtgtcacaga gcaggacagc 180
 aaggacacga cctacagcct cagcagcacc ctgacgctga gcaaaggaga ctacgagaaa 240
 cacaaggctc acgcctgcga agtcacccat cagggcctga gtcgcccgt cacaaggagc 300
 ttcaacaggg gagagtta g 321

SEQ ID NO: 161 moltype = AA length = 441
 FEATURE Location/Qualifiers
 REGION 1..441
 note = Engineered antibody sequence
 source 1..441
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 161
 EVQLVESGGG LVQPGGSLRL SCAVSGIDLS GYYMNWVRQA PGKGLEWVGV IGINGATYYA 60
 SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
 PLAPSSKSTS CGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
 TVPSSSLGTQ TYICNVNHPK SNTKVDKRVE PKSCDKTHTC PPCPAPELIG GPSVFLFPPK 240
 PKDTLMISR PFEVTCVVVD SHEDPEVKFN WYDGVVEVHN AKTKPREEQY ASTYRVVSL 300
 TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
 CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSSFL YSKLTVDKSR WQQGNVFSCS 420
 VMHEALHNHY TQKSLSLSPG K 441

SEQ ID NO: 162 moltype = AA length = 111
 FEATURE Location/Qualifiers
 REGION 1..111
 note = Engineered antibody sequence
 source 1..111
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 162
 EVQLVESGGG LVQPGGSLRL SCAVSGIDLS GYYMNWVRQA PGKGLEWVGV IGINGATYYA 60
 SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS S 111

SEQ ID NO: 163 moltype = AA length = 30
 FEATURE Location/Qualifiers
 REGION 1..30
 note = Engineered antibody sequence
 source 1..30
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 163
 EVQLVESGGG LVQPGGSLRL SCAVSGIDLS 30

SEQ ID NO: 164 moltype = AA length = 5
 FEATURE Location/Qualifiers
 REGION 1..5
 note = Engineered antibody sequence
 source 1..5
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 164
 GYYMN 5

SEQ ID NO: 165 moltype = AA length = 14
 FEATURE Location/Qualifiers
 REGION 1..14
 note = Engineered antibody sequence
 source 1..14
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 165
 WVRQAPGKGL EWVG 14

SEQ ID NO: 166 moltype = AA length = 16
 FEATURE Location/Qualifiers
 REGION 1..16
 note = Engineered antibody sequence
 source 1..16
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 166
 VIGINGATYY ASWAKG 16

SEQ ID NO: 167 moltype = AA length = 32
 FEATURE Location/Qualifiers
 REGION 1..32
 note = Engineered antibody sequence
 source 1..32

-continued

```

mol_type = protein
organism = synthetic construct

SEQUENCE: 167
RFTISRDNSK TTVYLOMNSL RAEDTAVYFC AR                                32

SEQ ID NO: 168      moltype = length =
SEQUENCE: 168
000

SEQ ID NO: 169      moltype = AA length = 11
FEATURE
REGION
1..11
note = Engineered antibody sequence
1..11
source
mol_type = protein
organism = synthetic construct

SEQUENCE: 169
WGQGTLVTVS S                                              11

SEQ ID NO: 170      moltype = AA length = 330
FEATURE
REGION
1..330
note = Engineered antibody sequence
1..330
source
mol_type = protein
organism = synthetic construct

SEQUENCE: 170
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSSVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELGG 120
PSVFLFPPKP KDLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK                                330

SEQ ID NO: 171      moltype = DNA length = 1326
FEATURE
misc_feature
1..1326
note = Engineered antibody sequence
1..1326
source
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 171
gagggtcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60
tccctgtcagc tctctggaat cgacctcagt ggctactaca tgaactgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggtcgaggatc attggattata atggtgcac atactacgcg 180
agctggcgca aaggccgatt caccatctcc agagacaattt ccaagaccac ggtgtatctt 240
caaataatggaca gcctgagacg tgaggacact gctgtgtatt tctgtgttag aggggacatc 300
tggggccaag ggaccctcgat caccgtctcg agggcctcca ccaaggcccc atcggctttc 360
cccctggcac cctccctccaa gagcacctct gggggcacaag cggccctggg ctgcgtggc 420
aaggactact tcccgaaacc ggtacggctg tcgttgcactt caggccccc gaccaggccc 480
gtgcacacact tcccggtgt ctacatcgcc tcaggactct actccctcg caggcgtgg 540
accgtgcctt ccaggcgttt gggcccccac acctacatctt ccaacgtgaa tcacaaggcc 600
agcaacacca aggtggacaa gagagttgag cccaaatctt gtgacaaaac tcacacatgc 660
ccaccgtgcg caccgtcgact acctctgggg ggaccgtcaacttccctt ccccccacaaa 720
cccaaggaca ccctcatgtat ctccggccg cctgaggatca catcgctgtt ggtggacgt 780
agccacaaag accctggatc caagtcaac ttgtacgtgg acggcgtgaa ggtgcataat 840
gccaagacaa agcccgggga ggagcgtac gcccacgtt accgtgttgtt cagcgtcctc 900
accgtcttcg accaggactt gctaatggc aaggagatca aatgtcaaggctt ctccaaacaaa 960
ggccatcccg ccccatcgaa gaaaatggca tccaaatggca aaggccggcc cccgagaacca 1020
cagggtgtaca ccctggccca atccggagatc gagatgttca agaaccaggat cagctgtacc 1080
tgcgtgttca aaggcttcta tcccgccgac atcgccgtgg agtggggagag caatggccag 1140
ccggagaaaca actacaagac caecgcctcc gttgtggactt ccgaaggctc cttttctc 1200
tacagcaagc tcaccgtggca caagagcagg tggcagcagg ggaacgtttt ctcatgttcc 1260
gtgtatgtatc aggtctgtca caaccactac acgcagaaga gcctctccctt gtctccgggt 1320
aatatga                                         1326

SEQ ID NO: 172      moltype = DNA length = 333
FEATURE
misc_feature
1..333
note = Engineered antibody sequence
1..333
source
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 172
gagggtcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60
tccctgtcagc tctctggaat cgacctcagt ggctactaca tgaactgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggtcgaggatc attggattata atggtgcac atactacgcg 180
agctggcgca aaggccgatt caccatctcc agagacaattt ccaagaccac ggtgtatctt 240
caaataatggaca gcctgagacg tgaggacact gctgtgtatt tctgtgttag aggggacatc 300

```

-continued

tggggccaag ggaccctcg	caccgtctcg	agc	333	
SEQ ID NO: 173	moltype = DNA length = 90			
FEATURE	Location/Qualifiers			
misc_feature	1..90			
	note = Engineered antibody sequence			
source	1..90			
	mol_type = other DNA			
	organism = synthetic construct			
SEQUENCE: 173				
gagggtgcagc ttgtggagtc	tgggggaggo	ttgggtccagc	ctggggggtc cctgagactc	60
tcctgtcgac	tctctggaaat	cgacccatcgat		90
SEQ ID NO: 174	moltype = DNA length = 15			
FEATURE	Location/Qualifiers			
misc_feature	1..15			
	note = Engineered antibody sequence			
source	1..15			
	mol_type = other DNA			
	organism = synthetic construct			
SEQUENCE: 174				
ggctactaca tgaac				15
SEQ ID NO: 175	moltype = DNA length = 42			
FEATURE	Location/Qualifiers			
misc_feature	1..42			
	note = Engineered antibody sequence			
source	1..42			
	mol_type = other DNA			
	organism = synthetic construct			
SEQUENCE: 175				
tgggtccgtc aggctccagg	gaaggggctg	gagtgggtcg	ga	42
SEQ ID NO: 176	moltype = DNA length = 48			
FEATURE	Location/Qualifiers			
misc_feature	1..48			
	note = Engineered antibody sequence			
source	1..48			
	mol_type = other DNA			
	organism = synthetic construct			
SEQUENCE: 176				
gtcatttgta ttaatggtg	cacatactac	gcgagctggg	cgaaaggc	48
SEQ ID NO: 177	moltype = DNA length = 96			
FEATURE	Location/Qualifiers			
misc_feature	1..96			
	note = Engineered antibody sequence			
source	1..96			
	mol_type = other DNA			
	organism = synthetic construct			
SEQUENCE: 177				
cgattcacca tctccagaga	caattccaag	accacgggt	atcttcaa	60
agagctgagg	acactgctgt	gtatttctgt	gctaga	96
SEQ ID NO: 178	moltype = length =			
SEQUENCE: 178				
000				
SEQ ID NO: 179	moltype = DNA length = 33			
FEATURE	Location/Qualifiers			
misc_feature	1..33			
	note = Engineered antibody sequence			
source	1..33			
	mol_type = other DNA			
	organism = synthetic construct			
SEQUENCE: 179				
tggggccaag ggaccctcg	caccgtctcg	agc	33	
SEQ ID NO: 180	moltype = DNA length = 993			
FEATURE	Location/Qualifiers			
misc_feature	1..993			
	note = Engineered antibody sequence			
source	1..993			
	mol_type = other DNA			
	organism = synthetic construct			
SEQUENCE: 180				
gcctccacca agggcccatc	ggctttcccc	ctggcaccc	cctccaagag	60
ggcacagcgg	ccctgggtcg	cctgtcaag	gactacttcc	120
tggaacttag	cgccctcgac	cagccgcgtg	cacacccctcc	180

-continued

```

ggactctact ccctcagcacg cgtggtgacc gtgccttcca gcagcttggg caccaggacc 240
tatatctgca acgtgaatca caagccagc aacaccaagg tggacaagag agttgagccc 300
aaatcttgtg aaaaaactca cacatgccca ccgtgccccag caccctgact cctgggggg 360
ccgtcagtct tcctttccc cccaaaaccc aaggacacc ccatgatctc ccggaccct 420
gaggtcacat gogtggtggt ggacgtgago cacaagacc ctggggctaa gttcaactgg 480
tacgtggacg gctgtggaggt gcataatgco aagacaaagc cgccggggaga gcagtacgcc 540
agcacgtacc gtgtggtcag cgtcttcacc gtctgcacc aggactggt gaatggcaag 600
gagtacaagt gcaaggcttc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 660
aaagccaaag ggccagccccg agaaccacag gtgtacacc tgccccccatc ccggggaggag 720
atgaccaaga accaggctcg cctgacccgc ctggtcaatgg gcttctatcc cagcgacatc 780
gcgggtggagt gggagagcaa tggcagccg gagaacaacaa acaagaccac gcctccctgt 840
ctggactccg acggcttcctt cttectctac agcaagctca ccgtggacaa gaggcagggtgg 900
caacaggggaa acgtttctc atgtccctgtg atgcatgagg ctctgcacaa ccactacacg 960
cagaagggcc ttccctgtc tccggtaaa tga 993

```

```

SEQ ID NO: 181      moltype = AA length = 219
FEATURE          Location/Qualifiers
REGION           1..219
note = Engineered antibody sequence
source            1..219
mol_type = protein
organism = synthetic construct

```

```

SEQUENCE: 181
QVLTQSPSSL SASVGDRVTI NCQASQSVYH NTYLAWYQQK PGKVPKQLIY DASTLASGVP 60
SRFSGSGSGT DFTLTISLQ PEDVATYYCL GSYDCTNGDC FVFGGGTKVE IKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTLTLKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 219

```

```

SEQ ID NO: 182      moltype = AA length = 113
FEATURE          Location/Qualifiers
REGION           1..113
note = Engineered antibody sequence
source            1..113
mol_type = protein
organism = synthetic construct

```

```

SEQUENCE: 182
QVLTQSPSSL SASVGDRVTI NCQASQSVYH NTYLAWYQQK PGKVPKQLIY DASTLASGVP 60
SRFSGSGSGT DFTLTISLQ PEDVATYYCL GSYDCTNGDC FVFGGGTKVE IKR 113

```

```

SEQ ID NO: 183      moltype = AA length = 22
FEATURE          Location/Qualifiers
REGION           1..22
note = Engineered antibody sequence
source            1..22
mol_type = protein
organism = synthetic construct

```

```

SEQUENCE: 183
QVLTQSPSSL SASVGDRVTI NC 22

```

```

SEQ ID NO: 184      moltype = AA length = 13
FEATURE          Location/Qualifiers
REGION           1..13
note = Engineered antibody sequence
source            1..13
mol_type = protein
organism = synthetic construct

```

```

SEQUENCE: 184
QASQSVYHNT YLA 13

```

```

SEQ ID NO: 185      moltype = AA length = 15
FEATURE          Location/Qualifiers
REGION           1..15
note = Engineered antibody sequence
source            1..15
mol_type = protein
organism = synthetic construct

```

```

SEQUENCE: 185
WYQQKPGKVP KQLIY 15

```

```

SEQ ID NO: 186      moltype = AA length = 7
FEATURE          Location/Qualifiers
REGION           1..7
note = Engineered antibody sequence
source            1..7
mol_type = protein
organism = synthetic construct

```

```

SEQUENCE: 186
DASTLAS 7

```

-continued

SEQ ID NO: 187 moltype = AA length = 32
 FEATURE Location/Qualifiers
 REGION 1..32
 note = Engineered antibody sequence
 source 1..32
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 187
 GVPNSRFSGSG SGTDFTLTIS SLQPEDVATY YC 32

SEQ ID NO: 188 moltype = AA length = 13
 FEATURE Location/Qualifiers
 REGION 1..13
 note = Engineered antibody sequence
 source 1..13
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 188
 LGSYDCTNGD CFV 13

SEQ ID NO: 189 moltype = AA length = 11
 FEATURE Location/Qualifiers
 REGION 1..11
 note = Engineered antibody sequence
 source 1..11
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 189
 FGGGTKEIK R 11

SEQ ID NO: 190 moltype = AA length = 106
 FEATURE Location/Qualifiers
 REGION 1..106
 note = Engineered antibody sequence
 source 1..106
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 190
 TAAAPSVIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
 KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC 106

SEQ ID NO: 191 moltype = DNA length = 660
 FEATURE Location/Qualifiers
 misc_feature 1..660
 note = Engineered antibody sequence
 source 1..660
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 191
 caagtgtga cccagtcctcc atcctccctg tctgcattcg taggagacag agtcaccatc 60
 aattgccagg ccagtcaagag tgtttatcat aacacctacc tggcctggta tcagcagaaa 120
 ccaggaaag ttcctaagca actgatctat gatgcattca ctctggcatc tggggtccca 180
 ttcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240
 cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtactaa tggtgattgt 300
 ttgttttcg gcgaggaaac caaggtggaa atcaaacgtca cggggctgc accatctgtc 360
 ttcatcttcc cgccatctgt tgacgatgtt aatctggaa ctgccttgt tggtgctcg 420
 ctgaataact tctatcccag agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
 tcggtaact cccaggagag tgccacagag caggacacgc acagacgtc 540
 agcagcaccc tgacgcttag caaagcagac tacggagaaac acaaagtcta cgcctgcgaa 600
 gtcacccatc agggccttag ctgcggccgtc acaaagcgtc tcaacagggg agagtgttag 660

SEQ ID NO: 192 moltype = DNA length = 339
 FEATURE Location/Qualifiers
 misc_feature 1..339
 note = Engineered antibody sequence
 source 1..339
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 192
 caagtgtga cccagtcctcc atcctccctg tctgcattcg taggagacag agtcaccatc 60
 aattgccagg ccagtcaagag tgtttatcat aacacctacc tggcctggta tcagcagaaa 120
 ccaggaaag ttcctaagca actgatctat gatgcattca ctctggcatc tggggtccca 180
 ttcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240
 cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtactaa tggtgattgt 300
 ttgttttcg gcgaggaaac caaggtggaa atcaaacgtca 339

SEQ ID NO: 193 moltype = DNA length = 66
 FEATURE Location/Qualifiers
 misc_feature 1..66

-continued

```

source          note = Engineered antibody sequence
               1..66
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 193
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtaccatc 60
aattgc                                     66

SEQ ID NO: 194      moltype = DNA length = 39
FEATURE          Location/Qualifiers
misc_feature     1..39
note = Engineered antibody sequence
source          1..39
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 194
caggccagtc agagtgttta tcataaacacc tacctggcc                                39

SEQ ID NO: 195      moltype = DNA length = 45
FEATURE          Location/Qualifiers
misc_feature     1..45
note = Engineered antibody sequence
source          1..45
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 195
tggttatcagc agaaaaccagg gaaagttcct aagcaactga tctat                                45

SEQ ID NO: 196      moltype = DNA length = 21
FEATURE          Location/Qualifiers
misc_feature     1..21
note = Engineered antibody sequence
source          1..21
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 196
gatgcatcca ctctggcatc t                                         21

SEQ ID NO: 197      moltype = DNA length = 96
FEATURE          Location/Qualifiers
misc_feature     1..96
note = Engineered antibody sequence
source          1..96
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 197
ggggtcccat ctcgtttcag tggcagtgg a tctgggacag atttcactct caccatcagc 60
aggcctgcagc ctgaagatgt tgcaacttat tactgt                               96

SEQ ID NO: 198      moltype = DNA length = 39
FEATURE          Location/Qualifiers
misc_feature     1..39
note = Engineered antibody sequence
source          1..39
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 198
ctgggcagtt atgattgtac taatggtgat tgttttgtt                                39

SEQ ID NO: 199      moltype = DNA length = 33
FEATURE          Location/Qualifiers
misc_feature     1..33
note = Engineered antibody sequence
source          1..33
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 199
ttcggcggag gaaccaaggt ggaaatcaaa cgt                                33

SEQ ID NO: 200      moltype = DNA length = 321
FEATURE          Location/Qualifiers
misc_feature     1..321
note = Engineered antibody sequence
source          1..321
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 200
acggtgtggctg caccatctgt ctcatcttc ccgcacatcg atgagcagg tt gaaatctgg 60
actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120

```

-continued

```
aagggtggata acggccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc 180
aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaaggaga ctacgagaaa 240
cacaaggatct acgcctgcga agtcacccat cagggcctga gctcgccctg cacaaggagc 300
ttcaacacggg gagagtgtta g 321
```

```
SEQ ID NO: 201 moltype = AA length = 441
FEATURE Location/Qualifiers
REGION 1..441
note = Engineered antibody sequence
source 1..441
mol_type = protein
organism = synthetic construct
SEQUENCE: 201
EVQLVESGGG LVQPGGSLRL SCAVSGIDLS GYYMNWVRQA PGKGLEWGV IGINGATYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
PLAPSSKSTS GGTAAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
TVPSSSLGTO TYICCNVNHKP SNTKVDARVE PKSCDKTHTC PPCPAPELLG GPSVFLPPK 240
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVSVSL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLSDGSFFL YSKLTVDKSR WQQGNVFSCS 420
VMHEALHNHY TQKSLSLSPG K 441
```

```
SEQ ID NO: 202 moltype = AA length = 111
FEATURE Location/Qualifiers
REGION 1..111
note = Engineered antibody sequence
source 1..111
mol_type = protein
organism = synthetic construct
SEQUENCE: 202
EVQLVESGGG LVQPGGSLRL SCAVSGIDLS GYYMNWVRQA PGKGLEWGVV IGINGATYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS S 111
```

```
SEQ ID NO: 203 moltype = AA length = 30
FEATURE Location/Qualifiers
REGION 1..30
note = Engineered antibody sequence
source 1..30
mol_type = protein
organism = synthetic construct
SEQUENCE: 203
EVQLVESGGG LVQPGGSLRL SCAVSGIDLS 30
```

```
SEQ ID NO: 204 moltype = AA length = 5
FEATURE Location/Qualifiers
REGION 1..5
note = Engineered antibody sequence
source 1..5
mol_type = protein
organism = synthetic construct
SEQUENCE: 204
GYYMN 5
```

```
SEQ ID NO: 205 moltype = AA length = 14
FEATURE Location/Qualifiers
REGION 1..14
note = Engineered antibody sequence
source 1..14
mol_type = protein
organism = synthetic construct
SEQUENCE: 205
WVRQAPGKGL EWVG 14
```

```
SEQ ID NO: 206 moltype = AA length = 16
FEATURE Location/Qualifiers
REGION 1..16
note = Engineered antibody sequence
source 1..16
mol_type = protein
organism = synthetic construct
SEQUENCE: 206
VIGINGATYY ASWAKG 16
```

```
SEQ ID NO: 207 moltype = AA length = 32
FEATURE Location/Qualifiers
REGION 1..32
note = Engineered antibody sequence
source 1..32
mol_type = protein
```

-continued

organism = synthetic construct

SEQUENCE: 207
RFTISRDN SK TTVYLQMN SL RAEDTAVYFC AR 32

SEQ ID NO: 208 moltype = length =
SEQUENCE: 208
000

SEQ ID NO: 209 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Engineered antibody sequence
source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 209
WQQGTLVTVS S 11

SEQ ID NO: 210 moltype = AA length = 330
FEATURE Location/Qualifiers
REGION 1..330
note = Engineered antibody sequence
source 1..330
mol_type = protein
organism = synthetic construct

SEQUENCE: 210
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYPPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDARVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKP KDTLMSIRTP EVTCVVVDVS HEDPEVKPNW YVDGVEVHNA KTKPREEQYA 180
STYRVSVS VLT LHQDWLNKG EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPSSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSSFLY SKLTVDKSRW 300
QQGNVFS CSV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 211 moltype = DNA length = 1326
FEATURE Location/Qualifiers
misc_feature 1..1326
note = Engineered antibody sequence
source 1..1326
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 211
gagggtcagc ttgtggagtc tggggggagc ttgggtccagc ctgggggggc cctgagactc 60
tccctgtcgag tctctggaaat cgacccctagt ggctactaca tgaactgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggtcgagtc attggattata atgggtccac atactacgct 180
agctggcgca aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
caaataaaca gctgtggagc tgaggacact gctgtgtatt tctgtgttag agggggacatc 300
tggggcaagc ggaccctgtg caccgttcag acgcctccaa ccaaggcccc atcgggtttc 360
ccacctggcc accctccaa gacccctctt gggggcacac cggccctggg ctgctggc 420
aaggactact tcccccaacc ggtgacgggtg tcgtggaaact caggccctcc gaccagccgc 480
gtgcacacact tcccggtctg cctacagtc tcaggactct actccctccag cagcgtggtg 540
accgtgcctc accagcgtt gggccccc acctacatctt gcaacgtgaa tcacaaggccc 600
agaacacacca aggtggacgc gagagtttag cccaaatctt gtgacaaaac tcacacatgc 660
ccaccgtgcc cagcacctga actctgggg ggaccgtca ctttcccttt ccccccaaaa 720
cccaaggaca ccctcatgtat ctcggggc cctgagggtca catgcgttgt ggtggacgtg 780
agccacgaaag accctggatg caagttaac tggtacgtgg acggcgtgg a ggtgcataat 840
gccaagacaa accccgggg gggcgttac gggccacactt accgtgttgtt cagcgtctcc 900
accgtcttc accaggactg gctgaatggc aaggagtaca agtgcacagg ctccaaacaaa 960
gcctccccc gccccatcgaa gaaaaccatc tccaaagccca aaggccggcc ccgagaacca 1020
cagggtgtaca ccctggcccc atccggggag gagatggccca agaaaccaggat cagcgtgacc 1080
tgccctgttca aagggttcta tcccgacactt atccgggtt gatggggagag caatggccag 1140
ccggagaaca actacaagac cacgcctccc gtgtggact ccgacggctc cttttcttc 1200
tacagcaacg tcaccgttga caagagcagg tggcagcagg gaaacgtttt ctcatgtcc 1260
gtgtatgtatg aggctctgca caaccactac acgcagaaga gctctccctt gtctccgggt 1320
aaatga 1326

