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(54) **TREATMENT OF HEADACHE USING ANTI-CGRP ANTIBODIES**(71) Applicant: **H. LUNDBECK A/S**, Valby (DK)(72) Inventors: **Roger K. Cady**, Bothell, WA (US);
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See application file for complete search history.

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(57) **ABSTRACT**

Methods for immediate relief of migraine or headache are provided comprising the administration of an anti-CGRP antagonist antibody to a patient in need thereof.

21 Claims, 64 Drawing Sheets

Specification includes a Sequence Listing.

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Figure 1A - Heavy Chain Protein Sequence

Sequence Name	FR1	CDR1	FR2	CDR2
Ab1	QSLEESGGRLVTPGTLPLTILCTVSGIDLIS	SYMMQ	WVRQAFGKGLEWIG	VIGINDNTYYASWAKG
Ab2	EVQLVESGGGLVQPGSIRLISCAVSGIDLIS	SYMMQ	WVRQAFGKGLEWIG	VIGINDNTYYASWAKG
Ab3	EVQLVESGGGLVQPGSIRLISCAVSGIDLIS	SYMMQ	WVRQAFGKGLEWIG	VIGINDNTYYASWAKG
Ab4	QSLEESGGRLVTPGTLPLTICSVSGIDLIS	GYMMN	WVRQAFGKGLEWIG	VIGINGATYYASWAKG
Ab5	EVQLVESGGGLVQPGSIRLISCAVSGIDLIS	GYMMN	WVRQAFGKGLEWIG	VIGINGATYYASWAKG
Ab6	EVQLVESGGGLVQPGSIRLISCAVSGIDLIS	GYMMN	WVRQAFGKGLEWIG	VIGINGATYYASWAKG
Ab7	QEQLKESSGRRLVTPTGSLLTICTVSGIDLIS	NHYMQ	WVRQAFGKGLEWIG	VVGINGRTYYASWAKG
Ab8	EVQLVESGGGLVQPGSIRLISCAVSGIDLIS	NYMMQ	WVRQAFGKGLEWIG	VVGINGRTYYASWAKG
Ab9	QSLEESGGRLVTPGTLPLTICTVSGIGLS	SYMMQ	WVRQSPGRGLEWIG	VIGSDGKTYYATWAKG
Ab10	EVQLVESGGGLVQPGSIRLISCAVSGIGLS	SYMMQ	WVRQAFGKGLEWIG	VIGSDGKTYYATWAKG
Ab11	QSLEESGGRLVTPGGSLLTICTVSGIDVT	NYMMQ	WVRQAFGKGLEWIG	VIGYNGKRYYASWAKG
Ab12	EVQLVESGGGLVQPGSIRLISCAVSGIDVT	NYMMQ	WVRQAFGKGLEWIG	VIGYNGKRYYASWAKG
Ab13	QSVEESEGGGLVQPEGSLLTICTAASGFDES	SNAMW	WVRQAFGKGLEWIG	CIYNGDSTYYASWVNG
Ab14	EVQLVESGGGLVQPGSIRLISCAVSGIGLS	SYMMQ	WVRQAFGKGLEWIG	VIGSDGKTYYATWAKG