SEQ ID NO: 212 moltype = DNA length = 333
FEATURE Location/Qualifiers
misc_feature 1..333
note = Engineered antibody sequence
source 1..333
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 212
gagggtcagc ttgtggagtc tggggggagc ttgggtccagc ctgggggggc cctgagactc 60
tccctgtcgag tctctggaaat cgacccctagt ggctactaca tgaactgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggtcgagtc attggattata atgggtccac atactacgct 180
agctggcgca aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
caaataaaca gctgtggagc tgaggacact gctgtgtatt tctgtgttag agggggacatc 300
tggggcaagc ggaccctgtg caccgttcag agc 333

-continued

```

SEQ ID NO: 213      moltype = DNA length = 90
FEATURE
misc_feature
1..90
note = Engineered antibody sequence
1..90
source
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 213
gaggtgcagc ttgtggagtc tggggggggc ttgggtccagc ctggggggtc cctgagactc 60
tccctgtcag tctctggaaat cgacactcagt 90

SEQ ID NO: 214      moltype = DNA length = 15
FEATURE
misc_feature
1..15
note = Engineered antibody sequence
1..15
source
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 214
ggctactaca tgaac 15

SEQ ID NO: 215      moltype = DNA length = 42
FEATURE
misc_feature
1..42
note = Engineered antibody sequence
1..42
source
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 215
tgggtccgtc aggctccagg gaaggggctg gagtggtcg ga 42

SEQ ID NO: 216      moltype = DNA length = 48
FEATURE
misc_feature
1..48
note = Engineered antibody sequence
1..48
source
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 216
gtcatttgttataatgggtc cacatactac gcgagctggg cgaaaaggc 48

SEQ ID NO: 217      moltype = DNA length = 96
FEATURE
misc_feature
1..96
note = Engineered antibody sequence
1..96
source
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 217
cgatttacca tctccagaga caattccaag accacgggt atcttcaaat gaacagcctg 60
agagctgagg acactgtgt gtatttctgt gctaga 96

SEQ ID NO: 218      moltype = length =
SEQUENCE: 218
000

SEQ ID NO: 219      moltype = DNA length = 33
FEATURE
misc_feature
1..33
note = Engineered antibody sequence
1..33
source
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 219
tggggccaag ggaccctcgta caccgtctcg agc 33

SEQ ID NO: 220      moltype = DNA length = 993
FEATURE
misc_feature
1..993
note = Engineered antibody sequence
1..993
source
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 220
gcctccacca agggccccatc ggtttcccc ctggcacccct cctccaagag cacctctggg 60
ggcacagccgg ccctgggctg cctggtcaag gactacttcc cggaaaccggt gacgggtcg 120
tggaaactcg gcgcctgtc cagccggctg cacaccccttcc cggctgtct acagtcctca 180
ggactctact ccctcagcag cgtggtgacc gtgcctcca gcagcttggg caccaggacc 240

```

-continued

```
tacatctgca acgtgaatca caagccago aacaccaagg tggacgcgag agttgagccc 300
aaatcttgcg aaaaaactca cacatgccc cctgtcccc cacctgaact cctgggggga 360
ccgtcagtct tcctcttccc cccaaaaccc aaggacacc tcatacatc cccgacccct 420
gagggtcacat gctgtgggtt ggacgtgago cacgaagacc ctgagggtcaa gttcaactgg 480
taacgtggacg gctgtggggat gcataatgcc aagacaaaacg cgcggggaga gcagtacgcc 540
agcacgtacc gtgtggtcag cgtccctacc gtcctgcacc aggactggat gaatggcaag 600
gagttacaatg gcaagggtctc caaaagcc ctcccgaccc ccatacgaaaa aaccatctcc 660
aaagccaaag ggcagccccg agaaccacag gtgtacacc tgccccccatc cccggaggag 720
atgaccaaga accagggtcg cctgacccgc ctgtcaatgg gcttctatcc cagcgacatc 780
gccgtggagt gggagagcaat tggcagccg gagaacaact acaagaccac gcctcccttg 840
ctggactccg acggccctt ctteccatca agcaagtcg cctgtggacca gaggcgtgg 900
cagcaggggg acgttttctc atgtccgtg atgtcatgagg ctctgcacaa ccactacacg 960
cagaagggcc tctccctgtc tccgggtaaa tga 993
```

```
SEQ ID NO: 221 moltype = AA length = 219
FEATURE Location/Qualifiers
REGION 1..219
note = Engineered antibody sequence
source 1..219
mol_type = protein
organism = synthetic construct
SEQUENCE: 221
QVLTQSPSSL SASVGDRVTI NCQASQSVYH NTYLAWYQQK PGKVPKQLIY DASTLASGVP 60
SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCTNGDC FVFGGGTKVE IKRTVAAPSV 120
FIPPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STLTLASKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 219
```

```
SEQ ID NO: 222 moltype = AA length = 113
FEATURE Location/Qualifiers
REGION 1..113
note = Engineered antibody sequence
source 1..113
mol_type = protein
organism = synthetic construct
SEQUENCE: 222
QVLTQSPSSL SASVGDRVTI NCQASQSVYH NTYLAWYQQK PGKVPKQLIY DASTLASGVP 60
SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCTNGDC FVFGGGTKVE IKR 113
```

```
SEQ ID NO: 223 moltype = AA length = 22
FEATURE Location/Qualifiers
REGION 1..22
note = Engineered antibody sequence
source 1..22
mol_type = protein
organism = synthetic construct
SEQUENCE: 223
QVLTQSPSSL SASVGDRVTI NC 22
```

```
SEQ ID NO: 224 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
note = Engineered antibody sequence
source 1..13
mol_type = protein
organism = synthetic construct
SEQUENCE: 224
QASQSVYHNT YLA 13
```

```
SEQ ID NO: 225 moltype = AA length = 15
FEATURE Location/Qualifiers
REGION 1..15
note = Engineered antibody sequence
source 1..15
mol_type = protein
organism = synthetic construct
SEQUENCE: 225
WYQQKPGKVP KQLIY 15
```

```
SEQ ID NO: 226 moltype = AA length = 7
FEATURE Location/Qualifiers
REGION 1..7
note = Engineered antibody sequence
source 1..7
mol_type = protein
organism = synthetic construct
SEQUENCE: 226
DASTLAS 7
```

```
SEQ ID NO: 227 moltype = AA length = 32
```

-continued

FEATURE Location/Qualifiers
REGION 1..32
note = Engineered antibody sequence
source 1..32
mol_type = protein
organism = synthetic construct
SEQUENCE: 227
GVPSRFSGSG SGTDFTLTIS SLQPEDVATY YC 32
SEQ ID NO: 228 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
note = Engineered antibody sequence
source 1..13
mol_type = protein
organism = synthetic construct
SEQUENCE: 228
LGSYDCTNGD CFV 13
SEQ ID NO: 229 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Engineered antibody sequence
source 1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 229
FGGGTKVEIK R 11
SEQ ID NO: 230 moltype = AA length = 106
FEATURE Location/Qualifiers
REGION 1..106
note = Engineered antibody sequence
source 1..106
mol_type = protein
organism = synthetic construct
SEQUENCE: 230
TVAAPSVFIF PPSDEQLKSG TASVVCLLN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC 106
SEQ ID NO: 231 moltype = DNA length = 660
FEATURE Location/Qualifiers
misc_feature 1..660
note = Engineered antibody sequence
source 1..660
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 231
caagtgtga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccagg ccagtcatcg tgtttatcat aacacctacc tggcctggta tcagcagaaa 120
ccagggaaag ttccctaagca actgtatctt gatgcacatcca ctctggcata tgggtcaca 180
tctcggttca gtggcagttgg atctgggaca gatttcactt tcaccatcag cagctgcag 240
cctgaagatg ttgcaacttta ttactgtctg ggcagttatg attgtactaa tggtgatgt 300
tttgttttcg ggggagggaaac caagggtggaa atcaaacttca cgggtggotgc accatctgtc 360
ttcatcttcc cgccatcttca tgacgttgg aaatcttggaa ctgcctctgt tggtgcttg 420
ctgaataact ttatccatc agggccaaa gtacagtggaa aggtggataa cgccttc当地 480
tcgggtaact cccaggagag tgcacatcg caggacacca aggacagcac ctacagctc 540
agcagcaccc tgacgttgg caaacggacac tacggagaaa acaaagtctt cgcctcgaa 600
gtcacccatc agggccttag ctcggccatc acaaagggcgt tcaacaggagg 660
SEQ ID NO: 232 moltype = DNA length = 339
FEATURE Location/Qualifiers
misc_feature 1..339
note = Engineered antibody sequence
source 1..339
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 232
caagtgtga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccagg ccagtcatcg tgtttatcat aacacctacc tggcctggta tcagcagaaa 120
ccagggaaag ttccctaagca actgtatctt gatgcacatcca ctctggcata tgggtcaca 180
tctcggttca gtggcagttgg atctgggaca gatttcactt tcaccatcag cagctgcag 240
cctgaagatg ttgcaacttta ttactgtctg ggcagttatg attgtactaa tggtgatgt 300
tttgttttcg ggggagggaaac caagggtggaa atcaaacttca cgcctcgaa 339
SEQ ID NO: 233 moltype = DNA length = 66
FEATURE Location/Qualifiers
misc_feature 1..66
note = Engineered antibody sequence

-continued

```

source          1..66
               mol_type = other DNA
               organism = synthetic construct
SEQUENCE: 233
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgc                                66

SEQ ID NO: 234      moltype = DNA  length = 39
FEATURE
misc_feature       Location/Qualifiers
1..39
note = Engineered antibody sequence
source            1..39
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 234
caggccagtc agagtgttta tcataaacacc tacctggcc                                39

SEQ ID NO: 235      moltype = DNA  length = 45
FEATURE
misc_feature       Location/Qualifiers
1..45
note = Engineered antibody sequence
source            1..45
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 235
tggtatcagc agaaaaccagg gaaagttcct aagcaactga tctat                                45

SEQ ID NO: 236      moltype = DNA  length = 21
FEATURE
misc_feature       Location/Qualifiers
1..21
note = Engineered antibody sequence
source            1..21
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 236
gatgcatcca ctctggcatc t                                21

SEQ ID NO: 237      moltype = DNA  length = 96
FEATURE
misc_feature       Location/Qualifiers
1..96
note = Engineered antibody sequence
source            1..96
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 237
gggttcccat ctcgtttcag tggcagtgaa tctgggacag atttcactct caccatcagc 60
aggctgcagc ctgaagatgt tgcaacttat tactgt                                96

SEQ ID NO: 238      moltype = DNA  length = 39
FEATURE
misc_feature       Location/Qualifiers
1..39
note = Engineered antibody sequence
source            1..39
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 238
ctgggcagtt atgattgtac taatggtgat tgttttgtt                                39

SEQ ID NO: 239      moltype = DNA  length = 33
FEATURE
misc_feature       Location/Qualifiers
1..33
note = Engineered antibody sequence
source            1..33
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 239
ttcggcggag gaaccaaggt ggaaatcaaa cgt                                33

SEQ ID NO: 240      moltype = DNA  length = 321
FEATURE
misc_feature       Location/Qualifiers
1..321
note = Engineered antibody sequence
source            1..321
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 240
acggtgtggctg caccatctc ccgcctatctg atgagcagggt gaaatctgga 60
actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
aagggtggata acgcctcca atcgggttaac tcccaggaga gtgtcacaga gcaggacagc 180

```

-continued

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaaggcaga ctacgagaaa 240
 cacaaggct acgcctgcga agtcacccat cagggcctga gtcgcccgt cacaaggagc 300
 ttcaacaggg gagagtgtta g 321

SEQ ID NO: 241 moltype = AA length = 440
 FEATURE Location/Qualifiers
 REGION 1..440
 note = Engineered antibody sequence
 source 1..440
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 241
 QEQLKESGGR LVTPGTSLTL TCTVSGIDLS NHYMQWVRQA PGKGLEWIGV VGINGRTYYA 60
 SWAKGRFTIS RTSSTTVDLK MTRLTTEDTA TYFCARGDIW GPGTLVTVSS ASTKGPSVFP 120
 LAPSSSKTSG CTAALGCLV DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT 180
 VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP 240
 KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA STYRVVSVLT 300
 VLHQDWLNKG EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPLPSREE MTKNQVSLTC 360
 LVKGFYPSDI AVEWESNGQ ENNYKTTTPV LDSDGSFFLY SKLTVDKSROW QQGNVFSCSV 420
 MHEALHNHYT QKSLSLSPGK 440

SEQ ID NO: 242 moltype = AA length = 110
 FEATURE Location/Qualifiers
 REGION 1..110
 note = Engineered antibody sequence
 source 1..110
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 242
 QEQLKESGGR LVTPGTSLTL TCTVSGIDLS NHYMQWVRQA PGKGLEWIGV VGINGRTYYA 60
 SWAKGRFTIS RTSSTTVDLK MTRLTTEDTA TYFCARGDIW GPGTLVTVSS 110

SEQ ID NO: 243 moltype = AA length = 30
 FEATURE Location/Qualifiers
 REGION 1..30
 note = Engineered antibody sequence
 source 1..30
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 243
 QEQLKESGGR LVTPGTSLTL TCTVSGIDLS 30

SEQ ID NO: 244 moltype = AA length = 5
 FEATURE Location/Qualifiers
 REGION 1..5
 note = Engineered antibody sequence
 source 1..5
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 244
 NHYMQ 5

SEQ ID NO: 245 moltype = AA length = 14
 FEATURE Location/Qualifiers
 REGION 1..14
 note = Engineered antibody sequence
 source 1..14
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 245
 WVRQAPGKGL EWIG 14

SEQ ID NO: 246 moltype = AA length = 16
 FEATURE Location/Qualifiers
 REGION 1..16
 note = Engineered antibody sequence
 source 1..16
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 246
 VVGINGRTYY ASWAKG 16

SEQ ID NO: 247 moltype = AA length = 31
 FEATURE Location/Qualifiers
 REGION 1..31
 note = Engineered antibody sequence
 source 1..31
 mol_type = protein
 organism = synthetic construct

-continued

SEQUENCE: 247
RFTISRTSST TVDLKMTRLT TEDTATYFCA R 31

SEQ ID NO: 248 moltype = length =
SEQUENCE: 248
000

SEQ ID NO: 249 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Engineered antibody sequence
source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 249
WGPGLTVTS S 11

SEQ ID NO: 250 moltype = AA length = 330
FEATURE Location/Qualifiers
REGION 1..330
note = Engineered antibody sequence
source 1..330
mol_type = protein
organism = synthetic construct

SEQUENCE: 250
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLEPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESENQGP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVVFSCSV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 251 moltype = DNA length = 1323
FEATURE Location/Qualifiers
misc_feature 1..1323
note = Engineered antibody sequence
source 1..1323
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 251
caggagcgc tgaaggagtc cgggggtcgc ctggtcacgc ctggggacatc cctgacactc 60
acctgcaccc tctctgttaa cgacccatcgta aaccactaca tgcaatgggt ccggccaggct 120
ccagggaaagg ggctggagt gatggggatc ttgggttata atggtcgcac atactacgcg 180
agctggcgca aaggccgatt caccatctcc agaacctcggt cgaccacgggt ggatctgaaa 240
atgaccaggc tgacaaccgc ggacacggcc acctattttct gtgccagagg ggacatctgg 300
ggcccaaggca ccctggtcac cgatctcgacg gcctccacca aggggcccatc ggtcttcccc 360
ctggcaccct ctcctcaagag cacctctggg ggcacagcggg ccctgggttg cctggtecaag 420
gactactccc ccgaacccgt gacgggtcg tgaaacttcg ggcgcctgac cagcggcggt 480
cacaccttcc cggctgtccct acagtcttcg tgactctact ccctcagcag cgtggtgacc 540
gtgcccttca gaagccggatc caccggatc tacatctgcga acgtgaatca caagcccg 600
aacaccaagg tggacaaggag agttggaccc aaatcttggt acaaaaactca cacatggcca 660
ccgtgcggcc caccctgaaact cctgggggca ccgtcagtttcccttccccc cccaaaaacc 720
aaggacaccc tcatgtatctc cgggacccct gaggttcacat gctgtgggtt ggacgtgagc 780
cacaagacc ctgggttcaat gttcaactgg tacgtggacg gctgtggagt gcataatggcc 840
aagacaaaggcc cggccggatc gcaatggcc accgtacgttccatggatggatcacc 900
gtctgttccca aggactggct gaatggcaag qgatcagaatc gcaagggttcc caacaaaggcc 960
ctcccaaggcc ccatcgagaa aaccatctcc aaagccaaag ggcagccccc agaaccacag 1020
gtgtacaccc tggcccccattt cccggggaggat atgaccaaggaa accagggttccatggatggatcc 1080
ctgggttcaat gtttctatcc cagcgacatc gccgtggatg gggagagcaa tggccggcc 1140
gagaacaactt acaagaccac gcctccctgt ctggactccg acggcttccctt cttcttcc 1200
agcaagtc tggatggacaa gaggcaggatgg cagcaggggaa acgttttccatggatggatcc 1260
atgcatgagg ctctgcacaa ccactacacgc cagaagggcc tctccctgtc tccgggtaaa 1320
tga 1323

SEQ ID NO: 252 moltype = DNA length = 330
FEATURE Location/Qualifiers
misc_feature 1..330
note = Engineered antibody sequence
source 1..330
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 252
caggagcgc tgaaggagtc cgggggtcgc ctggtcacgc ctggggacatc cctgacactc 60
acctgcaccc tctctgttaa cgacccatcgta aaccactaca tgcaatgggt ccggccaggct 120
ccagggaaagg ggctggagt gatggggatc ttgggttata atggtcgcac atactacgcg 180
agctggcgca aaggccgatt caccatctcc agaacctcggt cgaccacgggt ggatctgaaa 240
atgaccaggc tgacaaccgc ggacacggcc acctattttct gtgccagagg ggacatctgg 300
ggcccaaggca ccctggtcac cgatctcgacg gcctccacca aggggcccatc ggtcttcccc 330

-continued

SEQ ID NO: 253 moltype = DNA length = 90
 FEATURE Location/Qualifiers
 misc_feature 1..90
 note = Engineered antibody sequence
 source 1..90
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 253
 caggagcgc tgaaggagt cgggggtcg ctggtcacgc ctgggacatc cctgacactc 60
 acctgcacg tctctggat cgacctcagt 90

SEQ ID NO: 254 moltype = DNA length = 15
 FEATURE Location/Qualifiers
 misc_feature 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 254
 aaccactaca tgcaa 15

SEQ ID NO: 255 moltype = DNA length = 42
 FEATURE Location/Qualifiers
 misc_feature 1..42
 note = Engineered antibody sequence
 source 1..42
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 255
 tgggtccgcc aggctccagg gaaggggctg gagtggatcg ga 42

SEQ ID NO: 256 moltype = DNA length = 48
 FEATURE Location/Qualifiers
 misc_feature 1..48
 note = Engineered antibody sequence
 source 1..48
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 256
 gtcgttgta ttaatggtgc cacatactac gcgagctggg cgaaaggc 48

SEQ ID NO: 257 moltype = DNA length = 93
 FEATURE Location/Qualifiers
 misc_feature 1..93
 note = Engineered antibody sequence
 source 1..93
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 257
 cgattcacca tctccagaac ctgcgtgacc acgggtggatc tgaaaatgac caggctgaca 60
 accgaggaca cggccaccta ttctgtgcc aga 93

SEQ ID NO: 258 moltype = length =
 SEQUENCE: 258
 000

SEQ ID NO: 259 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33
 note = Engineered antibody sequence
 source 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 259
 tggggcccaag gcaccctggt caccgtctcg agc 33

SEQ ID NO: 260 moltype = DNA length = 993
 FEATURE Location/Qualifiers
 misc_feature 1..993
 note = Engineered antibody sequence
 source 1..993
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 260
 gcctccacca agggccccatc ggtttcccc ctggcacccct cctccaagag caccctctggg 60
 ggcacagcgg ccctgggctg cctggtcaag gactacttc cccgaaaccggt gacgggtgtcg 120
 tggaactcag ggcgcctgac cagcggcgtg cacacccctcc cggctgtctc acagttctca 180
 ggactctact ccctcagcag cgtggtgacc gtgccttcca gcagcttggg caccagacc 240
 tacatctgca acgtgaatca aacaccaagg tggacaagag agttgagccc 300

-continued

```

aaatcttgtc acaaaaactca cacatgcccc cctgtggccag cacctgaact cctgggggg 360
ccgtcagtct tcctttccc cccaaaaccc aaggacacc tcatgatctc ccggaccct 420
gaggtcacat gctgtgggtt ggacgtgago cacgaagacc ctgaggtaa gttcaactgg 480
tacgtggacg cgctggaggt gcataatgcc aagacaaagg cgccggagga gcagtacgcc 540
agcacgtacc gtgtggtcag cgtcttcacc gtctgcacc aggactggta gaatggcaag 600
gagttacaatgtt gcaagggttcc caacaaaggcc ctccccagccc ccattcgaaaa aaccatctcc 660
aaagccaaag ggcagcccc agaaccacag gtgtacacc tgccccatcc ccgggaggag 720
atgaccaaga accaggtagt cctgacctgc ctgtcaaa gcttctatcc cagcgacatc 780
gcgcgtggagt gggagagcaa ttggcagccg gagaacaact acaagaccac gcctccctg 840
ctggacttc acggcttcctt cttccttcac agcaagcttcc ctggacaa gagcagggtgg 900
cagcaggggaa acgttttctc atgtccctgtt atgcatgagg ctctgcacaa ccactacacg 960
cagaagagcc tctccctgtc tccgggtaaa tga 993

```

```

SEQ ID NO: 261      moltype = AA length = 219
FEATURE
REGION          1..219
note = Engineered antibody sequence
source           1..219
mol_type = protein
organism = synthetic construct
SEQUENCE: 261
QVLTQTASPV SAAVGSTVTI NCQASQSVYN YNYLAWYQQK PGQPPKQLIY STSTLASGVS 60
SRPKGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSTGDC FVFGGGTEVV VKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTLTLKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 219

```

```

SEQ ID NO: 262      moltype = AA length = 113
FEATURE
REGION          1..113
note = Engineered antibody sequence
source           1..113
mol_type = protein
organism = synthetic construct
SEQUENCE: 262
QVLTQTASPV SAAVGSTVTI NCQASQSVYN YNYLAWYQQK PGQPPKQLIY STSTLASGVS 60
SRPKGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSTGDC FVFGGGTEVV VRK 113

```

```

SEQ ID NO: 263      moltype = AA length = 22
FEATURE
REGION          1..22
note = Engineered antibody sequence
source           1..22
mol_type = protein
organism = synthetic construct
SEQUENCE: 263
QVLTQTASPV SAAVGSTVTI NC 22

```

```

SEQ ID NO: 264      moltype = AA length = 13
FEATURE
REGION          1..13
note = Engineered antibody sequence
source           1..13
mol_type = protein
organism = synthetic construct
SEQUENCE: 264
QASQSVVN YLA 13

```

```

SEQ ID NO: 265      moltype = AA length = 15
FEATURE
REGION          1..15
note = Engineered antibody sequence
source           1..15
mol_type = protein
organism = synthetic construct
SEQUENCE: 265
WYQQKPGQPP KQLIY 15

```

```

SEQ ID NO: 266      moltype = AA length = 7
FEATURE
REGION          1..7
note = Engineered antibody sequence
source           1..7
mol_type = protein
organism = synthetic construct
SEQUENCE: 266
STSTLAS 7

```

```

SEQ ID NO: 267      moltype = AA length = 32
FEATURE

```

-continued

REGION 1..32
note = Engineered antibody sequence

source 1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 267
GVSSRFKGSG SGTQFTLTIS DVQCDDAATY YC 32

SEQ ID NO: 268 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
note = Engineered antibody sequence

source 1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 268
LGSYDCSTGD CFV 13

SEQ ID NO: 269 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Engineered antibody sequence

source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 269
FGGGTEVVVK R 11

SEQ ID NO: 270 moltype = AA length = 106
FEATURE Location/Qualifiers
REGION 1..106
note = Engineered antibody sequence

source 1..106
mol_type = protein
organism = synthetic construct

SEQUENCE: 270
TVAAPSVIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSST LTLSKADYEK HKVYACEVTN QGLSSPVTKS FNRGEC 106

SEQ ID NO: 271 moltype = DNA length = 660
FEATURE Location/Qualifiers
misc_feature 1..660
note = Engineered antibody sequence

source 1..660
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 271
caagtgtga cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
aattgccagg ccagtcatcg tggcttataat tacaactacc ttgcctggta tcagcagaaa 120
ccaggcgcg ctcccaagca actgtatctt tctacatcca ctctggcatc tgggtctca 180
tcgcgattca aaggcactgg atctgggaca cagttcactt tcaccatcag cgacgtgcag 240
tgtgacgatg ctgcccactt ctactgtcta ggcagttatg actgttagtac tggtgattgt 300
tttggtttcg gcgaggggac cgagggtggt gtcaaacgtt cggctggctgc accatctgtc 360
ttcatcttcc cgcccatctg tgacgatgtt aaatctggaa ctgcctctgt tggtgctcg 420
ctgaataact tctatcccg agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcggtaactt cccaggagag tggcacatcg cagggacacca aggacacac ctacagctc 540
agcagccccc tgacgctgag caaaggcagac tacgagaaac acaaagtcta cgcctgcgaa 600
gttacccatc agggccttagt ctcggccgtc acaaagggc agagtgttag 660

SEQ ID NO: 272 moltype = DNA length = 339
FEATURE Location/Qualifiers
misc_feature 1..339
note = Engineered antibody sequence

source 1..339
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 272
caagtgtga cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
aattgccagg ccagtcatcg tggcttataat tacaactacc ttgcctggta tcagcagaaa 120
ccaggcgcg ctcccaagca actgtatctt tctacatcca ctctggcatc tgggtctca 180
tcgcgattca aaggcactgg atctgggaca cagttcactt tcaccatcag cgacgtgcag 240
tgtgacgatg ctgcccactt ctactgtcta ggcagttatg actgttagtac tggtgattgt 300
tttggtttcg gcgaggggac cgagggtggt gtcaaacgtt 339

SEQ ID NO: 273 moltype = DNA length = 66
FEATURE Location/Qualifiers
misc_feature 1..66
note = Engineered antibody sequence

source 1..66

-continued

```

mol_type = other DNA
organism = synthetic construct

SEQUENCE: 273
caagtgtga cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
aattgc                                         66

SEQ ID NO: 274      moltype = DNA length = 39
FEATURE           Location/Qualifiers
misc_feature      1..39
note = Engineered antibody sequence
source            1..39
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 274
caggccagtc agagtgttta taattacaac taccttgcc                                         39

SEQ ID NO: 275      moltype = DNA length = 45
FEATURE           Location/Qualifiers
misc_feature      1..45
note = Engineered antibody sequence
source            1..45
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 275
tggtatcagc agaaaccagg gcagccccc aagcaactga tctat                                         45

SEQ ID NO: 276      moltype = DNA length = 21
FEATURE           Location/Qualifiers
misc_feature      1..21
note = Engineered antibody sequence
source            1..21
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 276
tctacatcca ctctggcatc t                                         21

SEQ ID NO: 277      moltype = DNA length = 96
FEATURE           Location/Qualifiers
misc_feature      1..96
note = Engineered antibody sequence
source            1..96
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 277
gggttctcat cgcgattcaa aggcaagtgg a tctgggacac agttcactct caccatcagc 60
gacgtgcagt gtgacgatgc tgccacttac tactgt                                         96

SEQ ID NO: 278      moltype = DNA length = 39
FEATURE           Location/Qualifiers
misc_feature      1..39
note = Engineered antibody sequence
source            1..39
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 278
ctaggcagtt atgactgttag tactggtgat tgttttgtt                                         39

SEQ ID NO: 279      moltype = DNA length = 33
FEATURE           Location/Qualifiers
misc_feature      1..33
note = Engineered antibody sequence
source            1..33
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 279
ttcggcggag ggaccggaggt ggtggtcaaa cgt                                         33

SEQ ID NO: 280      moltype = DNA length = 321
FEATURE           Location/Qualifiers
misc_feature      1..321
note = Engineered antibody sequence
source            1..321
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 280
acggtgtggctg caccatctgt cttcatcttc ccgccatctg atgagcaggat gaaatctgg 60
actgcctctg ttgtgtgcct gctgaataac ttcatatccca gagaggccaa agtacagtgg 120
aagggtggata acggcctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc 180
aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaaggcaga ctacgagaaa 240

```

-continued

cacaaggct acgcctgcga agtcacccat cagggcctga gctcgccgt cacaaggagc 300
ttcaacaggg gagagtgtta g 321

SEQ ID NO: 281 moltype = AA length = 441
FEATURE Location/Qualifiers
REGION 1..441
note = Engineered antibody sequence
source 1..441
mol_type = protein
organism = synthetic construct

SEQUENCE: 281
EVQLVESGGG LVQPGGSLRL SCAVSGIDLS NHYMQWVRQA PGKGLEWVG VGINGRTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
PLAPSSKSTS CGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
TVPSSSLGTO TYICCNVNHKP SNTKVDKRV E PKSCDKTHTC PPCPAPELLG GPSVPLFPPK 240
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVVSVL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSR E MTKNQVSLT 360
CLVKGFYPSD IAVEWESNGQ PENNYKTTPPP VLSDGGSFFL YSKLTVDKSR WQQGNVFSCS 420
VMHEALHHY TQKSLSLSPG K 441

SEQ ID NO: 282 moltype = AA length = 111
FEATURE Location/Qualifiers
REGION 1..111
note = Engineered antibody sequence
source 1..111
mol_type = protein
organism = synthetic construct

SEQUENCE: 282
EVQLVESGGG LVQPGGSLRL SCAVSGIDLS NHYMQWVRQA PGKGLEWVG VGINGRTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS S 111

SEQ ID NO: 283 moltype = AA length = 30
FEATURE Location/Qualifiers
REGION 1..30
note = Engineered antibody sequence
source 1..30
mol_type = protein
organism = synthetic construct

SEQUENCE: 283
EVQLVESGGG LVQPGGSLRL SCAVSGIDLS 30

SEQ ID NO: 284 moltype = AA length = 5
FEATURE Location/Qualifiers
REGION 1..5
note = Engineered antibody sequence
source 1..5
mol_type = protein
organism = synthetic construct

SEQUENCE: 284
NHYMQ 5

SEQ ID NO: 285 moltype = AA length = 14
FEATURE Location/Qualifiers
REGION 1..14
note = Engineered antibody sequence
source 1..14
mol_type = protein
organism = synthetic construct

SEQUENCE: 285
WVRQAPGKGL EWVG 14

SEQ ID NO: 286 moltype = AA length = 16
FEATURE Location/Qualifiers
REGION 1..16
note = Engineered antibody sequence
source 1..16
mol_type = protein
organism = synthetic construct

SEQUENCE: 286
VVGINGRTYY ASWAKG 16

SEQ ID NO: 287 moltype = AA length = 32
FEATURE Location/Qualifiers
REGION 1..32
note = Engineered antibody sequence
source 1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 287

-continued

RFTISRDNSK TTVYLQMNLS RAEDTAVYFC AR

32

SEQ ID NO: 288 moltype = length =
 SEQUENCE: 288
 000

SEQ ID NO: 289 moltype = AA length = 11
 FEATURE Location/Qualifiers
 REGION 1..11
 note = Engineered antibody sequence
 source 1..11
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 289
 WQQGTLVTVS S 11

SEQ ID NO: 290 moltype = AA length = 330
 FEATURE Location/Qualifiers
 REGION 1..330
 note = Engineered antibody sequence
 source 1..330
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 290
 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYPPEPVTVS WNSGALTSGV HTFPAVLQSS 60
 GLYSLSVSVT VPSSSLGTQT YICNVNHNPKS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
 PSVFLFPKPK KDTLMISRTP EYTCVVVDVS HEDPEVKPNW YVDGVEVHNA KTKPREEQYA 180
 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPPSREE 240
 MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300
 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 291 moltype = DNA length = 1326
 FEATURE Location/Qualifiers
 misc_feature 1..1326
 note = Engineered antibody sequence
 source 1..1326
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 291
 gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60
 tcctgtgcag tctctggaat cgacctcagt aaccactaca tgcaatgggt ccgtcaggct 120
 ccaggaaagg ggctggagtg ggtcgaggatc gtggatcatc atggtcgcac atactacgcg 180
 agctggcgca aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
 caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgttag aggggacatc 300
 tggggccaag ggacctctgt caccgtctcg agcgcctcca ccaaggccc atcggtttc 360
 cccctggcac ctccctccaa gaggacctctt gggggcacag cggccctggg ctgcctggc 420
 aaggactact tcccccgaacc ggtgcgggtg tctgcggactt caggcgccct gaccagccgc 480
 gtgcacaccc tcccggtctgt cttcaggactt tcaggactt actccctcag cagcgtgtt 540
 accgtgcacctt ccaggcagtt gggccaccccg acctacatctt gcaacgtgaa tcacaagccc 600
 agcaacaccaa aggtggacaa gagatgttg cccaaatctt gtgacaaaac tcacacatgc 660
 ccacccgttccacccatgtca actctggggg ggaccgtcaat ttttcttttcccccaaaa 720
 cccaaaggaca cccatcatgtat ctcggggacc cctggaggatca catcgctgtt ggtggacgtg 780
 agccacgaag acctctggaggta caagtcaac tggatcgatc acggcgctgg ggtgcataat 840
 gccaagacaa acggccgggg ggacggactt gccagcactt accgtgtgtt cagcgtctc 900
 accgttcctgc accaggactt gctgaatggc aaggatgtca agtgcgttccatc 960
 gcccctcccaag ccccatcgaa aaaaaccatc tccaaagccca aaggccggccc ccgagaacca 1020
 cagggtgtaca ccctggccccc atccggggag gagatgtacca agaaccaggat cagcgttgcacc 1080
 tgccctggta aaggcttcta tcccgacgc atccgggtgg agtggggagag caatgggcag 1140
 ccggagaaca actacaagac cacgcctccc gtgcgtggact ccgcacggctc ctcttcctc 1200
 tacagcaacgc tcaccgtggc aaagcggagg ggaacgttccctt ctcatgttcc 1260
 gtgtatgcatg aggctctgca caaccactac acgcagaaga gcctctccctt gtctccgggt 1320
 aaatga 1326

SEQ ID NO: 292 moltype = DNA length = 333
 FEATURE Location/Qualifiers
 misc_feature 1..333
 note = Engineered antibody sequence
 source 1..333
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 292
 gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60
 tcctgtgcag tctctggaat cgacctcagt aaccactaca tgcaatgggt ccgtcaggct 120
 ccaggaaagg ggctggagtg ggtcgaggatc gtggatcatc atggtcgcac atactacgcg 180
 agctggcgca aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
 caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgttag aggggacatc 300
 tggggccaag ggacctctgt caccgtctcg agc 333

SEQ ID NO: 293 moltype = DNA length = 90

-continued

FEATURE Location/Qualifiers
 misc_feature 1..90
 note = Engineered antibody sequence
 source 1..90
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 293
 gaggtgcagc ttgtggagtc tgggggaggc ttgggtccagc ctggggggtc cctgagactc 60
 tcctgtcgat tctctgaaat cgacccctcag 90

SEQ ID NO: 294 moltype = DNA length = 15
 FEATURE Location/Qualifiers
 misc_feature 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 294
 aaccactaca tgcaa 15

SEQ ID NO: 295 moltype = DNA length = 42
 FEATURE Location/Qualifiers
 misc_feature 1..42
 note = Engineered antibody sequence
 source 1..42
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 295
 tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga 42

SEQ ID NO: 296 moltype = DNA length = 48
 FEATURE Location/Qualifiers
 misc_feature 1..48
 note = Engineered antibody sequence
 source 1..48
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 296
 gtcgttggta tcaatggtcg cacatactac gcgagctggg cgaaaggc 48

SEQ ID NO: 297 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 297
 cgattcacca tctccagaga caattccaag accacggtgt atcttcaaat gaacagcctg 60
 agagctgagg acactgctgt gtatttctgt gctaga 96

SEQ ID NO: 298 moltype = length =
 SEQUENCE: 298
 000

SEQ ID NO: 299 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33
 note = Engineered antibody sequence
 source 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 299
 tggggccaag ggaccctcgt caccgtctcg agc 33

SEQ ID NO: 300 moltype = DNA length = 993
 FEATURE Location/Qualifiers
 misc_feature 1..993
 note = Engineered antibody sequence
 source 1..993
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 300
 gcctccacca agggcccata ggtttcccc ctggcaccc cctccaagag cacctctggg 60
 ggcacagcgg ccctgggctg cctggtcaag gactactcc cccaaacgggt gacgggtcg 120
 tggaaacttag cgcgcctgac cagcggcgtg cacacctcc cggctgtcct acagtcccta 180
 ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg caccagacc 240
 tacatctgca acgtgaatca caagccca aacaccaagg tggacaagag agttgagccc 300
 aaatcttgcg acaaactca cacatggcca ccgtgcccag caccctgaact cctgggggga 360

-continued

ccgtcagtc tccctttccc cccaaaacc accggacacc tcatgatctc ccggaccct 420
 gaggtcacat gcgtgggtt ggacgtgago cacgaagacc ctgaggtaa gttcaactgg 480
 tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgccggagga gcagtacgcc 540
 agcacgtacc gtgtggtcag cgtctcacc gtcctgcacc aggactggt gaatggcaag 600
 gagtacaagt gcaaggcttc caacaaagcc ctccccagccc ccatecgagaa aaccatctcc 660
 aaagccaaag ggcaagcccg agaaccacag gtgtacaccc tgccccatc ccgggaggag 720
 atgaccaaga accaggctcag cctgacctgc ctgtcaaa gcttctatcc cagcgacatc 780
 gccgtggagt gggagagcaa tggcagccg gagaacaact acaagaccac gcctccctg 840
 ctggactccg acggctcctt ctctctac agcaagctca ccgtggacaa gaggcagggtgg 900
 cagcaggggaa acgttttctc atgtccgtg atgcatgagg ctctgcacaa ccactacacg 960
 cagaagaggc ttcctgtc tccggtaaa tga 993

SEQ ID NO: 301 moltype = AA length = 219
 FEATURE Location/Qualifiers
 REGION 1..219
 note = Engineered antibody sequence
 source 1..219
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 301 NCQASQSVYN YNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 QVLTQSPSSL SASVGDRVTI NCQASQSVYN YNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSAGSGT DFTLTISLQ PEDVATYYCL GSYDCSTGDC FVFGGGTKVE IKRTVAAPSV 120
 FIRPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
 STSTLTLKAD YEHKHVYACE VTHQGLSSPV TKSFNRRGEC 219

SEQ ID NO: 302 moltype = AA length = 113
 FEATURE Location/Qualifiers
 REGION 1..113
 note = Engineered antibody sequence
 source 1..113
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 302 NCQASQSVYN YNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 QVLTQSPSSL SASVGDRVTI NCQASQSVYN YNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSAGSGT DFTLTISLQ PEDVATYYCL GSYDCSTGDC FVFGGGTKVE IKR 113

SEQ ID NO: 303 moltype = AA length = 22
 FEATURE Location/Qualifiers
 REGION 1..22
 note = Engineered antibody sequence
 source 1..22
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 303 NCQASQSVYN YNYLAWYQQK PGKVPKQLIY STSTLASGVP 22
 QVLTQSPSSL SASVGDRVTI NC 22

SEQ ID NO: 304 moltype = AA length = 13
 FEATURE Location/Qualifiers
 REGION 1..13
 note = Engineered antibody sequence
 source 1..13
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 304 NCQASQSVYN YLA 13

SEQ ID NO: 305 moltype = AA length = 15
 FEATURE Location/Qualifiers
 REGION 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 305 WYQQKPGKVP KQLIY 15

SEQ ID NO: 306 moltype = AA length = 7
 FEATURE Location/Qualifiers
 REGION 1..7
 note = Engineered antibody sequence
 source 1..7
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 306 STSTLAS 7

SEQ ID NO: 307 moltype = AA length = 32
 FEATURE Location/Qualifiers
 REGION 1..32

-continued

```

source          note = Engineered antibody sequence
1..32
mol_type = protein
organism = synthetic construct
SEQUENCE: 307
GVPSRFSGSG SGTDFTLTIS SLQPEDVATY YC                                32

SEQ ID NO: 308      moltype = AA length = 13
FEATURE          Location/Qualifiers
REGION           1..13
note = Engineered antibody sequence
source          1..13
mol_type = protein
organism = synthetic construct
SEQUENCE: 308
LGSYDCSTGD CFV                                              13

SEQ ID NO: 309      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Engineered antibody sequence
source          1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 309
FGGGTKVEIK R                                              11

SEQ ID NO: 310      moltype = AA length = 106
FEATURE          Location/Qualifiers
REGION           1..106
note = Engineered antibody sequence
source          1..106
mol_type = protein
organism = synthetic construct
SEQUENCE: 310
TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC                  106

SEQ ID NO: 311      moltype = DNA length = 660
FEATURE          Location/Qualifiers
misc_feature     1..660
note = Engineered antibody sequence
source          1..660
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 311
caagtgtcga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgcagg ccagtcagag tgtttacaat tacaactacc ttgcctggta tcagcagaaa 120
ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tgggtccca 180
tctcgtttca gtggcagtgg atctgggaca gatttcactc tcacatcag cagcctgcag 240
cctgaagatg ttgcacatc ttactgtctg ggcagttatg atttgtatc tggtgatgt 300
tttgttttcg goggaggaac caagggtggaa atcaaacgtt cgggtggotgc accatctgtc 360
ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tggtgctgt 420
ctgaataact tctatccccag agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcgggttaact cccaggagacat gttcacagag caggacagcac aggacagcac ctacagcctc 540
agcagcaccc tgacgtcgtac caaaacgacat tggatgttgc acaaaggttca cgcctgcgaa 600
gtcacccatc agggccttag ctcggccgtc acaaaggttca acacacgggg agagtgttag 660

SEQ ID NO: 312      moltype = DNA length = 339
FEATURE          Location/Qualifiers
misc_feature     1..339
note = Engineered antibody sequence
source          1..339
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 312
caagtgtcga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgcagg ccagtcagag tgtttacaat tacaactacc ttgcctggta tcagcagaaa 120
ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tgggtccca 180
tctcgtttca gtggcagtgg atctgggaca gatttcactc tcacatcag cagcctgcag 240
cctgaagatg ttgcacatc ttactgtctg ggcagttatg atttgtatc tggtgatgt 300
tttgttttcg goggaggaac caagggtggaa atcaaacgtt cgggtggotgc accatctgtc 339

SEQ ID NO: 313      moltype = DNA length = 66
FEATURE          Location/Qualifiers
misc_feature     1..66
note = Engineered antibody sequence
source          1..66
mol_type = other DNA

```

-continued

```

organism = synthetic construct
SEQUENCE: 313
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgc                                         66

SEQ ID NO: 314      moltype = DNA  length = 39
FEATURE
misc_feature        Location/Qualifiers
1..39
note = Engineered antibody sequence
source              1..39
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 314
caggccagtc agagtgttta caattacaac taccttgcc                                         39

SEQ ID NO: 315      moltype = DNA  length = 45
FEATURE
misc_feature        Location/Qualifiers
1..45
note = Engineered antibody sequence
source              1..45
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 315
tggtatcagc agaaaccagg gaaaagttcct aagcaactgaa tctat                                         45

SEQ ID NO: 316      moltype = DNA  length = 21
FEATURE
misc_feature        Location/Qualifiers
1..21
note = Engineered antibody sequence
source              1..21
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 316
tctacatcca ctctggcatc t                                         21

SEQ ID NO: 317      moltype = DNA  length = 96
FEATURE
misc_feature        Location/Qualifiers
1..96
note = Engineered antibody sequence
source              1..96
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 317
gggggtcccat ctcgtttcag tggcagtgga tctggggacag atttcactct caccatcagc 60
agcctgcagc ctgaagatgt tgcaacttat tactgt                                         96

SEQ ID NO: 318      moltype = DNA  length = 39
FEATURE
misc_feature        Location/Qualifiers
1..39
note = Engineered antibody sequence
source              1..39
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 318
ctgggcagtt atgattgttag tactggtgat tgttttgtt                                         39

SEQ ID NO: 319      moltype = DNA  length = 33
FEATURE
misc_feature        Location/Qualifiers
1..33
note = Engineered antibody sequence
source              1..33
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 319
ttcggcggag gaaccaagggt ggaaatcaaa cgt                                         33

SEQ ID NO: 320      moltype = DNA  length = 321
FEATURE
misc_feature        Location/Qualifiers
1..321
note = Engineered antibody sequence
source              1..321
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 320
acgggtggctg caccatctgt cttcatcttc ccggccatctg atgagcagggtt gaaatctgga 60
actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
aagggtggata acggccctcca atcgggttaac tcccaggaga gtgtcacaga gcaggacagc 180
aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa 240
cacaaggatct acgcctgcga agtcacccat caggccctga gctcgccccgt cacaaggagc 300