Sequence Name	FR3	CDR3	FR4
Ab1	RFTISRASSSTVDIKMTSLLTEDTATYFCAR	GDI	WGPGBTIVTVSS
Ab2	RFTISRDNSSKTTVYIQLQMNSSLRAEDTAVYFCAR	GDI	WGQGTIVTVSS
Ab3	RFTISRDNSSKTTVYIQLQMNSSLRAEDTAVYFCAR	GDI	WGQGTIVTVSS
Ab4	RFTISKTSSTTVDIKMTSLLTEDTATYFCAR	GDI	WGPGBTIVTVSS
Ab5	RFTISRDNSSKTTVYIQLQMNSSLRAEDTAVYFCAR	GDI	WGQGTIVTVSS
Ab6	RFTISRDNSSKTTVYIQLQMNSSLRAEDTAVYFCAR	GDI	WGQGTIVTVSS
Ab7	RFTISRTSSTTVDIKMTRLITEDTATYFCAR	GDI	WGPGBTIVTVSS
Ab8	RFTISRDNSSKTTVYIQLQMNSSLRAEDTAVYFCAR	GDI	WGQGTIVTVSS
Ab9	RFTISKTSSTTVDILMASLITTEDTATYFCAR	GDI	WGPGBTIVTVSS
Ab10	RFTISRDNSSKTTVYIQLQMNSSLRAEDTAVYFCAR	GDI	WGQGTIVTVSS
Ab11	RFTISKTSSTTVDIKMTSLLTEDTATYFCAR	GDI	WGPGBTIVTVSS
Ab12	RFTISRDNSSKTTVYIQLQMNSSLRAEDTAVYFCAR	GDI	WGQGTIVTVSS
Ab13	RFSISKTSSTTVDILQNLNSLTVADTATYFCAR	DLDL	WGPGBTIVTVSS
Ab14	RFTISRDNSSKTTVYIQLQMNSSLRAEDTAVYFCAR	GDI	WGQGTIVTVSS

Figure 1B - Heavy Chain Protein Sequence

Figure 1C - Heavy Chain Protein Sequence

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

Figure 1D - Heavy Chain Protein Sequence

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

Figure 1E - Heavy Chain Protein Sequence

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

Figure 1F - Heavy Chain Protein Sequence

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

Figure 2A - Light Chain Protein Sequence

Sequence	FR1	CDR1	FR2	CDR2
Name				
Ab1	QVLTQTAASPVSAAVGSTVTTINC	QASQSVYDNNYLA	WYQQKPGQPPKQLIY	STSTLAS
Ab2	QVLTQSESSLSASVGDRTVTINC	QASQSVYDNNYLA	WYQQKPGKVPKQLIY	STSTLAS
Ab3	QVLTQSESSLSASVGDRTVTINC	QASQSVYDNNYLA	WYQQKPGKVPKQLIY	STSTLAS
Ab4	QVLTQTPSPVSAAVGSTVTTINC	QASQSVYHNTYLA	WYQQKPGQPPKQLIY	DASTLAS
Ab5	QVLTQSESSLSASVGDRTVTINC	QASQSVYHNTYLA	WYQQKPGKVPKQLIY	DASTLAS
Ab6	QVLTQSESSLSASVGDRTVTINC	QASQSVYHNTYLA	WYQQKPGKVPKQLIY	DASTLAS
Ab7	QVLTQTAASPVSAAVGSTVTTINC	QASQSVYHNTYLA	WYQQKPGQPPKQLIY	STSTLAS
Ab8	QVLTQSESSLSASVGDRTVTINC	QASQSVYHNTYLA	WYQQKPGKVPKQLIY	STSTLAS
Ab9	QVLTQTPSPVSAAVGSTVTTINC	QASQSVYNNNYLA	WYQQKPGQPPKQLIY	STSTLAS
Ab10	QVLTQSESSLSASVGDRTVTINC	QASQSVYNNNYLA	WYQQKPGKVPKQLIY	STSTLAS
Ab11	QVLTQTAASPVSAAVGSTVTTINC	QASQSVYNNNYLA	WYQQKPGQPPKQLIY	STSTLAS
Ab12	QVLTQSESSLSASVGDRTVTINC	RASQSVYNNNYLA	WYQQKPGKVPKQLIY	STSTLAS
Ab13	AIVNTOIPSSKSVPVGDTVTINC	QASQSVLYNNNALA	WFQQKPGQPPKRLIY	DASKLAS
Ab14	QVLTQSESSLSASVGDRTVTINC	QASQSVYNNNYLA	WYQQKPGKVPKQLIY	STSTLAS