```

-continued

```

ttcaacaggg gagagtgtta g                                321
SEQ ID NO: 321      moltype = AA  length = 439
FEATURE
REGION
1..439
note = Engineered antibody sequence
source
1..439
mol_type = protein
organism = synthetic construct
SEQUENCE: 321
QSLEESGGRL VTPGTPLTLT CTVSGIGLSS YYMQWVRQSP GRGLEWIGVI GSDGKTYYAT 60
WAKGRFTISK TSSTTVDLRM ASLTTEDTAT YFCTRGDIWG PGTLVTVSSA STKGPSVFPL 120
APSSKSTGG TAALGCLVKD YFPEPVTSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV 180
PSSSLGTQTY ICNVNHPKSN TKVDKRVEPKV SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 240
DTLMISRTP E VTCVVVDVSH EDPEVKFNWY VDGVEVHNAAK TKPREEQYAS TYRVVSVLTV 300
LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL 360
VKGFYPSDIA VEWESNGQPE NNYKTPPPVL DSDGSFFFLYS KLTVDKSRWQ QGNVFSCVM 420
HEALHNHYTQ KSLSLSPKG                                439

SEQ ID NO: 322      moltype = AA  length = 109
FEATURE
REGION
1..109
note = Engineered antibody sequence
source
1..109
mol_type = protein
organism = synthetic construct
SEQUENCE: 322
QSLEESGGRL VTPGTPLTLT CTVSGIGLSS YYMQWVRQSP GRGLEWIGVI GSDGKTYYAT 60
WAKGRFTISK TSSTTVDLRM ASLTTEDTAT YFCTRGDIWG PGTLVTVSS                                109

SEQ ID NO: 323      moltype = AA  length = 29
FEATURE
REGION
1..29
note = Engineered antibody sequence
source
1..29
mol_type = protein
organism = synthetic construct
SEQUENCE: 323
QSLEESGGRL VTPGTPLTLT CTVSGIGLSS                                29

SEQ ID NO: 324      moltype = AA  length = 5
FEATURE
REGION
1..5
note = Engineered antibody sequence
source
1..5
mol_type = protein
organism = synthetic construct
SEQUENCE: 324
SYMQ                                5

SEQ ID NO: 325      moltype = AA  length = 14
FEATURE
REGION
1..14
note = Engineered antibody sequence
source
1..14
mol_type = protein
organism = synthetic construct
SEQUENCE: 325
WVRQSPGRGL EWIG                                14

SEQ ID NO: 326      moltype = AA  length = 16
FEATURE
REGION
1..16
note = Engineered antibody sequence
source
1..16
mol_type = protein
organism = synthetic construct
SEQUENCE: 326
VIGSDGKTYY ATWAKG                                16

SEQ ID NO: 327      moltype = AA  length = 31
FEATURE
REGION
1..31
note = Engineered antibody sequence
source
1..31
mol_type = protein
organism = synthetic construct
SEQUENCE: 327
RFTISKTSST TVDLRMASLT TEDTATYFCT R                                31

```

-continued

```

SEQ ID NO: 328      moltype = length =
SEQUENCE: 328
000

SEQ ID NO: 329      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
source            note = Engineered antibody sequence
1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 329
WGPGTIVTVS S                               11

SEQ ID NO: 330      moltype = AA length = 330
FEATURE          Location/Qualifiers
REGION           1..330
source            note = Engineered antibody sequence
1..330
mol_type = protein
organism = synthetic construct
SEQUENCE: 330
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
STYRVSVSLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPSPREE 240
MTKNQVSLTC LVKGFPYPSDI AVEWESENQQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK                               330

SEQ ID NO: 331      moltype = DNA length = 1320
FEATURE          Location/Qualifiers
misc_feature     1..1320
source            note = Engineered antibody sequence
1..1320
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 331
cagtcgctgg aggagtccgg gggtcgcctg gtcacgcctg ggacaccccct gacactcacc 60
tgcacagtct ctggaaatcg  cctcagtagc tactacatgc agtgggtccgg ccagtctcca 120
gggggggggc tggaaatggat cggaggatcatt ggttagttagt gtaagacata ctacgcgacc 180
tgggcgaaag ggcgattcac catctcccaag acctcgtcg  ccacgggtgg  tctgagaatg 240
gccagtcgtga caaccggagga cacggccacc  tatttctgtga ccaggggg  catctggggc 300
ccggggacc  tcgtcaccgt  ctcgagcgc  tccaccaagg  gcccacgg  cttccccctg 360
gcaccctctt ccaagagcac ctctggggc  acagggccc  tgggctgc  ggtcaaggac 420
tacttcctcg aaccggtgac ggtgtcg  aactcaggc  ccctgacc  cggcggtgcac 480
accttcccg  ctgttcata  gtccctcagg  ctctactcc  tcaggcagc  ggtgaccgtg 540
ccctccagca gtttgggcac  ccagacccac  atctgcaac  tgaatcacaa  gcccaccaac 600
accaagggtg acaagagagt tgagccaaa  tcttgcaca  aaactcacac  atgcccacccg 660
tgcggcagc  ctgaactctt  gggggggacc  tcagttctcc  tttttttttt  aaaacccaaag 720
gacaccctca tgatctcccg  gacccctgg  gtcaacatgc  tgggtgtgg  cgtgagccac 780
gaagaccctt aggtcaagtt  caactggta  gtggacggcc  tggagggtgc  taatgccaag 840
acaaagccgc  gggaggagca  gtacggcc  acgttaccgt  tggtcagc  cctcaccgtc 900
ctgcaccagg  actgggtgaa  tggcaaggag  tacaatgtca  aggttcccaa  caaaggccctc 960
ccagggggca  tggagaaaaac  catctccaaa  gcccaaggggc  agccccggaa  accacagggt 1020
tacacccttc  ccccatcccg  ggaggagatg  accaagaacc  aggtcaac  gacccgtc 1080
gtcaaaaggct tctatcccg  cgacatgc  gtggagtggg  agagcaatgg  gcagccggag 1140
acaactaca  agaccacgac  tccctgtgt  gactccgac  gtccttctt  cctctacacg 1200
aagctccacg  tggaaagag  cagggtggc  caggggaacg  ttttctcatg  ctcctgtatg 1260
catagggttc  tgcacaacca  ctacacgc  aagacccct  ccctgttcc  gggtaaatga 1320

SEQ ID NO: 332      moltype = DNA length = 327
FEATURE          Location/Qualifiers
misc_feature     1..327
source            note = Engineered antibody sequence
1..327
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 332
cagtcgctgg aggagtccgg gggtcgcctg gtcacgcctg ggacaccccct gacactcacc 60
tgcacagtct ctggaaatcg  cctcagtagc tactacatgc agtgggtccgg ccagtctcca 120
gggggggggc tggaaatggat cggaggatcatt ggttagttagt gtaagacata ctacgcgacc 180
tgggcgaaag ggcgattcac catctcccaag acctcgtcg  ccacgggtgg  tctgagaatg 240
gccagtcgtga caaccggagga cacggccacc  tatttctgtga ccaggggg  catctggggc 300
ccggggacc  tcgtcaccgt  ctcgagcgc  tccaccaagg  gcccacgg  cttccccctg 327

SEQ ID NO: 333      moltype = DNA length = 87
FEATURE          Location/Qualifiers
misc_feature     1..87

```

-continued

```

source          note = Engineered antibody sequence
1..87
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 333
cagtcgtgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60
tgcacagtct ctggaatcgg cctcgtg 87

SEQ ID NO: 334      moltype = DNA length = 15
FEATURE           Location/Qualifiers
misc_feature      1..15
note = Engineered antibody sequence
source            1..15
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 334
agctactaca tgcag 15

SEQ ID NO: 335      moltype = DNA length = 42
FEATURE           Location/Qualifiers
misc_feature      1..42
note = Engineered antibody sequence
source            1..42
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 335
tgggtccggc agtctccagg gagggggctg gaatggatcg ga 42

SEQ ID NO: 336      moltype = DNA length = 48
FEATURE           Location/Qualifiers
misc_feature      1..48
note = Engineered antibody sequence
source            1..48
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 336
gtcattggta gtgatggtaa gacatactac gcgacacctggg cgaaaggc 48

SEQ ID NO: 337      moltype = DNA length = 93
FEATURE           Location/Qualifiers
misc_feature      1..93
note = Engineered antibody sequence
source            1..93
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 337
cgattcacca tctccaagac ctcgtcgacc acgggtggatc tgagaatggc cagtctgaca 60
acccaggaca cggccaccta tttctgtacc aga 93

SEQ ID NO: 338      moltype = length =
SEQUENCE: 338
000

SEQ ID NO: 339      moltype = DNA length = 33
FEATURE           Location/Qualifiers
misc_feature      1..33
note = Engineered antibody sequence
source            1..33
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 339
tggggccccc ggaccctcgta caccgtctcg agc 33

SEQ ID NO: 340      moltype = DNA length = 993
FEATURE           Location/Qualifiers
misc_feature      1..993
note = Engineered antibody sequence
source            1..993
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 340
gcctccacca agggcccatc ggtcttcccc ctggcacccct cctccaaaggag cacctctggg 60
ggcacagcgg ccctgggtcg cctggtcaag gactacttcc cggaaagggt gacgggtgtcg 120
tggaaacttag cggccctgac cagcggcgtg cacaccttcc cggctgtctt acagtccctca 180
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaagcttggg cacccagacc 240
tacatctgca acgtgaatca caagcccagg aacaccaagg tggacaagag agttgagccc 300
aaatcttgtc acaaactca cacatgccc cccgtgcccag cacctgaact cctgggggg 360
ccgtcagtct tcctttccc cccaaaaccc aaggacaccc tcatgatctc ccggacccct 420
gagggtcacat gctgtgggt ggacgtgagc cacgaagacc ctgaggtaa gttcaactgg 480

```

-continued

tacggtggacg	gcgtggaggt	gcataatgcc	aagacaaaagc	cgcggggagga	gcagtacgcc	540
agcacgtacc	gtgtggtcag	cgtccctcacc	gtcctgcacc	aggactggct	gaatggcaag	600
gagtacaagt	gcaagggtctc	caacaaagcc	ctccccagccc	ccatcgagaa	aaccatctcc	660
aaagccaaag	ggcagccccg	agaaccacag	gtgtacaccc	tgcggccatc	ccggggaggag	720
atgaccaaga	accagggtcag	cctgacacctc	cttgtcaaaag	gcttctatcc	cagcgacatc	780
gcccgtggagt	gggagagcaa	tggcagccg	gagaacaact	acaagaccac	gcctcccttg	840
cttgactccg	acggctccctt	cttctctac	agcaagctca	ccgtggacaa	gagcaggctgg	900
cagcaggggg	acgttttctc	atgtccgtg	atgcatgagg	ctctgcacaa	ccactacacg	960
cagaagagcc	tctccctgtc	tccgggtaaa	tga			993
 SEQ ID NO: 341			molttype = AA	length = 219		
FEATURE			Location/Qualifiers			
REGION			1..219			
			note = Engineered antibody sequence			
source			1..219			
			mol_type = protein			
			organism = synthetic construct			
 SEQUENCE: 341						
QVLTQTPSPV	SAAVGSTVTI	NCQASQNLYNN	NNYLAWYQQK	PQOPPKQLIY	STSTLASGV	60
SRFRGSGSGT	QFTLTISDVQ	CDDAATYYCL	GSYDCSRGDC	FVFGGGTEVV	VKRTVAAPSV	120
FIIPPSDEQL	KSGTASVVCL	LNNFYPREAK	VQWKVDNALQ	SGNSQESVTE	QDSKDSTYSL	180
STSTTLSKAD	YEKHKVYACE	VTHQGLSSPV	TKSFNRGEC			219
 SEQ ID NO: 342			molttype = AA	length = 113		
FEATURE			Location/Qualifiers			
REGION			1..113			
			note = Engineered antibody sequence			
source			1..113			
			mol_type = protein			
			organism = synthetic construct			
 SEQUENCE: 342						
QVLTQTPSPV	SAAVGSTVTI	NCQASQNLYNN	NNYLAWYQQK	PQOPPKQLIY	STSTLASGV	60
SRFRGSGSGT	QFTLTISDVQ	CDDAATYYCL	GSYDCSRGDC	FVFGGGTEVV	VKR	113
 SEQ ID NO: 343			molttype = AA	length = 22		
FEATURE			Location/Qualifiers			
REGION			1..22			
			note = Engineered antibody sequence			
source			1..22			
			mol_type = protein			
			organism = synthetic construct			
 SEQUENCE: 343						
QVLTQTPSPV	SAAVGSTVTI	NC			22	
 SEQ ID NO: 344			molttype = AA	length = 13		
FEATURE			Location/Qualifiers			
REGION			1..13			
			note = Engineered antibody sequence			
source			1..13			
			mol_type = protein			
			organism = synthetic construct			
 SEQUENCE: 344						
QASQNVYNN YLA					13	
 SEQ ID NO: 345			molttype = AA	length = 15		
FEATURE			Location/Qualifiers			
REGION			1..15			
			note = Engineered antibody sequence			
source			1..15			
			mol_type = protein			
			organism = synthetic construct			
 SEQUENCE: 345						
WYQQKPGQPP KQLIY					15	
 SEQ ID NO: 346			molttype = AA	length = 7		
FEATURE			Location/Qualifiers			
REGION			1..7			
			note = Engineered antibody sequence			
source			1..7			
			mol_type = protein			
			organism = synthetic construct			
 SEQUENCE: 346						
STSTLAS					7	
 SEQ ID NO: 347			molttype = AA	length = 32		
FEATURE			Location/Qualifiers			
REGION			1..32			
			note = Engineered antibody sequence			
source			1..32			

-continued

```

mol_type = protein
organism = synthetic construct

SEQUENCE: 347
GVSSRFRGSG SGTQFTLTIS DVQCDDAATY YC 32

SEQ ID NO: 348      moltype = AA length = 13
FEATURE          Location/Qualifiers
REGION           1..13
source            note = Engineered antibody sequence
                  1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 348
LGSYDCSRGD CFV 13

SEQ ID NO: 349      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
source            note = Engineered antibody sequence
                  1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 349
FGGGTEVVVK R 11

SEQ ID NO: 350      moltype = AA length = 106
FEATURE          Location/Qualifiers
REGION           1..106
source            note = Engineered antibody sequence
                  1..106
mol_type = protein
organism = synthetic construct

SEQUENCE: 350
TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC 106

SEQ ID NO: 351      moltype = DNA length = 660
FEATURE          Location/Qualifiers
misc_feature     1..660
source            note = Engineered antibody sequence
                  1..660
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 351
caagtgtga cccagactcc atccccctgt tctgcagctg tgggaagcac agtcaccatc 60
aattggcagg ccagtcagaa tgtttataat aacaactacc tagcctggta tcagcagaaa 120
ccagggcagc ctcccaagca actgtatcat tctacgttca ctctggcatc tgggtctca 180
tcgcgattca gaggcagttg atctggaca cagttcactc tcaccatcg cgacgtgcag 240
tgtgacgatg ctgccactta ctactgtcta ggcatgtatg attgttagtcg tggtgatgt 300
tttgttttcg goggagggac cgagggtggtg gtcaaacgtt cgggtggctgc accatctgtc 360
ttcatcttcc cggccatctga tgagcaatggaa aaatctggaa ctgcctctgt tggtgctcg 420
ctgaataact tctatccag agaggccaaa gtacagtggaa aggtggataa cgccttccaa 480
tcgggttaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagctc 540
agcagcaccc tgacgttgag caaaggcac tacgagaaac acaaagtcta cgcctgcgaa 600
gtcacccatc agggccttag ctcggccatc acaaaggtt tcaacagggg agagtgttag 660

SEQ ID NO: 352      moltype = DNA length = 339
FEATURE          Location/Qualifiers
misc_feature     1..339
source            note = Engineered antibody sequence
                  1..339
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 352
caagtgtga cccagactcc atccccctgt tctgcagctg tgggaagcac agtcaccatc 60
aattggcagg ccagtcagaa tgtttataat aacaactacc tagcctggta tcagcagaaa 120
ccagggcagc ctcccaagca actgtatcat tctacgttca ctctggcatc tgggtctca 180
tcgcgattca gaggcagttg atctggaca cagttcactc tcaccatcg cgacgtgcag 240
tgtgacgatg ctgccactta ctactgtcta ggcatgtatg attgttagtcg tggtgatgt 300
tttgttttcg goggagggac cgagggtggtg gtcaaacgtt 339

SEQ ID NO: 353      moltype = DNA length = 66
FEATURE          Location/Qualifiers
misc_feature     1..66
source            note = Engineered antibody sequence
                  1..66
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 353

```

-continued

caagtgcgtga cccagactcc atccccgtg tctgcagctg tggaaagcac agtcaccatc aattgc	60 66
SEQ ID NO: 354 FEATURE misc_feature source SEQUENCE: 354 caggccagtc agaatgttta taataacaac tacctagcc	moltype = DNA length = 39 Location/Qualifiers 1..39 note = Engineered antibody sequence 1..39 mol_type = other DNA organism = synthetic construct 39
SEQ ID NO: 355 FEATURE misc_feature source SEQUENCE: 355 tggttatcagc agaaaaccagg gcagcctccc aagcaactga tctat	moltype = DNA length = 45 Location/Qualifiers 1..45 note = Engineered antibody sequence 1..45 mol_type = other DNA organism = synthetic construct 45
SEQ ID NO: 356 FEATURE misc_feature source SEQUENCE: 356 tctacgtcca ctctggcatc t	moltype = DNA length = 21 Location/Qualifiers 1..21 note = Engineered antibody sequence 1..21 mol_type = other DNA organism = synthetic construct 21
SEQ ID NO: 357 FEATURE misc_feature source SEQUENCE: 357 gggggtctcat cgcgatttag aggcagtgg a tctggggacac agttcactct caccatc gacgtgcagt gtgacgtatc tactgt	moltype = DNA length = 96 Location/Qualifiers 1..96 note = Engineered antibody sequence 1..96 mol_type = other DNA organism = synthetic construct 60 96
SEQ ID NO: 358 FEATURE misc_feature source SEQUENCE: 358 ctaggcagtt atgattgttag tcgtggatg tttttgtt	moltype = DNA length = 39 Location/Qualifiers 1..39 note = Engineered antibody sequence 1..39 mol_type = other DNA organism = synthetic construct 39
SEQ ID NO: 359 FEATURE misc_feature source SEQUENCE: 359 ttcggcggag ggaccggaggt ggtggtcaaa cgt	moltype = DNA length = 33 Location/Qualifiers 1..33 note = Engineered antibody sequence 1..33 mol_type = other DNA organism = synthetic construct 33
SEQ ID NO: 360 FEATURE misc_feature source SEQUENCE: 360 acgggtggctg caccatctgt cttcatcttc cgcgcattctg atgaggcagg taaatctgg actgcctctg ttgtgtgcct gctaataac ttctatccc gagaggccaa agtacatgg aagggtggata acggccatcc a tccggtaac tcccaggaga gtgtcacaga gcaggac aaggacagca cttacacgcct cagcagcacc ctgacgcgtg gcaaaaggcaga ctac cacaaggatct acgcctgcga agtcacccat caggccctga gctcgccctg cacaagg ttcaacagggg gagatgttta g	moltype = DNA length = 321 Location/Qualifiers 1..321 note = Engineered antibody sequence 1..321 mol_type = other DNA organism = synthetic construct 60 120 180 240 300 321

US 12,391,749 B2

179

180

-continued

SEQ ID NO: 361 moltype = AA length = 441
 FEATURE Location/Qualifiers
 REGION 1..441
 note = Engineered antibody sequence
 source 1..441
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 361
 EVQLVESGG LVQPGGSLRL SCAVSGIGLS SYMMQWVRQA PGKGLEWVGV IGSDGKTYYA 60
 TWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCTRGDI WGQGTLVTVS SASTKGPSVF 120
 PLAPSSKSTS CGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
 TVPSSSLGTQ TYICCNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK 240
 PKDTLTMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVVSVL 300
 TVLHQDWLNG SEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPSSRE EMTKNQVSLT 360
 CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSPF YSKLTVDKSR WQQGNVFSCS 420
 VMHEALHNHY TQKSLSLSPG K 441

SEQ ID NO: 362 moltype = AA length = 111
 FEATURE Location/Qualifiers
 REGION 1..111
 note = Engineered antibody sequence
 source 1..111
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 362
 EVQLVESGGG LVQPGGSLRL SCAVSGIGLS SYMMQWVRQA PGKGLEWVGV IGSDGKTYYA 60
 TWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCTRGDI WGQGTLVTVS S 111

SEQ ID NO: 363 moltype = AA length = 30
 FEATURE Location/Qualifiers
 REGION 1..30
 note = Engineered antibody sequence
 source 1..30
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 363
 EVQLVESGGG LVQPGGSLRL SCAVSGIGLS 30

SEQ ID NO: 364 moltype = AA length = 5
 FEATURE Location/Qualifiers
 REGION 1..5
 note = Engineered antibody sequence
 source 1..5
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 364
 SYMMQ 5

SEQ ID NO: 365 moltype = AA length = 14
 FEATURE Location/Qualifiers
 REGION 1..14
 note = Engineered antibody sequence
 source 1..14
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 365
 WVRQAPGKGL EWVG 14

SEQ ID NO: 366 moltype = AA length = 16
 FEATURE Location/Qualifiers
 REGION 1..16
 note = Engineered antibody sequence
 source 1..16
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 366
 VIGSDGKTYY ATWAKG 16

SEQ ID NO: 367 moltype = AA length = 32
 FEATURE Location/Qualifiers
 REGION 1..32
 note = Engineered antibody sequence
 source 1..32
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 367
 RFTISRDN SK TTVYLQMNSL RAEDTAVYFC TR 32

SEQ ID NO: 368 moltype = length =

-continued

SEQUENCE: 368
000

SEQ ID NO: 369 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Engineered antibody sequence
source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 369
WGQGTLVTVS S 11

SEQ ID NO: 370 moltype = AA length = 330
FEATURE Location/Qualifiers
REGION 1..330
note = Engineered antibody sequence
source 1..330
mol_type = protein
organism = synthetic construct

SEQUENCE: 370
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPPKP KDLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
STYRVRVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESENQQP ENNYKTPPPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 371 moltype = DNA length = 1326
FEATURE Location/Qualifiers
misc_feature 1..1326
note = Engineered antibody sequence
source 1..1326
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 371
gagggtgcagc ttgtggagtc tgggggaggo ttgggtccagc ctggggggtc cctgagactc 60
tccctgtcagc tctctggaat cgccctcaagt agtactaca tgcaatgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggtcgaggatc attggtagtg atggtaagac atactacgct 180
acctggcgata aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatcc 240
caaataatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtaccag agggggacatc 300
tggggcacaag ggaccctcgat cacccgtctcg agggccctcca ccaaggggccc atcggcttcc 360
ccccctggcac cctctggcaa gagccatctggatcggccacac cggggcttggg ctgcctggtc 420
aaggactact tcccccgaacc ggtgacgggtg tcgttggaaact caggccgcctt gaccacggc 480
gtgcacacact tcccggtctgt cctacagtcc tcaggactct actccctca gaggctggtg 540
accgtgcctt ccaggcatggt gggccacccatg acctacatcc gcaacgtgaa tcacaagccc 600
agcaacacca aagggtggaaa gagatggtagtgg cccaaatctt gtgacaaaatc tcacacatgc 660
ccaccgtgcc cagcacatca actcttgggg ggaccgtcaat ttttcttccc ccccccaaaa 720
cccaaggaca ccctcatgtat ctcccgacc cctgaggatca catgcgttgtt ggtggacgtg 780
agccacacaaaggccatggatc caagtcaac tggtacgtgg acggcgtgaa ggtgcataat 840
gccaagacaa aggccgggaa ggacatggatc gcaacgtgaa acctgttgtt cagcgtctc 900
accgtcttc accaggactg gctaatggc aagggttaca agtgcacggt ctccaaacaaa 960
gcctcccaag ccccccatacgaa gaaaaccatc tccaaagccca aaggccggcc ccgagaacca 1020
caagggttaca ccctggccccc atccccgggg gagatggacca agaaccatgt cagctgtacc 1080
tgcctggatca aaggcttctca tcccgccgc acatggccgtgg agtggggagag caatggccag 1140
cccgagaaaca actacaagac caccgttccq tgcgttggact ccggccgttc cttttcttc 1200
tacagcaagc tcaccgtggaa caagacggg tggcagcagg ggaacgtttt ctcatgtcc 1260
gtgtatgcatg aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1320
aaatga 1326

SEQ ID NO: 372 moltype = DNA length = 333
FEATURE Location/Qualifiers
misc_feature 1..333
note = Engineered antibody sequence
source 1..333
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 372
gagggtgcagc ttgtggagtc tgggggaggo ttgggtccagc ctggggggtc cctgagactc 60
tccctgtcagc tctctggaat cgccctcaagt agtactaca tgcaatgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggtcgaggatc attggtagtg atggtaagac atactacgct 180
acctggcgata aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatcc 240
caaataatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtaccag agggggacatc 300
tggggcacaag ggaccctcgat cacccgtctcg agc 333

SEQ ID NO: 373 moltype = DNA length = 90
FEATURE Location/Qualifiers
misc_feature 1..90
note = Engineered antibody sequence

-continued

source 1..90
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 373
 gaggtgcagc ttgtggagt tgggggaggo ttgggtccagc ctggggggtc cctgagactc 60
 tcctgtcagc tctctggaaat cggcctcagt 90

SEQ ID NO: 374 moltype = DNA length = 15
 FEATURE
 misc_feature 1..15
 note = Engineered antibody sequence

source 1..15
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 374
 agctactaca tgcaa 15

SEQ ID NO: 375 moltype = DNA length = 42
 FEATURE
 misc_feature 1..42
 note = Engineered antibody sequence

source 1..42
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 375
 tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga 42

SEQ ID NO: 376 moltype = DNA length = 48
 FEATURE
 misc_feature 1..48
 note = Engineered antibody sequence

source 1..48
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 376
 gtcatttgta gtgatggtaa gacatactac gcgacacctggc cgaaaggc 48

SEQ ID NO: 377 moltype = DNA length = 96
 FEATURE
 misc_feature 1..96
 note = Engineered antibody sequence

source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 377
 cgattcacca tctccagaga caattccaag accacgggtt atcttcaat gaacagctg 60
 agagctgagg caactgctgt gtatttctgt accaga 96

SEQ ID NO: 378 moltype = length =
 SEQUENCE: 378
 000

SEQ ID NO: 379 moltype = DNA length = 33
 FEATURE
 misc_feature 1..33
 note = Engineered antibody sequence

source 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 379
 tggggccaag ggaccctcgta caccgtctcg agc 33

SEQ ID NO: 380 moltype = DNA length = 993
 FEATURE
 misc_feature 1..993
 note = Engineered antibody sequence

source 1..993
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 380
 gcctccacca agggcccata ggtttcccc ctggcacccct cctccaagag cacctctggg 60
 ggcacagccgg ccctgggtcg cctggtaag gactacttcc cccgaacccgtt gacgggtgtcg 120
 tggaaacttag cgcggccgtac cagccgggttg cacacccttcc cggctgtctt acagtcccta 180
 ggactctact ccctcagcagc cgtgggtgacc gtggccctca cggatgggg caccggacc 240
 tacatctgca acgtgaatca caagccca gacaccaagg tggacaagag agttgagggcc 300
 aaatcttggta acaaactca cacatggcca cccgtggccat cacctgaact cctgggggg 360
 ccgtcagtct tctctttccc cccaaaaccc aaggacacc tcatgatctc cccggaccct 420
 gaggtcacat gcgtgggtgtt ggacgtgago cacgaagacc ctggaggtaa gttcaactgg 480
 tacgtggacg cgcgtggaggt gcataatggc aagacaaaagc cccggggaggc gcagtacgcc 540

-continued

agcacgtacc gtgtggtcag cgtccctcacc gtcctgcacc aggactggct gaatggcaag 600
 gaggataagt gcaaggcttc caacaagcc ctcccagccc ccatcgagaa aaccatctcc 660
 aaagccaaag ggcagccccg agaaccacag gtgtacacc tgccccatc cgggaggag 720
 atgaccaaga accaggctcg cctgacactgc ctggtaaaag gtttctatcc cagcgacatc 780
 gccgtggagt gggagagcaa tggcagccg gagaacaact acaagcac acgcacccg 840
 ctggactccg acggctcattt ctgcctcatac agcaagctca cctggacaa gagcaggctgg 900
 cagcaggggaa acgtcttc tgcgttccatc atgcatgagg ctctgcacaa ccactacacg 960
 cagaagagcc tctccctgtc tccgggtaaa tga 993

SEQ ID NO: 381 moltype = AA length = 219
 FEATURE Location/Qualifiers
 REGION 1..219
 note = Engineered antibody sequence
 source 1..219
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 381
 QVLTQSPSSL SASVGDRVTI NCQASQNLYNNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISLQ PEDVATYYCL GSYDCSRGDC FVFGGGTKVE IKRTVAAPSV 120
 FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
 STSTLTLKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 219

SEQ ID NO: 382 moltype = AA length = 113
 FEATURE Location/Qualifiers
 REGION 1..113
 note = Engineered antibody sequence
 source 1..113
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 382
 QVLTQSPSSL SASVGDRVTI NCQASQNLYNNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISLQ PEDVATYYCL GSYDCSRGDC FVFGGGTKVE IKR 113

SEQ ID NO: 383 moltype = AA length = 22
 FEATURE Location/Qualifiers
 REGION 1..22
 note = Engineered antibody sequence
 source 1..22
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 383
 QVLTQSPSSL SASVGDRVTI NC 22

SEQ ID NO: 384 moltype = AA length = 13
 FEATURE Location/Qualifiers
 REGION 1..13
 note = Engineered antibody sequence
 source 1..13
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 384
 QASQNLYNNYLAWYQQK PGKVPKQLIY 13

SEQ ID NO: 385 moltype = AA length = 15
 FEATURE Location/Qualifiers
 REGION 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 385
 WYQQKPGKVP KQLIY 15

SEQ ID NO: 386 moltype = AA length = 7
 FEATURE Location/Qualifiers
 REGION 1..7
 note = Engineered antibody sequence
 source 1..7
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 386
 STSTLAS 7

SEQ ID NO: 387 moltype = AA length = 32
 FEATURE Location/Qualifiers
 REGION 1..32
 note = Engineered antibody sequence
 source 1..32
 mol_type = protein

-continued

organism = synthetic construct

SEQUENCE: 387
GVPSRFSGSG SGTDFLTIS SLQPEDVATY YC 32

SEQ ID NO: 388 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
source note = Engineered antibody sequence
1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 388
LGSYDCSRGD CFV 13

SEQ ID NO: 389 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
source note = Engineered antibody sequence
1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 389
FGGGTKVEIK R 11

SEQ ID NO: 390 moltype = AA length = 106
FEATURE Location/Qualifiers
REGION 1..106
source note = Engineered antibody sequence
1..106
mol_type = protein
organism = synthetic construct

SEQUENCE: 390
TVAAPSVIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSST LTLSKADYEK HKVYACEVTN QGLSSPVTKS FNRGEC 106

SEQ ID NO: 391 moltype = DNA length = 660
FEATURE Location/Qualifiers
misc_feature 1..660
source note = Engineered antibody sequence
1..660
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 391
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccagg ccagtcaagaa tgtttacaat aacaactacc tagcctggta tcagcagaaaa 120
ccaggaaag ttccataagca actgtatcatc tctacatcca ctctggcatc tggggtccca 180
tctcggttca gtggcagtg 180
atctgggaca gatttcactc tcaccatcg cagcctgcag 240
cctgaagatg ttgcacttta ttactgtctg ggcagttatg attgttagtc tggtgatgt 300
tttgtttcg gcccggaaac caaggtggaa atcaaacgtg cggctggctgc accatctgtc 360
ttcatcttcc cgcctatctg tgacgttg aaatctgtggaa ctgcctctgt tggtgctcg 420
ctgatataact ttatccccag agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcggtaact cccaggagag tgtcacagag caggacac ctagacgtc 540
agcagcaccc tgacgtcgag caaaggacac tacggagaac acaaagtcta cgcctgcgaa 600
gtcacccatc agggccttag ctcggccgtc acaaagagct tcaacagggg agagtgttag 660

SEQ ID NO: 392 moltype = DNA length = 339
FEATURE Location/Qualifiers
misc_feature 1..339
source note = Engineered antibody sequence
1..339
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 392
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccagg ccagtcaagaa tgtttacaat aacaactacc tagcctggta tcagcagaaaa 120
ccaggaaag ttccataagca actgtatcatc tctacatcca ctctggcatc tggggtccca 180
tctcggttca gtggcagtg 180
atctgggaca gatttcactc tcaccatcg cagcctgcag 240
cctgaagatg ttgcacttta ttactgtctg ggcagttatg attgttagtc tggtgatgt 300
tttgtttcg gcccggaaac caaggtggaa atcaaacgtg 339

SEQ ID NO: 393 moltype = DNA length = 66
FEATURE Location/Qualifiers
misc_feature 1..66
source note = Engineered antibody sequence
1..66
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 393
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60

-continued

aattgc	66
SEQ ID NO: 394	moltype = DNA length = 39
FEATURE	Location/Qualifiers
misc_feature	1..39
	note = Engineered antibody sequence
source	1..39
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 394	
caggccagtc agaaatgttta caataacaac taccttagcc	39
SEQ ID NO: 395	moltype = DNA length = 45
FEATURE	Location/Qualifiers
misc_feature	1..45
	note = Engineered antibody sequence
source	1..45
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 395	
tggtatcagc agaaaccagg gaaagttcct aagcaactga tctat	45
SEQ ID NO: 396	moltype = DNA length = 21
FEATURE	Location/Qualifiers
misc_feature	1..21
	note = Engineered antibody sequence
source	1..21
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 396	
tctacatcca ctctggcatc t	21
SEQ ID NO: 397	moltype = DNA length = 96
FEATURE	Location/Qualifiers
misc_feature	1..96
	note = Engineered antibody sequence
source	1..96
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 397	
gggggtcccat ctcgtttcag tggcgatgga tctgggacag atttcactct caccatcagc	60
agcctgcagc ctgaagatgt tgcaacttat tactgt	96
SEQ ID NO: 398	moltype = DNA length = 39
FEATURE	Location/Qualifiers
misc_feature	1..39
	note = Engineered antibody sequence
source	1..39
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 398	
ctgggcagtt atgattgttag tcgtggtgat tgttttgtt	39
SEQ ID NO: 399	moltype = DNA length = 33
FEATURE	Location/Qualifiers
misc_feature	1..33
	note = Engineered antibody sequence
source	1..33
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 399	
ttcggcggag ggaccaaggt ggaaaatcaaa cgt	33
SEQ ID NO: 400	moltype = DNA length = 321
FEATURE	Location/Qualifiers
misc_feature	1..321
	note = Engineered antibody sequence
source	1..321
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 400	
acgggtggctg caccatctgt ctcatcttc ccggccatctg atgaggcaggat gaaatctgga	60
actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg	120
aagggtggata acggccatcca atcggttaac tcccaggaga gtgtcacaga gcaggacagc	180
aaggacacgca cttacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa	240
cacaaagtct acgcctgcga agtcacccat cagggcctga gtcgcggcgt cacaaagagc	300
ttcaaacaggg gagagtgtta g	321
SEQ ID NO: 401	moltype = AA length = 439

-continued

FEATURE	Location/Qualifiers
REGION	1..439
	note = Engineered antibody sequence
source	1..439
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 401	
QSLEESGGRL VTPGGSLTLT CTVSGIDVTN YYMQWVRQAP GKGLEWIGVI GVNGKRYYAS	60
WAKGRFTISK TSSTTVDLKN TSLTTEDAT YFCARGDIWG PGTLVTVSSA STKGPSVFPL	120
APSSSKSTSGG TAALGCLVKD YFPEPVTWSW NSGALTSGVH TPPAVLQSSG LYSLSSVVTW	180
PSSSLGTQTY ICNVNHHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGH SVFLPPPKPK	240
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYAS TYRVVSVLTV	300
LHQDWLNKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL	360
VKGFYPSDIA VEWESNGQE NNYKTTPPVLS DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM	420
HEALHNHYTQ KSLSLSPGK	439
SEQ ID NO: 402	moltype = AA length = 109
FEATURE	Location/Qualifiers
REGION	1..109
	note = Engineered antibody sequence
source	1..109
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 402	
QSLEESGGRL VTPGGSLTLT CTVSGIDVTN YYMQWVRQAP GKGLEWIGVI GVNGKRYYAS	60
WAKGRFTISK TSSTTVDLKM TSLTTEDAT YFCARGDIWG PGTLVTVSS	109
SEQ ID NO: 403	moltype = AA length = 29
FEATURE	Location/Qualifiers
REGION	1..29
	note = Engineered antibody sequence
source	1..29
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 403	
QSLEESGGRL VTPGGSLTLT CTVSGIDVT	29
SEQ ID NO: 404	moltype = AA length = 5
FEATURE	Location/Qualifiers
REGION	1..5
	note = Engineered antibody sequence
source	1..5
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 404	
NYYMQ	5
SEQ ID NO: 405	moltype = AA length = 14
FEATURE	Location/Qualifiers
REGION	1..14
	note = Engineered antibody sequence
source	1..14
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 405	
WVRQAPGKGL EWIG	14
SEQ ID NO: 406	moltype = AA length = 16
FEATURE	Location/Qualifiers
REGION	1..16
	note = Engineered antibody sequence
source	1..16
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 406	
VIGVNGKRYY ASWAKG	16
SEQ ID NO: 407	moltype = AA length = 31
FEATURE	Location/Qualifiers
REGION	1..31
	note = Engineered antibody sequence
source	1..31
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 407	
RFTISKTSST TVDLKMTSLT TEDTATYFCA R	31
SEQ ID NO: 408	moltype = length =
SEQUENCE: 408	

-continued

000

SEQ ID NO: 409 moltype = AA length = 11
 FEATURE Location/Qualifiers
 REGION 1..11
 note = Engineered antibody sequence
 source 1..11
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 409
 WGPGLTVTS S 11

SEQ ID NO: 410 moltype = AA length = 330
 FEATURE Location/Qualifiers
 REGION 1..330
 note = Engineered antibody sequence
 source 1..330
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 410
 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVVS WNSGALTSGV HTFPAVLQSS 60
 GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
 PSVFLFPKPK KDTLMISRTP EVTCVVVDVS HEDPEVKFWN YVDGVENVNA KTKPREEQYA 180
 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPPSREE 240
 MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPPV LDSDGSFFLY SKLTVDKSRW 300
 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 411 moltype = DNA length = 1320
 FEATURE Location/Qualifiers
 misc_feature 1..1320
 note = Engineered antibody sequence
 source 1..1320
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 411
 caagtgcgtgg aggagtccgg gggtcgcctg gtacgcgcctg gaggatccct gacactcacc 60
 tgcacagtct ctggaaatcga cgtcaactaac tactatatgc aatgggtcccg ccaggctcca 120
 gggaaaggggc tggaaatggat cggagttcatt ggtgtgaatg gtaagagata ctacgcgagc 180
 tgggcgaaag gccgattcac catctccaaa acctcgtcgaa ccacgggtgaa tctgaaaatg 240
 accagtcgtga caacccgagga cacggccacc tatttctgtg ccagaggcga catctgggc 300
 cccggggacc tcgtcaccgt ctgcagcgcc tccaccaagg gcccatecggt cttccccctg 360
 gcaccctctt ccaaggacac ctctgggggg acacggggcc tggcgtcgct ggtaaaggac 420
 tactttcccg aaccgggtac ggtgtcggtg aactcaggcg ccctgaccag cggcgtgcac 480
 accttccccc ctgtcttaca gtccctcgaa ctctactccc tcagcagcgt ggtgaccgtg 540
 ccctccagca gtttgggacac ccagacccatc atctgcaacg tgaatcaca gccccagcaac 600
 accaagggtgg acaaaggaggt tgaggccaaa ttcttgtgacaa aaactcacac atgcccaccc 660
 tgccccagcac ctgaaactct gggggggaccc tcgtcttc ttttttttttcccaaaaaccaag 720
 gacaccctca tgatctcccg gaccccttagt gtacatcgcc tgggtgggtaa cgtgagccac 780
 gaagaccctg aggtcaagtt caactggtagt gtggacggcg tggagggtgca taatgccaag 840
 acaaaggccg gggaggagca gtaccccgac acgttacccgt tggtcacgct cttcacccgt 900
 ctgcaccagg actgggtgaa tggcaaggag tacaatgtca aggttccaa caaaggccctc 960
 ccagccccca tcggaaaaac catctccaaa gccaaaggcc accccccggaga accacagggt 1020
 tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagct gacctgcctg 1080
 gtc当地ccctt ctatcccg cgacatcgcc gtggagtggg agagcaatgg gc当地ccggag 1140
 aacaactaca agaccacccgcc tccctgtgtc gactccgacg gtc当地ctt cctctacagc 1200
 aagctcaccgg tggacaagag cagggtggacg caggggaaacg ttttcttcatg ctccgtatg 1260
 catgagggtc tgcacaacca ctacacgcac aagagccctc ccctgtctcc gggtaaatga 1320

SEQ ID NO: 412 moltype = DNA length = 327
 FEATURE Location/Qualifiers
 misc_feature 1..327
 note = Engineered antibody sequence
 source 1..327
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 412
 caagtgcgtgg aggagtccgg gggtcgcctg gtacgcgcctg gaggatccct gacactcacc 60
 tgcacagtct ctggaaatcga cgtcaactaac tactatatgc aatgggtcccg ccaggctcca 120
 gggaaaggggc tggaaatggat cggagttcatt ggtgtgaatg gtaagagata ctacgcgagc 180
 tgggcgaaag gccgattcac catctccaaa acctcgtcgaa ccacgggtgaa tctgaaaatg 240
 accagtcgtga caacccgagga cacggccacc tatttctgtg ccagaggcga catctgggc 300
 cccggggacc tcgtcaccgt ctgcagc 327

SEQ ID NO: 413 moltype = DNA length = 87
 FEATURE Location/Qualifiers
 misc_feature 1..87
 note = Engineered antibody sequence
 source 1..87
 mol_type = other DNA

-continued

organism = synthetic construct

SEQUENCE: 413
cactcgctgg aggagtccgg gggtcgcctg gtcacgcctg gaggatccct gacactcacc 60
tgcacagtct ctggaatcga cgtcact 87

SEQ ID NO: 414 moltype = DNA length = 15
FEATURE Location/Qualifiers
misc_feature 1..15
note = Engineered antibody sequence
source 1..15
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 414
aactactata tgcaa 15

SEQ ID NO: 415 moltype = DNA length = 42
FEATURE Location/Qualifiers
misc_feature 1..42
note = Engineered antibody sequence
source 1..42
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 415
tgggtccggc aggctccagg gaagggctg gaatggatcg ga 42

SEQ ID NO: 416 moltype = DNA length = 48
FEATURE Location/Qualifiers
misc_feature 1..48
note = Engineered antibody sequence
source 1..48
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 416
gtcattggtg tgaatggtaa gagataactac gcgagctggg cgaaaggc 48

SEQ ID NO: 417 moltype = DNA length = 93
FEATURE Location/Qualifiers
misc_feature 1..93
note = Engineered antibody sequence
source 1..93
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 417
cgattcacca tctccaaaac ctcgtcgacc acgggtggatc tgaaaaatgac cagtctgaca 60
accgaggaca cggccaccta tttctgtgcc aga 93

SEQ ID NO: 418 moltype = length =
SEQUENCE: 418
000

SEQ ID NO: 419 moltype = DNA length = 33
FEATURE Location/Qualifiers
misc_feature 1..33
note = Engineered antibody sequence
source 1..33
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 419
tggggccccgg ggaccctcg caccgtctcg agc 33

SEQ ID NO: 420 moltype = DNA length = 993
FEATURE Location/Qualifiers
misc_feature 1..993
note = Engineered antibody sequence
source 1..993
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 420
gcctccacca agggcccatc ggtttcccc ctggcacctc cctccaagag cacctctggg 60
ggcacagcgg ccctgggctg cctggtcaag gactactcc cggAACCGGT gacgggtgtcg 120
tggAACTCTGAG cagccgtgtc cacaccttcc cggctgtcct acagtccctca 180
ggactctact ccctcagcag cgtggtgacc gtggccctcca gcagcttggg caccggacc 240
tacatctgca acgtgaatca caagccca aacaccaagg tggacaagag agttgagccc 300
aaatcttgcg aaaaaactca cacatggca cctgtccca caccgtact cctgggggg 360
ccgtcagtct tcctcttccc cccaaaaccc aaggacacc tcatgtatcc ccggaccct 420
gagggtcacat gcgtgggt ggacgtgago cacgaagacc ctgagggtcaa gttcaactgg 480
tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcggggagga gcagtacgcc 540
agcacgtacc gtgtggctcacc gtcctgcacc aggactggct gaatggcaag 600
gagtagacaatgcgtacatgcgtacc caacaaagcc cttccagccc ccatcgagaa aaccatctcc 660

-continued

```

aaaggccaaag ggcagccccg agaaccacag gtgtacacc tgccccatc cggggaggag 720
atgaccaaga accaggtcg cctgacctgc ctggtaaag gtttatcc cagcgacatc 780
ggcggtggagt gggagagcaa tggcgaccc gagaacaact acaagaccac gcctcccttg 840
ctggactccg acggcttctt cttctctac agcaagctca ccgtggacaa gagcaggctgg 900
cagcagggggaa acgttcttc atgtccctgt atgcatgagg ctctgcacaa ccactacacg 960
cagaagagcc ttcctgtc tccggtaaa tga 993

```

```

SEQ ID NO: 421      moltype = AA length = 219
FEATURE          Location/Qualifiers
REGION           1..219
note = Engineered antibody sequence
source            1..219
mol_type = protein
organism = synthetic construct
SEQUENCE: 421
QVLQTQASPV SPAVGSTVTI NCRASQSVYY NNYLAWYQQK PGQPPKQLIY STSTLASGVS 60
SRFKGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSNGDC FVFGGGTEVV VKRTVAAPSV 120
FIFPPSDEQL KSGTASVVC LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTLTLASKD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 219

```

```

SEQ ID NO: 422      moltype = AA length = 113
FEATURE          Location/Qualifiers
REGION           1..113
note = Engineered antibody sequence
source            1..113
mol_type = protein
organism = synthetic construct
SEQUENCE: 422
QVLQTQASPV SPAVGSTVTI NCRASQSVYY NNYLAWYQQK PGQPPKQLIY STSTLASGVS 60
SRFKGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSNGDC FVFGGGTEVV VKR 113

```

```

SEQ ID NO: 423      moltype = AA length = 22
FEATURE          Location/Qualifiers
REGION           1..22
note = Engineered antibody sequence
source            1..22
mol_type = protein
organism = synthetic construct
SEQUENCE: 423
QVLQTQASPV SPAVGSTVTI NC 22