Figure 2B - Light Chain Protein Sequence

Sequence	FR3	CDR3	FR4
Name			
Ab1	GVSSRFKGSGETQFTLTIISDLECADATYYC	LGSYDCSSGDCFV	FGGGTEVVVKR
Ab2	GVPSRFSGSGSGTDFLTITISSLQPEDVATYYC	LGSYDCSSGDCFV	FGGGTKVEIKR
Ab3	GVPSRFSGSGSGTDFLTITISSLQPEDVATYYC	LGSYDCSSGDCFV	FGGGTKVEIKR
Ab4	GVPSRFSGSGSGTDFLTITISSLQPEDVATYYC	LGSYDCTNGDCFV	FGGGTEVVVKR
Ab5	GVPSRFSGSGSGTDFLTITISSLQPEDVATYYC	LGSYDCTNGDCFV	FGGGTKVEIKR
Ab6	GVPSRFSGSGSGTDFLTITISSLQPEDVATYYC	LGSYDCTNGDCFV	FGGGTKVEIKR
Ab7	GVSSRFKGSGETQFTLTIISDVCQDDAATYYC	LGSYDCSTGDCFV	FGGGTEVVVKR
Ab8	GVPSRFSGSGSGTDFLTITISSLQPEDVATYYC	LGSYDCSTGDCFV	FGGGTKVEIKR
Ab9	GVSSRFKGSGETQFTLTIISDVCQDDAATYYC	LGSYDCSRGDCFV	FGGGTEVVVKR
Ab10	GVPSRFSGSGSGTDFLTITISSLQPEDVATYYC	LGSYDCSRGDCFV	FGGGTKVEIKR
Ab11	GVSSRFKGSGETQFTLTIISDVCQDDAATYYC	LGSYDCSNGDCFV	FGGGTEVVVKR
Ab12	GVPSRFSGSGSGTDFLTITISSLQPEDVATYYC	LGSYDCSNGDCFV	FGGGTKVEIKR
Ab13	GVPSRSRGGGGSGTQFTLTIISDVCQDDAATYYC	GGYRSDSVDGVA	FAGGTTEVVVKR
Ab14	GVPSRFSGSGSGTDFLTITISSLQPEDVATYYC	LGSYDCSRGDCFV	FGGGTKVEIKR

Figure 2C - Light Chain Protein Sequence

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

Figure 2D - Light Chain Protein Sequence

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

Figure 3A - Heavy Chain DNA Sequence

Sequence	FR1
Name	
Ab1	CAGTCGCTGGAGGAGTCCGGGGTCGCCTGGCACGCCCTGGCAGACTCACCTGACAGTCTGGACTCGACCTCAGT
Ab2	GAGGTGCAAGCTTGTGAGSTCTGGGAGGCTTGTCAGGCTGGCTGGTCACGCCCTGGACACCCCTGACACTCACCTG
Ab3	GAGGTGCAAGCTTGTGAGSTCTGGGAGGCTTGTCAGGCTGGCTGGTCACGCCCTGGACACCCCTGACACTCACCTG
Ab4	CAGTCGCTGGAGGAGTCCGGGGTCGCCTGGCAGACTCACCTGACACTCACCTG
Ab5	GAGGTGCAAGCTTGTGAGSTCTGGGAGGCTTGTCAGGCTGGCTGGTCACGCCCTGGACACCCCTGACACTCACCTG
Ab6	GAGGTGCAAGCTTGTGAGSTCTGGGAGGCTTGTCAGGCTGGCTGGTCACGCCCTGGACACCCCTGACACTCACCTG
Ab7	CAGGGAGCAGCTGAAGGAGTCCGGGGAGGCTTGTCAGGCTGGCTGGTCACGCCCTGGACACCCCTGACACTCACCTG
Ab8	GAGGTGCAAGCTTGTGAGSTCTGGGAGGCTTGTCAGGCTGGCTGGTCACGCCCTGGACACCCCTGACACTCACCTG
Ab9	CAGTCGCTGGAGGAGTCCGGGGAGGCTTGTCAGGCTGGCTGGTCACGCCCTGGACACCCCTGACACTCACCTG
Ab10	GAGGTGCAAGCTTGTGAGSTCTGGGAGGCTTGTCAGGCTGGCTGGTCACGCCCTGGACACCCCTGACACTCACCTG
Ab11	CAGTCGCTGGAGGAGTCCGGGGAGGCTTGTCAGGCTGGCTGGTCACGCCCTGGACACCCCTGACACTCACCTG
Ab12	GAGGTGCAAGCTTGTGAGSTCTGGGAGGCTTGTCAGGCTGGCTGGTCACGCCCTGGACACCCCTGACACTCACCTG
Ab13	CAGTCGCTGGAGGAGTCCGGGGAGGCTTGTCAGGCTGGCTGGTCACGCCCTGGACACCCCTGACACTCACCTG
Ab14	GAGGTGCAAGCTTGTGAGSTCTGGGAGGCTTGTCAGGCTGGCTGGTCACGCCCTGGACACCCCTGACACTCACCTG

Figure 3B - Heavy Chain DNA Sequence

Sequence	FR1	FR2
Name		
Ab1	AGCTACTACATGCAA	TGGGTCCGCCAGGGTCCAGGGAAAGGGGCTGGAATGGATCGGA
Ab2	AGCTACTACATGCAA	TGGGTCCCGTCAGGCTCAGGGAAAGGGGCTGGAATGGATCGGA
Ab3	AGCTACTACATGCAA	TGGGTCCGCCAGGGTCCAGGGAAAGGGGCTGGAATGGATCGGA
Ab4	GGCTACTACATGAAAC	TGGGTCCCGTCAGGCTCAGGGAAAGGGGCTGGAATGGATCGGA
Ab5	GGCTACTACATGAAAC	TGGGTCCCGTCAGGCTCAGGGAAAGGGGCTGGAATGGATCGGA
Ab6	GGCTACTACATGAAAC	TGGGTCCCGTCAGGCTCAGGGAAAGGGGCTGGAATGGATCGGA
Ab7	AACCCTACTACATGCAA	TGGGTCCGCCAGGGTCCAGGGAAAGGGGCTGGAATGGATCGGA
Ab8	AACCCTACTACATGCAA	TGGGTCCCGTCAGGCTCAGGGAAAGGGGCTGGAATGGATCGGA
Ab9	AGCTACTACATGCAA	TGGGTCCGCCAGGGTCCAGGGAAAGGGGCTGGAATGGATCGGA
Ab10	AGCTACTACATGCAA	TGGGTCCCGTCAGGCTCAGGGAAAGGGGCTGGAATGGATCGGA
Ab11	AACTACTATATGCAA	TGGGTCCGCCAGGGTCCAGGGAAAGGGGCTGGAATGGATCGGA
Ab12	AACTACTACATGCAA	TGGGTCCCGTCAGGCTCAGGGAAAGGGGCTGGAATGGATCGGA
Ab13	AGCAATGCAATGTGG	TGGGTCCGCCAGGGTCCAGGGAAAGGGGCTGGAATGGATCGGA
Ab14	AGCTACTACATGCAA	TGGGTCCCGTCAGGCTCAGGGAAAGGGGCTGGAATGGATCGGA

Figure 3C - Heavy Chain DNA Sequence

Sequence	CDR2
Name	
Ab1	GTCATTGGTAAATGATAACACATACTACCGGAGCTGGCGAAAGGC
Ab2	GTCATTGGTAAATGATAACACATACTACCGGAGCTGGCGAAAGGC
Ab3	GTCATTGGTAAATGATAACACATACTACCGGAGCTGGCGAAAGGC
Ab4	GTCATTGGTAAATGATAACACATACTACCGGAGCTGGCGAAAGGC
Ab5	GTCATTGGTAAATGTTGGGCCACATACCTACCGGAGCTGGCGAAAGGC
Ab6	GTCATTGGTAAATGTTGGGCCACATACCTACCGGAGCTGGCGAAAGGC
Ab7	GTCATTGGTAAATGTTGGGCCACATACCTACCGGAGCTGGCGAAAGGC
Ab8	GTCATTGGTAAATGTTGGGCCACATACCTACCGGAGCTGGCGAAAGGC
Ab9	GTCATTGGTAAATGTTGGGCCACATACCTACCGGAGCTGGCGAAAGGC
Ab10	GTCATTGGTAAATGTTGGGCCACATACCTACCGGAGCTGGCGAAAGGC
Ab11	GTCATTGGTAAATGTTGGGCCACATACCTACCGGAGCTGGCGAAAGGC
Ab12	GTCATTGGTAAATGTTGGGCCACATACCTACCGGAGCTGGCGAAAGGC
Ab13	TGCAATTACAATGGTGTAGCCAGCACATACTACCGGAGCTGGTGAATGGC
Ab14	GTCATTGGTAAATGTTGGGCCACATACCTACCGGAGCTGGCGAAAGGC