```

```

SEQ ID NO: 424      moltype = AA length = 13
FEATURE          Location/Qualifiers
REGION           1..13
note = Engineered antibody sequence
source            1..13
mol_type = protein
organism = synthetic construct
SEQUENCE: 424
RASQSVYNN YLA 13

```

```

SEQ ID NO: 425      moltype = AA length = 15
FEATURE          Location/Qualifiers
REGION           1..15
note = Engineered antibody sequence
source            1..15
mol_type = protein
organism = synthetic construct
SEQUENCE: 425
WYQQKPGQPP KQLIY 15

```

```

SEQ ID NO: 426      moltype = AA length = 7
FEATURE          Location/Qualifiers
REGION           1..7
note = Engineered antibody sequence
source            1..7
mol_type = protein
organism = synthetic construct
SEQUENCE: 426
STSTLAS 7

```

```

SEQ ID NO: 427      moltype = AA length = 32
FEATURE          Location/Qualifiers
REGION           1..32
note = Engineered antibody sequence
source            1..32
mol_type = protein
organism = synthetic construct
SEQUENCE: 427

```

-continued

GVSSRFKGSG SGTQFTLTIS DVQCDDAATY YC	32
SEQ ID NO: 428 moltype = AA length = 13	
FEATURE Location/Qualifiers	
REGION 1..13	
source note = Engineered antibody sequence	
1..13 mol_type = protein	
SEQUENCE: 428 organism = synthetic construct	
LGSYDCSNGD CFV	13
SEQ ID NO: 429 moltype = AA length = 11	
FEATURE Location/Qualifiers	
REGION 1..11	
source note = Engineered antibody sequence	
1..11 mol_type = protein	
SEQUENCE: 429 organism = synthetic construct	
SEQUENCE: 429 FGGGTEVVVK R	11
SEQ ID NO: 430 moltype = AA length = 106	
FEATURE Location/Qualifiers	
REGION 1..106	
source note = Engineered antibody sequence	
1..106 mol_type = protein	
SEQUENCE: 430 organism = synthetic construct	
TVAAPSVIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS	60
KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC	106
SEQ ID NO: 431 moltype = DNA length = 660	
FEATURE Location/Qualifiers	
misc_feature 1..660	
source note = Engineered antibody sequence	
1..660 mol_type = other DNA	
SEQUENCE: 431 organism = synthetic construct	
caggtgtcga cccagactgc atccccgtg tctccagctg tgggaagcac agtcaccatc	60
aattgcccggg ccagtca gag tgtttattat aacaactacc tagcctggta tcagcagaaa	120
ccaggccggc cttccaaagca actgatctat tctacatcca ctctggcatc tggggctctca	180
tgcgggttca aaggcagtgg atctgggaca cagttcactc tcaccatcag cgacgtgcag	240
tgtgacgtat ctgccactta ctactgtcta ggcagttatg atttgtatgaa tggtgatgt	300
tttggtttcg gcgaggggac cgagggtggt gtcaaacgtg ctggggctgc accatctgtc	360
ttcatcttcc cgccatctga tgacgatgtt aaatctggaa ctgcctctgt tggtgctcg	420
ctgaataact tctatccag agaggccaaa gtacagtggaa aggtggataa cgccctccaa	480
tgcggtaact cccaggagag tgccacagac caggacacaa aggacacac ctacagctc	540
agcagcaccct tgacgcttag caaaggcagac tacgagaaa acaaagtcta cgccctgcgaa	600
gtcacccatc agggcctgag ctcggccgtc acaaagagct tcaacagggg agagtgttag	660
SEQ ID NO: 432 moltype = DNA length = 339	
FEATURE Location/Qualifiers	
misc_feature 1..339	
source note = Engineered antibody sequence	
1..339 mol_type = other DNA	
SEQUENCE: 432 organism = synthetic construct	
caggtgtcga cccagactgc atccccgtg tctccagctg tgggaagcac agtcaccatc	60
aattgcccggg ccagtca gag tgtttattat aacaactacc tagcctggta tcagcagaaa	120
ccaggccggc cttccaaagca actgatctat tctacatcca ctctggcatc tggggctctca	180
tgcgggttca aaggcagtgg atctgggaca cagttcactc tcaccatcag cgacgtgcag	240
tgtgacgtat ctgccactta ctactgtcta ggcagttatg atttgtatgaa tggtgatgt	300
tttggtttcg gcgaggggac cgagggtggt gtcaaacgtg	339
SEQ ID NO: 433 moltype = DNA length = 66	
FEATURE Location/Qualifiers	
misc_feature 1..66	
source note = Engineered antibody sequence	
1..66 mol_type = other DNA	
SEQUENCE: 433 organism = synthetic construct	
caggtgtcga cccagactgc atccccgtg tctccagctg tgggaagcac agtcaccatc	60
aattgc	66

-continued

SEQ ID NO: 434 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 434 cgggccagtc agagtgttta ttataacaac taccttagcc 39

SEQ ID NO: 435 moltype = DNA length = 45
 FEATURE Location/Qualifiers
 misc_feature 1..45
 note = Engineered antibody sequence
 source 1..45
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 435 tggtatcagc agaaaccagg gcagcctccc aagcaactga tctat 45

SEQ ID NO: 436 moltype = DNA length = 21
 FEATURE Location/Qualifiers
 misc_feature 1..21
 note = Engineered antibody sequence
 source 1..21
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 436 tctacatcca ctctggcata t 21

SEQ ID NO: 437 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 437 ggggtctcat cgcggttcaa aggcatgtga tctggggacac agttcactct caccatcagc 60
 gagctgcagt gtgacgatgc tgccacttac tactgt 96

SEQ ID NO: 438 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 438 cttaggcagtt atgattgttag taatggtgat tgttttgtt 39

SEQ ID NO: 439 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33
 note = Engineered antibody sequence
 source 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 439 ttccggcggag ggaccgaggt ggtggtcaaa cgt 33

SEQ ID NO: 440 moltype = DNA length = 321
 FEATURE Location/Qualifiers
 misc_feature 1..321
 note = Engineered antibody sequence
 source 1..321
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 440 acgggtggctg caccatctgt cttcatcttc ccgcctatctg atgagcagtt gaaatctgga 60
 actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
 aaggtggata acggccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc 180
 aaggacagca cttacagctt cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa 240
 cacaatgtct acgcctgcga agtcacccat caggccctga gctcgccctg cacaatggagc 300
 ttcaacacggg gagagtgtta g 321

SEQ ID NO: 441 moltype = AA length = 441
 FEATURE Location/Qualifiers
 REGION 1..441

-continued

```

source          note = Engineered antibody sequence
1..441
mol_type = protein
organism = synthetic construct

SEQUENCE: 441
EVQLVESGGG LVQPGGSLRL SCAVSGIDVT NYYMOWVRQA PGKGLEWGVG IGVNGKRYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
TVSSSSLGTQ TYICNVNHPK SNTKVDKRV E PKSCDKTHTC PPCPAPELLG GPSVPLFPPK 240
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVSVL 300
TVLHQDWLNG KEYKCKVSNI ALPAPIEKTI SKAKGQPREP QVYTLPPSR E MTKNQVSLT 360
CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLSDGSFFL YSKLTVDKSR WQQGNVFSCS 420
VMHEALHNY TQKSLSLSPG K                                         441

SEQ ID NO: 442      moltype = AA length = 111
FEATURE           Location/Qualifiers
REGION            1..111
source          note = Engineered antibody sequence
1..111
mol_type = protein
organism = synthetic construct

SEQUENCE: 442
EVQLVESGGG LVQPGGSLRL SCAVSGIDVT NYYMOWVRQA PGKGLEWGVG IGVNGKRYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS S             111

SEQ ID NO: 443      moltype = AA length = 30
FEATURE           Location/Qualifiers
REGION            1..30
source          note = Engineered antibody sequence
1..30
mol_type = protein
organism = synthetic construct

SEQUENCE: 443
EVQLVESGGG LVQPGGSLRL SCAVSGIDVT                                         30

SEQ ID NO: 444      moltype = AA length = 5
FEATURE           Location/Qualifiers
REGION            1..5
source          note = Engineered antibody sequence
1..5
mol_type = protein
organism = synthetic construct

SEQUENCE: 444
NYMQ                                         5

SEQ ID NO: 445      moltype = AA length = 14
FEATURE           Location/Qualifiers
REGION            1..14
source          note = Engineered antibody sequence
1..14
mol_type = protein
organism = synthetic construct

SEQUENCE: 445
WVRQAPGKGL EWVG                                         14

SEQ ID NO: 446      moltype = AA length = 16
FEATURE           Location/Qualifiers
REGION            1..16
source          note = Engineered antibody sequence
1..16
mol_type = protein
organism = synthetic construct

SEQUENCE: 446
VIGVNGKRYY ASWAKG                                         16

SEQ ID NO: 447      moltype = AA length = 32
FEATURE           Location/Qualifiers
REGION            1..32
source          note = Engineered antibody sequence
1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 447
RFTISRDNSK TTVYLOMNSL RAEDTAVYFC AR                                         32

SEQ ID NO: 448      moltype = length =
SEQUENCE: 448
000

```

-continued

SEQ ID NO: 449 moltype = AA length = 11
 FEATURE Location/Qualifiers
 REGION 1..11
 note = Engineered antibody sequence
 source 1..11
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 449
 WGQGTLVTVS S 11

SEQ ID NO: 450 moltype = AA length = 330
 FEATURE Location/Qualifiers
 REGION 1..330
 note = Engineered antibody sequence
 source 1..330
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 450
 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
 PSVFLFPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNM YVDGVEVHNA KTKPREEQYA 180
 STYRVSLSVLT VLHQDWLNKG EYKCKVSNSKA LPAPIEKTIIS KAKGQPREPQ VYTLPSSREE 240
 MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPPV LDSDGSFFLY SKLTVDKSRW 300
 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 451 moltype = DNA length = 1326
 FEATURE Location/Qualifiers
 misc_feature 1..1326
 note = Engineered antibody sequence
 source 1..1326
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 451
 gaggtgcagc ttgtggagtc tgggggaggc ttgggtccagc ctggggggtc cctgagactc 60
 tccgtgcag tctctggaaat cgacgtcaact aactactaca tgcaatgggt ccgtcaggct 120
 ccagggaaagg ggctggagtg ggtcgaggc attgggtgtga atggtaaaggatatactacgcg 180
 agctggcgca aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
 caaatgaaca gcctggagac tgaggacact gctgtgttatt tctgtgcacag aggaggacatc 300
 tggggccaag ggaccctcg taccgtctcg agcgcctcca ccaaggcccc atcggcttc 360
 cccctggcac cttccctccaa gagcacctct gggggcacag cggccctggg ctgctggc 420
 aaggactact tccccgaacc ggtgacgggt tcgtgaaact caggcgccct gaccagccgc 480
 gtgcacaccc tccccgggtc cctcagacttc tcaggactct actccctcag cagcgtggg 540
 accgtgcctt ccaggcgttt gggccccc acctacatctt gcaacgtgaa tcacaaggccc 600
 agcaacacca aggtggacaa gagagtttag cccaaatctt gtgacaaaac tcacacatgc 660
 ccaccgtgcc cagcacctga actctgggg ggaccgtcaag tttttttttt ccccccaaaa 720
 cccaaaggaca ccctcatgtat cccggggcctt cctgggggtca catggcgttgtt ggtggacgtg 780
 agccacacca agccgtgggtt caagttaacd tgggtacgtgg acggcgtggaa ggtgcataat 840
 gccaagacaa aggccggggaa ggacgtacac ggccacgtt accgtgttgtt cagcgtctc 900
 accgtctcgc accaggactg gctgaatggc aaggagtaca agtgcacgtt ctccaaacaaa 960
 gcccctcccaag cccccatcgaa gaaaaccatc tccaaaggc aaggccggcc ccgagaacca 1020
 cagggttaca ccctggggccatccggggatggatggacca agaaccagggtt cagcgttacc 1080
 tgctgttca aagggttcta tccccggcgtt atccgggtt gttggggatggatggc 1140
 ccggagaaca actacaagac cacgttcccg tgggtggactt ccggcggctc cttttctc 1200
 tacagcaacg tcaccgttgcgaa aggtgttgcgatccggcggactt cttttttttt 1260
 gtgtatgttgcgatccggcggactt cttttttttt 1320
 aaatgtatccggcggactt cttttttttt 1326

SEQ ID NO: 452 moltype = DNA length = 333
 FEATURE Location/Qualifiers
 misc_feature 1..333
 note = Engineered antibody sequence
 source 1..333
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 452
 gaggtgcagc ttgtggagtc tgggggaggc ttgggtccagc ctggggggtc cctgagactc 60
 tccgtgcag tctctggaaat cgacgtcaact aactactaca tgcaatgggt ccgtcaggct 120
 ccagggaaagg ggctggagtg ggtcgaggc attgggtgtga atggtaaaggatatactacgcg 180
 agctggcgca aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
 caaatgaaca gcctggagac tgaggacact gctgtgttatt tctgtgcacag aggaggacatc 300
 tggggccaag ggaccctcg taccgtctcg agc 333

SEQ ID NO: 453 moltype = DNA length = 90
 FEATURE Location/Qualifiers
 misc_feature 1..90
 note = Engineered antibody sequence
 source 1..90
 mol_type = other DNA
 organism = synthetic construct

-continued

SEQUENCE: 453
 gaggtgcagc ttgtggagtc tgggggaggc ttggtccagc ctggggggtc cctgagactc 60
 tcctgtcagc tctctggaat cgacgtcaact 90

SEQ ID NO: 454 moltype = DNA length = 15
 FEATURE Location/Qualifiers
 misc_feature 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 454
 aactactaca tgcaa 15

SEQ ID NO: 455 moltype = DNA length = 42
 FEATURE Location/Qualifiers
 misc_feature 1..42
 note = Engineered antibody sequence
 source 1..42
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 455
 tgggtccgtc aggctccagg gaaggggctg gagtggtcg ga 42

SEQ ID NO: 456 moltype = DNA length = 48
 FEATURE Location/Qualifiers
 misc_feature 1..48
 note = Engineered antibody sequence
 source 1..48
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 456
 gtcattggtg tgaatggtaa gagatactac gcgagctggg cgaaaggc 48

SEQ ID NO: 457 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 457
 cgattcacca tctccagaga caattccaag accacgggt atcttcaaat gaacagcctg 60
 agagctgagg acactgctgt gtatttctgt gccaga 96

SEQ ID NO: 458 moltype = length =
 SEQUENCE: 458
 000

SEQ ID NO: 459 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33
 note = Engineered antibody sequence
 source 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 459
 tggggccaag ggaccctcg caccgtctcg agc 33

SEQ ID NO: 460 moltype = DNA length = 993
 FEATURE Location/Qualifiers
 misc_feature 1..993
 note = Engineered antibody sequence
 source 1..993
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 460
 gcctccacca agggcccatc ggtttcccc ctggcacccct cctccaagag cacctctggg 60
 ggcacagccg ccctgggctg cctgtcaag gactactcc cccaaacgggt gacgggttgtc 120
 tggaaactcg ggcgcctgac cagccggctg cacaccttc cggctgtctt acatgcctca 180
 ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc 240
 tacatctgca acgtgaatca caagcccagg aacccaagg tggacaagg agtttgagccc 300
 aaatcttgcg aaaaaactca cccatggcca cccgtggccagg cacctgaact cctgggggg 360
 ccgtcagtct tcctttccc cccaaaaccc aaggacacc cccatgtatctc cccggaccct 420
 gaggtcacaat gcgtgggtggt ggacgtgago cacgaagacc ctgagggtcaa gttcaactgg 480
 tacgtggacg gcgtggaggt gcataatgcc aagacaaaggc cccggggaggc gcagtagcc 540
 agcacgtacc gtgtggtcaag cgtcctcacc gtcctgcacc aggactggct gaatggcaag 600
 gtagtacaatg gcaagggtctc caacaaaggcc ctcggcggccccc ccacatctcc 660
 aaagccaaag ggccagccccg agaaccacag gtgtacaccc tgccccccatc cccggggaggag 720

-continued

atgaccaaga accaggtca	cctgacctgc ctggtaaa	gcttctatcc cagcgacatc	780
gcccgtggagt gggagacaa	tggcagccg gagaacaact	acaagaccac gcctccgtg	840
ctggactccg acggctcctt	cttcctctac agcaagctca	ccgtggacaa gagcagggtgg	900
cagcaggaaa acgttttctc	atgctccgtg atgcatgagg	ctctgcacaa ccactacacg	960
cagaagagcc ttcctctgtc	tccggtaaa tga		993

SEQ ID NO: 461 moltype = AA length = 219
 FEATURE Location/Qualifiers
 REGION 1..219
 note = Engineered antibody sequence
 source 1..219
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 461
 QVLTQSPSSL SASVGDRVTI NCRASQSVYY NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISLQ PEDVATYYCL GSYDCSNGDC FVFGGGTKVE IKRTVAAPSV 120
 FIFPPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
 STSTTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 219

SEQ ID NO: 462 moltype = AA length = 113
 FEATURE Location/Qualifiers
 REGION 1..113
 note = Engineered antibody sequence
 source 1..113
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 462
 QVLTQSPSSL SASVGDRVTI NCRASQSVYY NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISLQ PEDVATYYCL GSYDCSNGDC FVFGGGTKVE IKR 113

SEQ ID NO: 463 moltype = AA length = 22
 FEATURE Location/Qualifiers
 REGION 1..22
 note = Engineered antibody sequence
 source 1..22
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 463
 QVLTQSPSSL SASVGDRVTI NC 22

SEQ ID NO: 464 moltype = AA length = 13
 FEATURE Location/Qualifiers
 REGION 1..13
 note = Engineered antibody sequence
 source 1..13
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 464
 RASQSVYYNN YLA 13

SEQ ID NO: 465 moltype = AA length = 15
 FEATURE Location/Qualifiers
 REGION 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 465
 WYQQKPGKVP KQLIY 15

SEQ ID NO: 466 moltype = AA length = 7
 FEATURE Location/Qualifiers
 REGION 1..7
 note = Engineered antibody sequence
 source 1..7
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 466
 STSTLAS 7

SEQ ID NO: 467 moltype = AA length = 32
 FEATURE Location/Qualifiers
 REGION 1..32
 note = Engineered antibody sequence
 source 1..32
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 467
 GVPNSRFSGSG SGTDFTLTIS SLQPEDVATY YC 32

-continued

```

SEQ ID NO: 468      moltype = AA length = 13
FEATURE
REGION
1..13
note = Engineered antibody sequence
1..13
mol_type = protein
organism = synthetic construct
SEQUENCE: 468
LGSYDCSNGD CFV                                              13

SEQ ID NO: 469      moltype = AA length = 11
FEATURE
REGION
1..11
note = Engineered antibody sequence
1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 469
FGGGTKVEIK R                                              11

SEQ ID NO: 470      moltype = AA length = 106
FEATURE
REGION
1..106
note = Engineered antibody sequence
1..106
mol_type = protein
organism = synthetic construct
SEQUENCE: 470
TVAAPSVFIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC                106

SEQ ID NO: 471      moltype = DNA length = 660
FEATURE
misc_feature
1..660
note = Engineered antibody sequence
1..660
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 471
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgcggg ccagtcacatcg tgttactat aacaactacc tagcctgtta tcagcagaaa 120
ccaggaaag ttccataagca actgtatcatcttacatccca ctctggcatc tggggtccca 180
tctcggttca gtggcagttgg atctgggaca gatttcacttc tcaaccatcag cagctgcag 240
cctgaagatg ttgcaactta ttactgtctg ggcagttatg atttgtatgaa tggtgatgt 300
tttgttttcg gggggggaa caaaggatggaa atcaaaccgtt cgggtggctgc accatctgtc 360
ttcatcttccg cgccatctgttggatggaa aatatctggatggaa atggatggatggaa 420
ctgataataact tttatccatggatggaa aatatctggatggaa atggatggatggaa 480
tcgggttactt cccaggagatggatggaa aatatctggatggaa atggatggatggaa 540
aggcggccacc ttgacgttggatggaa aatatctggatggaa atggatggatggaa 600
gtcacccatc aaggcggccacc ttgacgttggatggaa aatatctggatggaa atggatggatggaa 660

SEQ ID NO: 472      moltype = DNA length = 339
FEATURE
misc_feature
1..339
note = Engineered antibody sequence
1..339
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 472
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgcggg ccagtcacatcg tgttactat aacaactacc tagcctgtta tcagcagaaa 120
ccaggaaag ttccataagca actgtatcatcttacatccca ctctggcatc tggggtccca 180
tctcggttca gtggcagttgg atctgggaca gatttcacttc tcaaccatcag cagctgcag 240
cctgaagatg ttgcaactta ttactgtctg ggcagttatg atttgtatgaa tggtgatgt 300
tttgttttcg gggggggaa caaaggatggaa atcaaaccgtt cgggtggctgc accatctgtc 339

SEQ ID NO: 473      moltype = DNA length = 66
FEATURE
misc_feature
1..66
note = Engineered antibody sequence
1..66
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 473
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgc                                              66

SEQ ID NO: 474      moltype = DNA length = 39

```

-continued

FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 474
 cgggccagtc agagtgttta ctataacaac tacctagcc 39

SEQ ID NO: 475 moltype = DNA length = 45
 FEATURE Location/Qualifiers
 misc_feature 1..45
 note = Engineered antibody sequence
 source 1..45
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 475
 tggttatcagc agaaaaccagg gaaagttcct aagcaactga tctat 45

SEQ ID NO: 476 moltype = DNA length = 21
 FEATURE Location/Qualifiers
 misc_feature 1..21
 note = Engineered antibody sequence
 source 1..21
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 476
 tctacatcca ctctggcatc t 21

SEQ ID NO: 477 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 477
 ggggtcccat ctcgtttcag tggcagtgga tctgggacag atttcactct caccatcagc 60
 agcctgcagc ctgaagatgt tgcaacttat tactgt 96

SEQ ID NO: 478 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 478
 ctgggcagtt atgattgttag taatggtgat tgttttgtt 39

SEQ ID NO: 479 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33
 note = Engineered antibody sequence
 source 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 479
 ttccggcgag gaaccaaggt ggaaatcaaa cgt 33

SEQ ID NO: 480 moltype = DNA length = 321
 FEATURE Location/Qualifiers
 misc_feature 1..321
 note = Engineered antibody sequence
 source 1..321
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 480
 acgggtggctg caccatctgt cttcatcttc ccggccatctg atgagcagtt gaaatctgga 60
 actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
 aagggtggata acggccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc 180
 aaggacacga cttacagcct cagcagcacc ctgacgctgaa gcaaaggaga ctacgagaaa 240
 cacaaggatct acgcctgcga agtcacccat cagggcctgaa gctcgcggcgt cacaaggagc 300
 ttcaacaggg gagagtgtta g 321

SEQ ID NO: 481 moltype = AA length = 441
 FEATURE Location/Qualifiers
 REGION 1..441
 note = Engineered antibody sequence

-continued

source 1..441
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 481
 QSVEEESGGGL VQPEGSLT LT CTASGDFDSS NAMWWVRQAP GKGLEWIGCI YNGDGSTYYA 60
 SWVNGRFSIS KTSSTTVTLQ LNSLTVADTA TYYCARDL DL WGPGTLVTV SASTKGPSVF 120
 PLAPSSKSTS CGTAALGCLV KDYPPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
 TVPVSSSLGTQ TYICCNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK 240
 PDKTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVVSVL 300
 TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
 CLVKGFYPSD IAVEWESNQG PENNYKTTTP VLSDSGSFFL YSKLTVDKSR WQQGNVFSCS 420
 VMHEALHNHY TQKSLSLSPG K 441

SEQ ID NO: 482 moltype = AA length = 111
 FEATURE Location/Qualifiers
 REGION 1..111
 note = Engineered antibody sequence
 source 1..111
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 482
 QSVEEESGGGL VQPEGSLT LT CTASGDFDSS NAMWWVRQAP GKGLEWIGCI YNGDGSTYYA 60
 SWVNGRFSIS KTSSTTVTLQ LNSLTVADTA TYYCARDL DL WGPGTLVTV S 111

SEQ ID NO: 483 moltype = AA length = 29
 FEATURE Location/Qualifiers
 REGION 1..29
 note = Engineered antibody sequence
 source 1..29
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 483
 QSVEEESGGGL VQPEGSLT LT CTASGDFDS 29

SEQ ID NO: 484 moltype = AA length = 5
 FEATURE Location/Qualifiers
 REGION 1..5
 note = Engineered antibody sequence
 source 1..5
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 484
 SNAMW 5

SEQ ID NO: 485 moltype = AA length = 14
 FEATURE Location/Qualifiers
 REGION 1..14
 note = Engineered antibody sequence
 source 1..14
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 485
 WVRQAPGKGL EWIG 14

SEQ ID NO: 486 moltype = AA length = 17
 FEATURE Location/Qualifiers
 REGION 1..17
 note = Engineered antibody sequence
 source 1..17
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 486
 CIYNGDGSTY YASWVNG 17

SEQ ID NO: 487 moltype = AA length = 31
 FEATURE Location/Qualifiers
 REGION 1..31
 note = Engineered antibody sequence
 source 1..31
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 487
 RFSISKTSST TVTLQLNSLT VADTATYYCA R 31

SEQ ID NO: 488 moltype = AA length = 4
 FEATURE Location/Qualifiers
 REGION 1..4
 note = Engineered antibody sequence
 source 1..4

-continued

```

mol_type = protein
organism = synthetic construct

SEQUENCE: 488
DLDL                                         4

SEQ ID NO: 489      moltype = AA  length = 11
FEATURE
REGION          Location/Qualifiers
1..11
note = Engineered antibody sequence
1..11
source          mol_type = protein
organism = synthetic construct

SEQUENCE: 489
WGPGTIVTVS S                                         11

SEQ ID NO: 490      moltype = AA  length = 330
FEATURE
REGION          Location/Qualifiers
1..330
note = Engineered antibody sequence
1..330
source          mol_type = protein
organism = synthetic construct

SEQUENCE: 490
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICNVNHHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPPKPK KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
STYRVSQVSLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPSPREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESENQQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK                                         330

SEQ ID NO: 491      moltype = DNA  length = 1326
FEATURE
misc_feature    Location/Qualifiers
1..1326
note = Engineered antibody sequence
1..1326
source          mol_type = other DNA
organism = synthetic construct

SEQUENCE: 491
cagtcgggtgg aggagtccgg gggaggccctg gtccagcctg agggatccct gacactcacc 60
tgcacagcctt ctggattcga cttcagtagc aatgcaatgt ggtgggtccg ccaggctcca 120
ggaaaggggc tggagtggat cgatgcatt tacaatggt atggcgcac atactacgcg 180
agctgggtga atggccgatt ctccatctcc aaaacctcgat cgaccacggt gactctgca 240
ctgaatagtc tgacagtcgc ggacacggcc acgtattatt gtgcgagaga tcttgacttg 300
tggggccccc gcacccctgt caccgtctcg aggcgcctcca ccaaggcccc atcggcttcc 360
ccccctggcac cctcctccaa gagcacctct gggggcacaq cggccctggg ctgcctggc 420
aaaggactact tcccgaaacc ggtcgggttg tcgtggaaact caggcgcctt gaccaggccc 480
gtgcacactt tcccggttgt cttagactt actccctcag cagcgtggtg 540
accgtgcctt ccagcagctt gggccccc acctacatctt gcaacgtgaa tcacaagccc 600
agcaacacca aggtggacaa gagagtttag cccaaatctt gtgacaaaac tcacacatgc 660
ccaccgtgcg cagcacctgtt acttcgtggg ggaccgttcgat tttccctt ccccccacaa 720
cccaaggaca cctctatgtat ctcggaccc cttgggtca catgcgttgtt ggtggacgtg 780
agccacaaag accctggaggta caagtcaac ttgttacgtgg acggcgtgaa ggtgcataat 840
gccaagacaa agccgcggga ggagcgtac gccagcactt accgtgttgtt cagcgtctcc 900
accgtcttc accaggactt gctaatggc aaggactaca agtgcgaaggctt ctcacacaaa 960
gcccattccatc gaaaaccatc tccaaagccca aaggccggcc cccggaaacca 1020
caaggatcaca cctctggccc atccgggag qagatgacca agaaccaggat cagcgttacc 1080
tgctgttca aaggcttcta tcccgacatc atcggctgg agtggggagag caatggcag 1140
ccggagaaaca actaaagac caegctccc gtgtgttactt ccggacggctc cttttctcc 1200
tacagcaagc tcaccgtggaa caagacggcgg tggcagcagg ggaacgtttt ctcatgttcc 1260
gtgtatgttca aggtctgtca caaccactac acgcagaaga gctctccctt gtctccgggt 1320
aaatga                                         1326

SEQ ID NO: 492      moltype = DNA  length = 333
FEATURE
misc_feature    Location/Qualifiers
1..333
note = Engineered antibody sequence
1..333
source          mol_type = other DNA
organism = synthetic construct

SEQUENCE: 492
cagtcgggtgg aggagtccgg gggaggccctg gtccagcctg agggatccct gacactcacc 60
tgcacagcctt ctggattcga cttcagtagc aatgcaatgt ggtgggtccg ccaggctcca 120
ggaaaggggc tggagtggat cgatgcatt tacaatggt atggcgcac atactacgcg 180
agctgggtga atggccgatt ctccatctcc aaaacctcgat cgaccacggt gactctgca 240
ctgaatagtc tgacagtcgc ggacacggcc acgtattatt gtgcgagaga tcttgacttg 300
tggggccccc gcacccctgt caccgtctcg agc                                         333

SEQ ID NO: 493      moltype = DNA  length = 87
FEATURE

```

-continued

```

misc_feature      1..87
source           note = Engineered antibody sequence
                1..87
                mol_type = other DNA
                organism = synthetic construct
SEQUENCE: 493
cagtccgtgg aggagtcggg gggaggcctg gtccagcctg agggatccct gacactcacc 60
tgcacagcct ctggattcga cttcagt                         87

SEQ ID NO: 494      moltype = DNA length = 15
FEATURE
misc_feature      1..15
source           note = Engineered antibody sequence
                1..15
                mol_type = other DNA
                organism = synthetic construct
SEQUENCE: 494
agcaatgcaa tgtgg                                         15

SEQ ID NO: 495      moltype = DNA length = 42
FEATURE
misc_feature      1..42
source           note = Engineered antibody sequence
                1..42
                mol_type = other DNA
                organism = synthetic construct
SEQUENCE: 495
tgggtcccgcc aggctccagg gaaggggctg gagtggatcg ga          42

SEQ ID NO: 496      moltype = DNA length = 51
FEATURE
misc_feature      1..51
source           note = Engineered antibody sequence
                1..51
                mol_type = other DNA
                organism = synthetic construct
SEQUENCE: 496
tgcatttaca atggtgtatgg cagcacatac tacgcgagct gggtaatgg c      51

SEQ ID NO: 497      moltype = DNA length = 93
FEATURE
misc_feature      1..93
source           note = Engineered antibody sequence
                1..93
                mol_type = other DNA
                organism = synthetic construct
SEQUENCE: 497
cgattctcca tctccaaaac ctcgtcgacc acggtgactc tgcaactgaa tagtctgaca 60
gtcgcggaca cggccacgta ttattgtgcg aga                         93

SEQ ID NO: 498      moltype = DNA length = 12
FEATURE
misc_feature      1..12
source           note = Engineered antibody sequence
                1..12
                mol_type = other DNA
                organism = synthetic construct
SEQUENCE: 498
gatcttgact tg                                         12

SEQ ID NO: 499      moltype = DNA length = 33
FEATURE
misc_feature      1..33
source           note = Engineered antibody sequence
                1..33
                mol_type = other DNA
                organism = synthetic construct
SEQUENCE: 499
tggggccccgg gcaccctcgt caccgtctcg agc                           33

SEQ ID NO: 500      moltype = DNA length = 993
FEATURE
misc_feature      1..993
source           note = Engineered antibody sequence
                1..993
                mol_type = other DNA
                organism = synthetic construct
SEQUENCE: 500
gcctccacca agggcccatc ggtttcccc ctggcacccct cctccaagag cacctctggg 60

```

-continued

```

ggcacacgccc ccctgggtcg cctggtaag gactacttcc cccaaaccgg gacgggtcg 120
tggaaactcg ggcgcctgac cagggcgtg cacaccttc cggctgtctt acagtccca 180
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg caccaggacc 240
tacatctgca acgtgaatca caagccccago aacaccaagg tggacaagag agttgagccc 300
aaatcttgtc aaaaaactca cacatggccca ccgtgcccag caccctgaact cctgggggga 360
ccgtcagtc tcccttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccct 420
gaggtcacat gogtggtggg ggacgtgago cacaagacc ctgaggtaaa gttcaactgg 480
tacgtggacg gogtggtggg gtcataatgcc aagacaaagg cgccgggagg gcaactacg 540
agcacgtacc tggtgggtcg cgttcctacc gtcctgcacc aggactggc gaatggcaag 600
gagtaactgt gcaagggttc caacaaaggcc cttccagggcc ccatcgagaa aaccatctcc 660
aaagccaaag ggcagccccgg aaaaacccag gtgtacacc cttccatcc ccgggaggag 720
atgaccaaga accagggtcg cctgacactc ctggtaaa gcttctatcc cagcgacatc 780
gcgggtggagt ggggagggac tggcggccgg gagaacaactc acaagaccac gcctccctg 840
ctggacttc acgggtcctt cttcttccatc agcaagctc ccgtggacaa gagcagggtgg 900
cagcaggggg acgttcttc atgtccgtg atgtccatgg ctctgcacaa ccactacacg 960
cagaagggcc tctccctgtc tccgggtaaa tga 993

```

```

SEQ ID NO: 501      moltype = AA length = 219
FEATURE
REGION          Location/Qualifiers
1..219
note = Engineered antibody sequence
source           1..219
mol_type = protein
organism = synthetic construct
SEQUENCE: 501
AIVMTQTPSS KSVPGDVT INCQASESLY NNNNALAWFQQ KPGQPPKRLI YDASKLASGV 60
PSRFSGGGSG TQFTLTISGV QCDDAATYYC GGYRSDSVVG VAFAGGTEVV VKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 219

```

```

SEQ ID NO: 502      moltype = AA length = 113
FEATURE
REGION          Location/Qualifiers
1..113
note = Engineered antibody sequence
source           1..113
mol_type = protein
organism = synthetic construct
SEQUENCE: 502
AIVMTQTPSS KSVPGDVT INCQASESLY NNNNALAWFQQ KPGQPPKRLI YDASKLASGV 60
PSRFSGGGSG TQFTLTISGV QCDDAATYYC GGYRSDSVVG VAFAGGTEVV VRK 113

```

```

SEQ ID NO: 503      moltype = AA length = 23
FEATURE
REGION          Location/Qualifiers
1..23
note = Engineered antibody sequence
source           1..23
mol_type = protein
organism = synthetic construct
SEQUENCE: 503
AIVMTQTPSS KSVPGDVT INC 23

```

```

SEQ ID NO: 504      moltype = AA length = 13
FEATURE
REGION          Location/Qualifiers
1..13
note = Engineered antibody sequence
source           1..13
mol_type = protein
organism = synthetic construct
SEQUENCE: 504
QASESLYNNN ALA 13

```

```

SEQ ID NO: 505      moltype = AA length = 15
FEATURE
REGION          Location/Qualifiers
1..15
note = Engineered antibody sequence
source           1..15
mol_type = protein
organism = synthetic construct
SEQUENCE: 505
WFQQKPGQPP KRLIY 15

```

```

SEQ ID NO: 506      moltype = AA length = 7
FEATURE
REGION          Location/Qualifiers
1..7
note = Engineered antibody sequence
source           1..7
mol_type = protein
organism = synthetic construct
SEQUENCE: 506

```

-continued

DASKLAS

7

```

SEQ ID NO: 507      moltype = AA length = 32
FEATURE          Location/Qualifiers
REGION           1..32
note = Engineered antibody sequence
source            1..32
mol_type = protein
organism = synthetic construct
SEQUENCE: 507
GVPSRFSGGG SGTQFTLTIS GVQCDDAATY YC                                32

SEQ ID NO: 508      moltype = AA length = 12
FEATURE          Location/Qualifiers
REGION           1..12
note = Engineered antibody sequence
source            1..12
mol_type = protein
organism = synthetic construct
SEQUENCE: 508
GGYRSRSDSVVG VA                                              12

SEQ ID NO: 509      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
note = Engineered antibody sequence
source            1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 509
FAGGTEVVVK R                                              11

SEQ ID NO: 510      moltype = AA length = 106
FEATURE          Location/Qualifiers
REGION          1..106
note = Engineered antibody sequence
source            1..106
mol_type = protein
organism = synthetic construct
SEQUENCE: 510
TVAAPSVIIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSST LTLSKADYEK HKVYACEVTN QGLSSPVTKS FNRGEC                106

SEQ ID NO: 511      moltype = DNA length = 660
FEATURE          Location/Qualifiers
misc_feature     1..660
note = Engineered antibody sequence
source            1..660
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 511
ggccatcgta tgacccagac tccatcttcc aagtctgtc ctgtgggaga cacagtcaacc 60
atcaattggc aggccagtga gagtcctttat aataacaacg cttggcctg gtttcagcag 120
aaaccaggcgcc agccctccaa gcgcctgtatcatgtcat ccaaactggc atctgggtc 180
ccatcgcggt tcagtgccgg tgggtctggg acatagttca ctctcaccat cagtggcgtg 240
cagtgtgacg atgctgccac ttactactgt ggaggctaca gaagtgtatag tggatgg 300
gttgcttcg ccggaggggac cgagggtgtg gtcaaacgtt cgggtggctgc accatctgtc 360
ttcatcttcc cggccatctga tgagcagtgg aaatctggaa ctgcctctgt tggatgtc 420
ctgaataact tctatcccg agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcggtaact cccaggagag tggcacagag caggacacgca ctagcgtcc 540
agcagcacc c tgacgtgac caaaggac tacgagaaac acaaagtcta cgcctgcgaa 600
gtcacccatc agggcctgag ctcggccgtc acaaagagct tcaacagggg agagtgttag 660

SEQ ID NO: 512      moltype = DNA length = 339
FEATURE          Location/Qualifiers
misc_feature     1..339
note = Engineered antibody sequence
source            1..339
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 512
ggccatcgta tgacccagac tccatcttcc aagtctgtc ctgtgggaga cacagtcaacc 60
atcaattggc aggccagtga gagtcctttat aataacaacg cttggcctg gtttcagcag 120
aaaccaggcgcc agccctccaa gcgcctgtatcatgtcat ccaaactggc atctgggtc 180
ccatcgcggt tcagtgccgg tgggtctggg acatagttca ctctcaccat cagtggcgtg 240
cagtgtgacg atgctgccac ttactactgt ggaggctaca gaagtgtatag tggatgg 300
gttgcttcg ccggaggggac cgagggtgtg gtcaaacgtt cgggtggctgc accatctgtc 360
ttcatcttcc cggccatctga tgagcagtgg aaatctggaa ctgcctctgt tggatgtc 420
ctgaataact tctatcccg agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcggtaact cccaggagag tggcacagag caggacacgca ctagcgtcc 540
agcagcacc c tgacgtgac caaaggac tacgagaaac acaaagtcta cgcctgcgaa 600
gtcacccatc agggcctgag ctcggccgtc acaaagagct tcaacagggg agagtgttag 660

SEQ ID NO: 513      moltype = DNA length = 69

```

-continued

```

FEATURE          Location/Qualifiers
misc_feature    1..69
                  note = Engineered antibody sequence
source          1..69
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 513
ggcatcgtga tgacccagac tccatcttcc aagtctgtcc ctgtgggaga cacagtcacc 60
atcaattgc                               69

SEQ ID NO: 514      moltype = DNA  length = 39
FEATURE          Location/Qualifiers
misc_feature    1..39
                  note = Engineered antibody sequence
source          1..39
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 514
caggccaaatc agagtcttta taataacaac gccttgcc                                39

SEQ ID NO: 515      moltype = DNA  length = 45
FEATURE          Location/Qualifiers
misc_feature    1..45
                  note = Engineered antibody sequence
source          1..45
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 515
tggtttcagc agaaaccagg gcagccccc aagcgcttgc tctat                                45

SEQ ID NO: 516      moltype = DNA  length = 21
FEATURE          Location/Qualifiers
misc_feature    1..21
                  note = Engineered antibody sequence
source          1..21
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 516
gatgcatcca aactggcatc t                                21

SEQ ID NO: 517      moltype = DNA  length = 96
FEATURE          Location/Qualifiers
misc_feature    1..96
                  note = Engineered antibody sequence
source          1..96
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 517
gggggtcccat cgccgttcag tggcggtggg tctgggacac agttcactct caccatcagt 60
ggcgtgcagt gtgacgatgc tgccacttac tactgt                                96

SEQ ID NO: 518      moltype = DNA  length = 36
FEATURE          Location/Qualifiers
misc_feature    1..36
                  note = Engineered antibody sequence
source          1..36
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 518
ggagggtaca gaagtgtatc tggtgtatgt gttgct                                36

SEQ ID NO: 519      moltype = DNA  length = 33
FEATURE          Location/Qualifiers
misc_feature    1..33
                  note = Engineered antibody sequence
source          1..33
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 519
ttcgccggag ggaccggatgt ggtggtcaaa cgt                                33

SEQ ID NO: 520      moltype = DNA  length = 321
FEATURE          Location/Qualifiers
misc_feature    1..321
                  note = Engineered antibody sequence
source          1..321
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 520

```

-continued

acggtgtgctg caccatctgt ctcatcttc cgcgcattcg atgaggcgtt gaaatctgga 60
actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
aagggtggata acgcctcca atcggtaac tcccaggaga gtgtcacaga gcaggacgc 180
aaggacagca cctacagcct cagcgcacc ctgacgctga gcaaaggaga ctacgagaaa 240
cacaaggctc acgcctgcga agtcacccat cagggcctga gctcgccgt cacaaggagc 300
ttcaacaggg gagagtgtta g 321

SEQ ID NO: 521 moltype = AA length = 441
FEATURE Location/Qualifiers
REGION 1..441
note = Engineered antibody sequence
source 1..441
mol_type = protein
organism = synthetic construct

SEQUENCE: 521
EVQLVESGGG LVQPGGSLRL SCAVSGIGLS SYYMQWVRQA PGKGLEWVGV IGSDGKTYA 60
TWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCTRIDI WGQGTLVTVS SASTKGPSVF 120
PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG SGLYSLSSVV 180
TVPSSSLGTO TYICVNHNKP SNTKVDARVE PKSCDKTHTC PPCPAPELLG GPSVFLPPK 240
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTPREEQY ASTYRVVSVL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSSFL YSKLTVDKSR WQQGNVFSCS 420
VMHEALHNHY TQKSLSLSPG K 441

SEQ ID NO: 522 moltype = AA length = 111
FEATURE Location/Qualifiers
REGION 1..111
note = Engineered antibody sequence
source 1..111
mol_type = protein
organism = synthetic construct

SEQUENCE: 522
EVQLVESGGG LVQPGGSLRL SCAVSGIGLS SYYMQWVRQA PGKGLEWVGV IGSDGKTYA 60
TWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCTRIDI WGQGTLVTVS S 111

SEQ ID NO: 523 moltype = AA length = 30
FEATURE Location/Qualifiers
REGION 1..30
note = Engineered antibody sequence
source 1..30
mol_type = protein
organism = synthetic construct

SEQUENCE: 523
EVQLVESGGG LVQPGGSLRL SCAVSGIGLS 30

SEQ ID NO: 524 moltype = AA length = 5
FEATURE Location/Qualifiers
REGION 1..5
note = Engineered antibody sequence
source 1..5
mol_type = protein
organism = synthetic construct

SEQUENCE: 524
SYYMQ 5

SEQ ID NO: 525 moltype = AA length = 14
FEATURE Location/Qualifiers
REGION 1..14
note = Engineered antibody sequence
source 1..14
mol_type = protein
organism = synthetic construct

SEQUENCE: 525
WVRQAPGKGL EWVG 14

SEQ ID NO: 526 moltype = AA length = 16
FEATURE Location/Qualifiers
REGION 1..16
note = Engineered antibody sequence
source 1..16
mol_type = protein
organism = synthetic construct

SEQUENCE: 526
VIGSDGKTYA ATWAKG 16

SEQ ID NO: 527 moltype = AA length = 32
FEATURE Location/Qualifiers
REGION 1..32
note = Engineered antibody sequence

-continued

source 1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 527
RFTISRDNSK TTVYLQMNSL RAEDTAVYFC TR 32

SEQ ID NO: 528 moltype = length =
SEQUENCE: 528
000

SEQ ID NO: 529 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Engineered antibody sequence
source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 529
WGGGTLTVTS S 11

SEQ ID NO: 530 moltype = AA length = 330
FEATURE Location/Qualifiers
REGION 1..330
note = Engineered antibody sequence
source 1..330
mol_type = protein
organism = synthetic construct