Figure 3D - Heavy Chain DNA Sequence

Sequence	FR3
Name	
Ab1	CGATTCAACCATTCCAGAGGCCCTCGTGACCAACGGGGATCTGAAAATGACACAGTCTGACAACGGGACACGGCACCTATTCTGTGCCAGA
Ab2	CGATTCAACCATTCCAGAGACAATTCCAAGACCAACGGGTGATCTTCAAATGAACAGCTGAGAGCTGAGGACACTGCTGTGTAATTCTGTGCTAGA
Ab3	CGATTCAACCATTCCAGAGACAATTCCAAGACCAACGGGTGATCTGAAAATGACACAGCTGACAACGGGACACGGCACCTATTCTGTGCTAGA
Ab4	CGATTCAACCATTCCAGAGACAATTCCAAGACCAACGGGTGATCTTCAAATGAACAGCTGAGAGCTGAGGACACTGCTGTGTAATTCTGTGCTAGA
Ab5	CGATTCAACCATTCCAGAGACAATTCCAAGACCAACGGGTGATCTTCAAATGAACAGCTGAGAGCTGAGGACACTGCTGTGTAATTCTGTGCTAGA
Ab6	CGATTCAACCATTCCAGAGACAATTCCAAGACCAACGGGTGATCTGAAAATGACACAGGTGAGAGCTGAGGACACTGCTGTGTAATTCTGTGCTAGA
Ab7	CGATTCAACCATTCCAGAGACAATTCCAAGACCAACGGGTGATCTTCAAATGAACAGCTGAGAGCTGAGGACACTGCTGTGTAATTCTGTGCTAGA
Ab8	CGATTCAACCATTCCAGAGACAATTCCAAGACCAACGGGTGATCTGAGAATGGCAGTCTGACAACCGGACACGGCACCTATTCTGTGCTAGA
Ab9	CGATTCAACCATTCCAGAGACAATTCCAAGACCAACGGGTGATCTGAGAATGGCAGTCTGACAACCGGACACGGCACCTATTCTGTGCTAGA
Ab10	CGATTCAACCATTCCAGAGACAATTCCAAGACCAACGGGTGATCTTCAAATGAACAGCTGAGAGCTGAGGACACTGCTGTGTAATTCTGTGCTAGA
Ab11	CGATTCAACCATTCCAGAGACAATTCCAAGACCAACGGGTGATCTTCAAATGAACAGCTGAGAGCTGAGGACACTGCTGTGTAATTCTGTGCTAGA
Ab12	CGATTCAACCATTCCAGAGACAATTCCAAGACCAACGGGTGACTCTGAAACTGAAGCTGAGGACACTGCTGTGTAATTCTGTGCTAGA
Ab13	CGATTCAACCATTCCAGAGACAATTCCAAGACCAACGGGTATCTTCAAATGAACAGCTGAGAGCTGAGGACACTGCTGTGTAATTCTGTGCTAGA
Ab14	CGATTCAACCATTCCAGAGACAATTCCAAGACCAACGGGTATCTTCAAATGAACAGCTGAGAGCTGAGGACACTGCTGTGTAATTCTGTGCTAGA