SEQUENCE: 530
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICNVNHPKS NTKVDARVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKPK KDTLMISRTP EVTCVVVDVS HEDPEVKPNW YVDGVEVHNA KTKPREEQVA 180
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESENQGP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 531 moltype = DNA length = 1326
FEATURE Location/Qualifiers
misc_feature 1..1326
note = Engineered antibody sequence
source 1..1326
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 531
gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60
tcctgtgcag tctctggaat cggcctcagt agctactaca tgcaatgggt ccgtcaggct 120
ccaggaaagg ggctggagtg ggctggagtc atggtagtgc atggtaagac atactacgct 180
acctggcgata aaggccgatt caccatctc agagacaattt ccaagaccac ggtgtatctt 240
caaatgaaca goctgagagc tgaggacact gctgtatatt tctgttaccag aggggacatc 300
tggggccaag ggacctctgt caccgtctcg agcgcctcca ccaaggccc atcggtttc 360
ccacctggcac cctccctccaa gagccactt gggggcacac cggccctggg ctgcttgct 420
aaggactact tcccccaacc ggtgacggtg tctgttgcact caggccgcct gaccagccgc 480
gtgcacaccc tcccggtctgt cctacagtcc tcaggactct actccctcag cagcgtggc 540
accgtgcacct ccacgcgactt gggccacccag acctacatctt gcaacgtgaa tcacaagccc 600
agcaacacca aggtggacac gagaatttgcat cccaaatctt gtgacaaaac tcacacatgc 660
ccacccgtgcc cagcacctgc actctggggc tggccgtcaq tcttcctttt ccccccaaaa 720
cccaaggacca ccctcatgtat ctcgggacc cttggaggta catcgcttgtt ggtggacgt 780
agccacacca accctggaggta caagtccaaat tggtagctgg acggcggtt ggtgcataat 840
gccaagacaa accccgggaa ggacggactt gccagcactt accgtgttgtt cagcgtctc 900
accgttcctgc accaggactt gctgaatggc aaggacttgcata agtgcacgg 960
ggccctcccgcc ccccatcgaa aaaaaccatc tccaaagccaa aaggccggcc cccgagaacca 1020
cagggtgtaca ccctggcccccc atccgggag gagatgacca agaaccaggta cagcgtgacc 1080
tgcctgttca aaggcttcta tcccgacatc atccgggtt ggtggagag caatgggcag 1140
ccggagaaca actacaagac caccgttcccg tggctggactt cccacggctc ctttcttc 1200
tacagcagaaccc tcaccgttgc aagacgggg tggcagcagg gaaacgtttt ctcatgttcc 1260
gtgtatgcattt aggctctgtca caaccactac acgcagaaga gctctccctt gtcctccgggt 1320
aaatga 1326

SEQ ID NO: 532 moltype = DNA length = 333
FEATURE Location/Qualifiers
misc_feature 1..333
note = Engineered antibody sequence
source 1..333
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 532
gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60
tcctgtgcag tctctggaat cggcctcagt agctactaca tgcaatgggt ccgtcaggct 120
ccaggaaagg ggctggagtg ggctggagtc atggtagtgc atggtaagac atactacgct 180
acctggcgata aaggccgatt caccatctc agagacaattt ccaagaccac ggtgtatctt 240

-continued

```

caaatgaaca gcctgagac tgaggacact gctgtgtatt tctgtaccag aggggacatc 300
tggggccaag ggaccctcg caccgtctcg agc 333

SEQ ID NO: 533      moltype = DNA length = 90
FEATURE             Location/Qualifiers
misc_feature        1..90
                      note = Engineered antibody sequence
source              1..90
                      mol_type = other DNA
                      organism = synthetic construct
SEQUENCE: 533
gaggtgcagc ttgtggagtc tgggggaggc ttgggccagc ctggggggc cctgagactc 60
tcctgtcag tctctgaaat cgccctcgat 90

SEQ ID NO: 534      moltype = DNA length = 15
FEATURE             Location/Qualifiers
misc_feature        1..15
                      note = Engineered antibody sequence
source              1..15
                      mol_type = other DNA
                      organism = synthetic construct
SEQUENCE: 534
agctactaca tgcaa 15

SEQ ID NO: 535      moltype = DNA length = 42
FEATURE             Location/Qualifiers
misc_feature        1..42
                      note = Engineered antibody sequence
source              1..42
                      mol_type = other DNA
                      organism = synthetic construct
SEQUENCE: 535
tgggtccgcaggc aggctccagg gaaggggctg gagtgggtcg ga 42

SEQ ID NO: 536      moltype = DNA length = 48
FEATURE             Location/Qualifiers
misc_feature        1..48
                      note = Engineered antibody sequence
source              1..48
                      mol_type = other DNA
                      organism = synthetic construct
SEQUENCE: 536
gtcattggta gtgatggtaa gacatactac gcgacacctggg cgaaaggc 48

SEQ ID NO: 537      moltype = DNA length = 96
FEATURE             Location/Qualifiers
misc_feature        1..96
                      note = Engineered antibody sequence
source              1..96
                      mol_type = other DNA
                      organism = synthetic construct
SEQUENCE: 537
cgattcacca tctccagaga caattccaag accacggtgt atcttcaaataa gaacagcctg 60
agagctgagg acactgctgt gtatttctgt accaga 96

SEQ ID NO: 538      moltype = length =
SEQUENCE: 538
000

SEQ ID NO: 539      moltype = DNA length = 33
FEATURE             Location/Qualifiers
misc_feature        1..33
                      note = Engineered antibody sequence
source              1..33
                      mol_type = other DNA
                      organism = synthetic construct
SEQUENCE: 539
tggggccaag ggaccctcg caccgtctcg agc 33

SEQ ID NO: 540      moltype = DNA length = 993
FEATURE             Location/Qualifiers
misc_feature        1..993
                      note = Engineered antibody sequence
source              1..993
                      mol_type = other DNA
                      organism = synthetic construct
SEQUENCE: 540
gcctccacca agggccccatc gggtttcccc ctggcacccct cctccaagag cacctctggg 60
ggcacagcgg ccctgggtcg cctggtaag gactactcc cccgaaaccggt gacgggtcg 120

```

-continued

```
tggaaactcag gcgcctgac cagggcggtg cacacccccc cggctgtctt acagtccca 180
ggactctact ccctcagcag cgtggtggacc gtgcctcca gcagctggg caccaggacc 240
tacatctgca acgtgaatca caagccccago aacaccaagg tggacgcggag agttgagccc 300
aaatcttgta acaaactca cacatgcaca ccgtgccccaa cacctgaact cctgggggga 360
ccgtcagtc tctcttcccc cccaaaaacc aaggacaccc tcgtatctt ccggaccct 420
gaggtcacat gctgtgggtt ggacgtggago cagaagaccc ctgaggtaaa gttcaactgg 480
tacggtggac gctgtggaggt gcataatgcc aagacaaacg cgccggggaga gcagtacgcc 540
agcacgtacc gtgtggtcag cgtccctcacc gtctgcacc aggactggct gaatggcaag 600
gagtacaaatg gcaaggctc caaacaaggccc ccatecgagaa aaccatctcc 660
aaaggccaaag ggccagcccccc aaaaacccatc tggtacaccctt ccggggaggag 720
atgaccaaga accaggctcag cctgacccctc ctgtcaaaatc gtttctatcc cagcgacatc 780
gccgtggagt gggagagcaa tggcagccg gagaacaact acaagaccac gcctccctg 840
ctggactccg acggctccctt ctccctcacc agcaagctca ccgtggacaa gagcagggtgg 900
cagcaggggaa acgttcttc atgtccctgtt atgcatgggg ctctgcacaa ccactacacg 960
cagaagggcc tccctgtc tccggtaaaa tga 993
```

```
SEQ ID NO: 541 moltype = AA length = 219
FEATURE Location/Qualifiers
REGION 1..219
note = Engineered antibody sequence
source 1..219
mol_type = protein
organism = synthetic construct
```

```
SEQUENCE: 541
QVLTQSPSSL SASVGDRVTI NCQASQNLYNNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSRGDC FVFGGGTKVE IKRTVAAPSV 120
FIPPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STLTLASKD YEKHKVYACE VTHQGLSSPV TKSFNRRGEC 219
```

```
SEQ ID NO: 542 moltype = AA length = 113
FEATURE Location/Qualifiers
REGION 1..113
note = Engineered antibody sequence
source 1..113
mol_type = protein
organism = synthetic construct
```

```
SEQUENCE: 542
QVLTQSPSSL SASVGDRVTI NCQASQNLYNNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSRGDC FVFGGGTKVE IKR 113
```

```
SEQ ID NO: 543 moltype = AA length = 22
FEATURE Location/Qualifiers
REGION 1..22
note = Engineered antibody sequence
source 1..22
mol_type = protein
organism = synthetic construct
```

```
SEQUENCE: 543
QVLTQSPSSL SASVGDRVTI NC 22
```

```
SEQ ID NO: 544 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
note = Engineered antibody sequence
source 1..13
mol_type = protein
organism = synthetic construct
```

```
SEQUENCE: 544
QASQNLYNNN YLA 13
```

```
SEQ ID NO: 545 moltype = AA length = 15
FEATURE Location/Qualifiers
REGION 1..15
note = Engineered antibody sequence
source 1..15
mol_type = protein
organism = synthetic construct
```

```
SEQUENCE: 545
WYQQKPGKVP KQLIY 15
```

```
SEQ ID NO: 546 moltype = AA length = 7
FEATURE Location/Qualifiers
REGION 1..7
note = Engineered antibody sequence
source 1..7
mol_type = protein
organism = synthetic construct
```

```
SEQUENCE: 546
STSTLAS 7
```

-continued

```

SEQ ID NO: 547      moltype = AA length = 32
FEATURE          Location/Qualifiers
REGION           1..32
source            note = Engineered antibody sequence
                  1..32
mol_type = protein
organism = synthetic construct
SEQUENCE: 547
GVPSRFSGSG SGTDFTLTIS SLQPEDVATY YC                                32

SEQ ID NO: 548      moltype = AA length = 13
FEATURE          Location/Qualifiers
REGION           1..13
source            note = Engineered antibody sequence
                  1..13
mol_type = protein
organism = synthetic construct
SEQUENCE: 548
LGSYDCSRGD CFV                                              13

SEQ ID NO: 549      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
source            note = Engineered antibody sequence
                  1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 549
FGGGTKEIK R                                              11

SEQ ID NO: 550      moltype = AA length = 106
FEATURE          Location/Qualifiers
REGION          1..106
source            note = Engineered antibody sequence
                  1..106
mol_type = protein
organism = synthetic construct
SEQUENCE: 550
TVAAPSVIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSPVTKS FNRGEC                                106

SEQ ID NO: 551      moltype = DNA length = 660
FEATURE          Location/Qualifiers
misc_feature     1..660
source            note = Engineered antibody sequence
                  1..660
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 551
caagtgtcga cccagtcctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60
aattgccagg ccagtcagaa tgtttacaat aacaactacc tagcctggta tcagcagaaa 120
ccagggaaag ttccctaagca actgatctat tctacatccca ctctggcatc tgggtccca 180
tctcggttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagctgcag 240
cctgaagatg ttgcaacttta ttactgtctg ggcagttatg attttagtctg tggtgatgt 300
tttgttttcg gcgaggaaac caagggtggaa atcaaacgtt cgggtgtgc accatctgtc 360
ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgggtgcctg 420
ctgaataact tctatccccag agaggccaaa gtacagtggaa aggtggataa cgccttccaa 480
tcgggttaact cccaggagag tgcacagag caggacagcac ctacagcctc 540
agcagcaccc tgacgtctgg caaaaggacatc acaaagtctt cgcctgcgaa 600
gtcacccatc agggccttag ctcggccgtc acaaaggatc tcaacagggg agagtgttag 660

SEQ ID NO: 552      moltype = DNA length = 339
FEATURE          Location/Qualifiers
misc_feature     1..339
source            note = Engineered antibody sequence
                  1..339
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 552
caagtgtcga cccagtcctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60
aattgccagg ccagtcagaa tgtttacaat aacaactacc tagcctggta tcagcagaaa 120
ccagggaaag ttccctaagca actgatctat tctacatccca ctctggcatc tgggtccca 180
tctcggttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagctgcag 240
cctgaagatg ttgcaacttta ttactgtctg ggcagttatg attttagtctg tggtgatgt 300
tttgttttcg gcgaggaaac caagggtggaa atcaaacgtt cgggtgtgc accatctgtc 339

SEQ ID NO: 553      moltype = DNA length = 66
FEATURE          Location/Qualifiers

```

-continued

```

misc_feature      1..66
                  note = Engineered antibody sequence
source           1..66
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 553
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgc                                     66

SEQ ID NO: 554      moltype = DNA length = 39
FEATURE
misc_feature      1..39
                  note = Engineered antibody sequence
source           1..39
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 554
caggccagtc agaatgttta caataacaac tacctagcc                                39

SEQ ID NO: 555      moltype = DNA length = 45
FEATURE
misc_feature      1..45
                  note = Engineered antibody sequence
source           1..45
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 555
tggtatcagc agaaaccagg gaaagttcct aagcaactga tctat                                45

SEQ ID NO: 556      moltype = DNA length = 21
FEATURE
misc_feature      1..21
                  note = Engineered antibody sequence
source           1..21
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 556
tctacatcca ctctggcatc t                                         21

SEQ ID NO: 557      moltype = DNA length = 96
FEATURE
misc_feature      1..96
                  note = Engineered antibody sequence
source           1..96
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 557
gggggtccccat ctcgtttcag tggcagtgga tctgggacag atttcactct caccatcagc 60
agectgcagc ctgaagatgt tgcaacctat tactgt                                96

SEQ ID NO: 558      moltype = DNA length = 39
FEATURE
misc_feature      1..39
                  note = Engineered antibody sequence
source           1..39
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 558
ctgggcagtt atgattgttag tcgtggtgat tgttttgtt                                39

SEQ ID NO: 559      moltype = DNA length = 33
FEATURE
misc_feature      1..33
                  note = Engineered antibody sequence
source           1..33
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 559
ttcggcggag gaaccaaggt ggaaaatcaaa cgt                                33

SEQ ID NO: 560      moltype = DNA length = 321
FEATURE
misc_feature      1..321
                  note = Engineered antibody sequence
source           1..321
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 560
acggtgtggctg caccatctgt ctcatcttc ccgcacatcg atgagcagtt gaaatctgga 60

```

-continued

actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
 aagggtgata acgcctcca atcggtaac tcccaggaga gtgtcacaga gcaggacagc 180
 aaggacacca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa 240
 cacaaggct acgcctgcga agtcacccat cagggcctga gtcgcccgt cacaaggagc 300
 ttcaacaggg gagagtgtta g 321

SEQ ID NO: 561 moltype = AA length = 37
 FEATURE Location/Qualifiers
 REGION 1..37
 note = C-term amidated
 source 1..37
 mol_type = protein
 organism = Homo sapiens
 SEQUENCE: 561 ACDTATCVTH RLAGLLSRSG GVVKNNFVPT NVGSKAF 37

SEQ ID NO: 562 moltype = AA length = 37
 FEATURE Location/Qualifiers
 REGION 1..37
 note = C-term amidated
 source 1..37
 mol_type = protein
 organism = Homo sapiens
 SEQUENCE: 562 ACNTATCVTH RLAGLLSRSG GMVKSNNFVPT NVGSKAF 37

SEQ ID NO: 563 moltype = AA length = 106
 FEATURE Location/Qualifiers
 source 1..106
 mol_type = protein
 organism = Homo sapiens
 SEQUENCE: 563 TWAAPSVIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
 KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC 106

SEQ ID NO: 564 moltype = AA length = 330
 FEATURE Location/Qualifiers
 REGION 1..330
 note = Engineered antibody sequence
 source 1..330
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 564 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
 PSVFLFPKP KDTLMSIRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE 240
 MTKNQVSLTC LVKGFYPSDI AVEWESENQGP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300
 QQGNVFSCSV MHEALHNHYT QKSLSLSPKG 330

SEQ ID NO: 565 moltype = AA length = 329
 FEATURE Location/Qualifiers
 REGION 1..329
 note = Engineered antibody sequence
 source 1..329
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 565 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
 PSVFLFPKP KDTLMSIRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE 240
 MTKNQVSLTC LVKGFYPSDI AVEWESENQGP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300
 QQGNVFSCSV MHEALHNHYT QKSLSLSPKG 329

SEQ ID NO: 566 moltype = AA length = 440
 FEATURE Location/Qualifiers
 REGION 1..440
 note = Engineered antibody sequence
 source 1..440
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 566 EVOLVESGGG LVQPGGSLRL SCAVSGIDLS GYYMNWRQAA PGKGLEWVGIGINGATYYA 60
 SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
 PLAPSSKSTS GGTAALGCLVK KDYFPEPVTV SWNSGALTSGVHTFPAVLQSS SGLYSLSSV 180
 TVPSSSLGTQ TYICNVNHKPS SNTKVDARVE PKSCDKTHTCP PPCPAPELLGG GPSVFLFPK 240
 PKDTLMISRT PEVTCVVVDV SHEDPEVKFNW YVDGVEVHN AKTKPREEQY ASTYRVVSVL 300
 TVLHQDWLNG KEYKCKVSNKA ALPAPIEKTIIS KAKGQPREPQ VYTLPPSRE EMTKNQVSLT 360

-continued

CLVKGFYPSD IAVEWESNGQ PENNYKTPPP VLDSDGSSFL YSKLTVDKSR WQQGNVFSCS	420
VMHEALHNHY TQKSLSLSPG	440

```

SEQ ID NO: 567      moltype = DNA length = 1323
FEATURE
misc_feature        Location/Qualifiers
1..1323
note = Engineered antibody sequence
source             1..1323
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 567
gagggtgcagc ttgtggagtc tggggggaggo ttgggtccagc ctgggggggtc cctgagactc 60
tccctgtgcag tctctggat cgacccatcg ggtactactaca tgaactgggt ccgtcagggt 120
ccaggaaagg ggctggatg ggtggaggat attggattata atgggtgcacat atactacgg 180
agctggcgca aaggccgatt caccatctcc agagacaattt ccaagaccac ggtgtatctt 240
caaataatgaaaca gccttgagagc tgaggacact gctgtgtatt tctgtgttag agggggacatc 300
tgggggccaag ggacccctcgat caccatctcc agccggctccca ccaagggccc atcggcttcc 360
ccccctggcac cctcttccaa gagecatctt gggggcacaag cggccctggg ctggctggc 420
aaggactact tcccccgaacc ggtgacgggtg tcgtggaaact cagggccccc gaccagccgc 480
gtgcacaccc tcccggtctgt cttacagtcc tcaggactctt actcccttag cagcgtgg 540
accgtgcctcc caagcagctt gggcacccag acctacatctt gcaacgtgaa tcacaaggcc 600
agaacacacca aggtggacgc gagagtttgag cccaaatattt gtgacaaaac tcacacatgc 660
ccaccgtgcc cagcacctga actcttggggg ggaccgtca gtttccctt cccccccaaa 720
cccaaggaca ccctcatgtat ctccggacc cctgagggtca catcgctggt ggtggacgtg 780
agccacacaaag accctggatgtt caagtttcaat tggtaacgtgg acggcgtgaa ggtgcataat 840
gccaagacaa agccgggggaa ggacggatgtt gccagcacgtt accgtgtggt cagcgtctc 900
accgtcttc accaggactg gctgtatggc aagggttaca atgtcaatgtt ctccaaacaaa 960
gcctcccaag ccccatcgaa gaaaaccatc tccaaagccaa aaggggcagcc cggagaacca 1020
cagggttaca ccctggcccccc atccccggag gagatgacca agaaccaggat cagcgtgacc 1080
tgctgtgtca aagggttcaat tcccgacgtt atcgccgtgg agtggggagag caatggccag 1140
ccggagaaca actacaagac cacgcctccc gtgtggactt ccgacggctt cttttcttc 1200
tacagcaacg tcaccgtggaa caagagcagg tggcagcagg ggaacgttctt ctcatgttcc 1260
gtgtatgttca aggtctgtca caaccactac acgcagaaga gcctctccctt gtctccgggt 1320
tga                                         1323

```

What is claimed is:

1. A method of treating migraine, comprising administering an effective amount of an anti-calcitonin gene related peptide (CGRP) antibody to a patient, wherein said administering is by intravenous infusion and begins while the patient has a headache of a migraine attack and within 30 hours of the onset of said headache, and wherein the anti-CGRP antibody comprises: (a) a variable light chain polypeptide comprising the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224, SEQ ID NO: 226, and SEQ ID NO: 228, respectively; and (b) a variable heavy chain polypeptide comprising the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204, SEQ ID NO: 206, and SEQ ID NO: 208, respectively.

2. The method of claim 1, wherein said administering begins within 18 hours, within 12 hours, within 6 hours, within 5 hours, within 4 hours, within 3 hours, within 2 hours, or within 1 hour of the onset of said headache.

3. The method of claim 1, wherein said administering begins between about 1-6 hours from the start of said migraine attack.

4. The method of claim 1, wherein said effective amount is: between about 100 mg and about 300 mg; or is about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg.

5. The method of claim 1, wherein: (a) the variable light chain polypeptide comprises the amino acid sequence of SEQ ID NO: 222; and (b) the variable heavy chain polypeptide comprises the amino acid sequence of SEQ ID NO: 202.

6. The method of claim 1, wherein said anti-CGRP antibody is an IgG molecule.

35 7. The method of claim 1, wherein said anti-CGRP antibody comprises: (a) the light chain polypeptide of SEQ ID NO: 221; and (b) the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

8. The method of claim 7, wherein said anti-CGRP antibody consists of said light and heavy chain polypeptides.

40 9. The method of claim 1, wherein said anti-CGRP antibody is expressed in or obtained by expression in: a yeast cell, optionally a *Pichia pastoris* cell; or a mammalian cell, optionally a CHO cell.

10. The method of claim 1, wherein the anti-CGRP antibody is administered in a 0.9% sodium chloride solution, optionally 100 ml of a 0.9% sodium chloride solution.

45 11. The method of claim 1, wherein said anti-CGRP antibody is an IgG1 molecule.

12. A method of treating migraine, comprising intravenously administering an effective amount of an anti-calcitonin gene related peptide (CGRP) antibody in a 0.9% sodium chloride solution to a patient, wherein said administering begins while the patient has a headache of a migraine attack and within 30 hours of the onset of said headache, and wherein the anti-CGRP antibody comprises: (a) a variable light chain polypeptide comprising the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224, SEQ ID NO: 226, and SEQ ID NO: 228, respectively; and (b) a variable heavy chain polypeptide comprising the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204, SEQ ID NO: 206, and SEQ ID NO: 208, respectively.

55 13. The method of claim 12, wherein the anti-CGRP antibody is administered in 100 ml of a 0.9% sodium chloride solution.

60 14. The method of claim 12, wherein said administering begins within 18 hours, within 12 hours, within 6 hours,

243

within 5 hours, within 4 hours, within 3 hours, within 2 hours, or within 1 hour of the onset of said headache.

15. The method of claim **12**, wherein said administering begins between about 1-6 hours from the start of said migraine attack. ⁵

16. The method of claim **12**, wherein said effective amount is: between about 100 mg and about 300 mg; or is about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg. ¹⁰

17. The method of claim **12**, wherein: (a) the variable light chain polypeptide comprises the amino acid sequence of SEQ ID NO: 222; and (b) the variable heavy chain polypeptide comprises the amino acid sequence of SEQ ID NO: 202. ¹⁵

18. The method of claim **12**, wherein said anti-CGRP antibody is an IgG molecule. ¹⁵

19. The method of claim **12**, wherein said anti-CGRP antibody comprises: (a) the light chain polypeptide of SEQ ID NO: 221; and (b) the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566. ²⁰

20. The method of claim **19**, wherein said anti-CGRP antibody consists of said light and heavy chain polypeptides. ²⁵

21. The method of claim **12**, wherein said anti-CGRP antibody is expressed in or obtained by expression in: a yeast cell, optionally a *Pichia pastoris* cell; or a mammalian cell, optionally a CHO cell. ²⁵

22. The method of claim **12**, wherein said anti-CGRP antibody is an IgG1 molecule. ³⁰

* * * * *

244