Figure 3E - Heavy Chain DNA Sequence

Sequence	Name	CDR3	FR4	Constant Region
	Ab1	GGGACATC	TGGGCCAAGGGACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC
	Ab2	GGGACATC	TGGGCCAAGGAACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC
	Ab3	GGGACATC	TGGGCCGGGACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC
	Ab4	GGGACATC	TGGGCCGGGACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC
	Ab5	GGGACATC	TGGGCCAAGGGACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC
	Ab6	GGGACATC	TGGGCCAAGGGACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC
	Ab7	GGGACATC	TGGGCCAGGACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC
	Ab8	GGGACATC	TGGGCCAAGGGACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC
	Ab9	GGGACATC	TGGGCCAAGGGACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC
	Ab10	GGGACATC	TGGGCCAAGGGACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC
	Ab11	GGGACATC	TGGGCCGGGACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC
	Ab12	GGGACATC	TGGGCCAAGGGACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC
	Ab13	GATCTTGACTTG	TGGGCCGGGACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC
	Ab14	GGGACATC	TGGGCCAAGGGACCCCTCGTACCGTCCTCGAGC	GCCTCCACAAGGCCCATCGGTCTTCCCCCTGGCACCCCTCTCC

Figure 3F - Heavy Chain DNA Sequence

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

Figure 3G - Heavy Chain DNA Sequence

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

Figure 3H - Heavy Chain DNA Sequence

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

Figure 3I - Heavy Chain DNA Sequence

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

Figure 3J - Heavy Chain DNA Sequence

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

Figure 3K - Heavy Chain DNA Sequence

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

Figure 3L - Heavy Chain DNA Sequence

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

Figure 3M - Heavy Chain DNA Sequence

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

Figure 3N - Heavy Chain DNA Sequence

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

Figure 3O - Heavy Chain DNA Sequence

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

Figure 3P - Heavy Chain DNA Sequence

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

Figure 4A - Light Chain DNA Sequence

Sequence	FR1
Name	
Ab1	CAAGTGGCTGACCCAGACTGCATCCCCGTGTCAGCTGTGGAAAGCACAGTCACCATCAATTGC
Ab2	CAAGTGGCTGCCAGTCATCCTCCCTGTCATCTGTGGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab3	CAAGTGGCTGCCAGTCATCCTCCCGTGTGGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab4	CAAGTGGCTGCCAGTCATCCTCCCGTGTGGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab5	CAAGTGGCTGCCAGTCATCCTCCCGTGTGGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab6	CAAGTGGCTGCCAGTCATCCTCCCGTGTGGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab7	CAAGTGGCTGCCAGTCATCCTCCCGTGTGGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab8	CAAGTGGCTGCCAGTCATCCTCCCGTGTGGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab9	CAAGTGGCTGCCAGTCATCCTCCCGTGTGGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab10	CAAGTGGCTGCCAGTCATCCTCCCGTGTGGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab11	CAGGTGGTGCCAGTCATCCTCCCGTGTGGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab12	CAAGTGGTGCCAGTCATCCTCCCGTGTGGCATCTGTAGGAGACAGAGTCACCATCAATTGC
Ab13	GCCATCGTGACCCAGTCATCTCCAAAGTCATCTCCATCTCCGTGTGGAGACACAGTCACCATCAATTGC
Ab14	CAAGTGGTGCCAGTCATCTCCATCTCCGTGTGGAGACAGAGTCACCATCAATTGC

Figure 4B - Light Chain DNA Sequence

Sequence	CDR1	CDR2
Name		
Ab1	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAAACCAGGGCAGCCTCCAAAGCAACTGATCTAT
Ab2	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCTTAAGCAACTGATCTAT
Ab3	CAGGCCAGTCAGAGTTTATGATAACAACCTAGCC	TGGTATCAGCAGAAACCAGGGCAGCCTCCAAACAACTGATCTAT
Ab4	CAGGCCAGTCAGAGTTTATGATAACAACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCTTAAGCAACTGATCTAT
Ab5	CAGGCCAGTCAGAGTTTATGATAACAACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCTTAAGCAACTGATCTAT
Ab6	CAGGCCAGTCAGAGTTTATGATAACAACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCTTAAGCAACTGATCTAT
Ab7	CAGGCCAGTCAGAGTTTATGATAACAACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCTTAAGCAACTGATCTAT
Ab8	CAGGCCAGTCAGAGTTTATGATAACAACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCTTAAGCAACTGATCTAT
Ab9	CAGGCCAGTCAGAGTTTATGATAACAACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCTTAAGCAACTGATCTAT
Ab10	CAGGCCAGTCAGAGTTTATGATAACAACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCTTAAGCAACTGATCTAT
Ab11	CAGGCCAGTCAGAGTTTATGATAACAACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCTTAAGCAACTGATCTAT
Ab12	CAGGCCAGTCAGAGTTTATGATAACAACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCTTAAGCAACTGATCTAT
Ab13	CAGGCCAGTCAGAGTTTATGATAACAACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCTTAAGCAACTGATCTAT
Ab14	CAGGCCAGTCAGAGTTTATGATAACAACCTACCTGGCC	TGGTATCAGCAGAAACCAGGGAAAGTTCTTAAGCAACTGATCTAT

Figure 4C - Light Chain DNA Sequence

Sequence	CDR2	FR3
Name		
Ab1	TCTACATCCACTCTGGCATCT	GGGGTCTCATCGGGTTCAAGGCAGTGGATCTGGGACACAGTCACTCACCA
Ab2	TCTACATCCACTCTGGCATCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTCACTCTCACCA
Ab3	TCTACATCCACTCTGGCATCT	GGGGTCCCCATCGGGTTCAAGGCAGTGGATCTGGGACACAGTCACTCACCA
Ab4	GATGCATCCACTCTGGGTCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTCACTCTCACCA
Ab5	GATGCATCCACTCTGGCATCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTCACTCTCACCA
Ab6	GATGCATCCACTCTGGCATCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTCACTCTCACCA
Ab7	TCTACATCCACTCTGGCATCT	GGGGTCTCATCGGATTCAAAGGCAGTGGATCTGGGACACAGTCACTCACCA
Ab8	TCTACATCCACTCTGGCATCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTCACTCTCACCA
Ab9	TCTACGTCCACTCTGGCATCT	GGGGTCTCATCGGATTCAAAGGCAGTGGATCTGGGACAGATTCACTCTCACCA
Ab10	TCTACATCCACTCTGGCATCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTCACTCTCACCA
Ab11	TCTACATCCACTCTGGCATCT	GGGGTCTCATCGGGTTCAAAGGCAGTGGATCTGGGACACAGTCACTCACCA
Ab12	TCTACATCCACTCTGGCATCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTCACTCTCACCA
Ab13	GATGCATCCAAACTGGCATCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACACAGTCACTCACCA
Ab14	TCTACATCCACTCTGGCATCT	GGGGTCCCCATCTCGTTTCAGTGGCAGTGGATCTGGGACAGATTCACTCTCACCA

Figure 4D - Light Chain DNA Sequence

Sequence	FR3	CDR3
Name		
Ab1	TCAGGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGT	CTAGGCAGTTATGATGTAGTTAGTAGTGGTGAATTGTTTTGTT
Ab2	TCAGCAGCCTGAGCCTGAAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATGTAGTTAGTAGTGGTGAATTGTTTTGTT
Ab3	TCAGCAGCCTGAGCCTGAAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATGTAGTTAGTAGTGGTGAATTGTTTTGTT
Ab4	TCAGGGCGGTGTAACGATGCTGCCTTACTACTGT	CTGGGCAGTTATGATGTAGTTAGTAGTGGTGAATTGTTTTGTT
Ab5	TCAGCAGCCTGAGCCTGAAAGATGTTGCAACTTATTACTGT	CTGGGCAGTTATGATGTAGTTAGTAGTGGTGAATTGTTTTGTT
Ab6	TCAGCAGCCTGAGCCTGAAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATGTAGTTAGTAGTGGTGAATTGTTTTGTT
Ab7	TCAGCAGCCTGAGCCTGAAAGATGTTGCAACTTATTACTGT	CTGGGCAGTTATGATGTAGTTAGTAGTGGTGAATTGTTTTGTT
Ab8	TCAGCAGCCTGAGCCTGAAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATGTAGTTAGTAGTGGTGAATTGTTTTGTT
Ab9	TCAGCAGCCTGAGCCTGAAAGATGTTGCAACTTATTACTGT	CTGGGCAGTTATGATGTAGTTAGTAGTGGTGAATTGTTTTGTT
Ab10	TCAGCAGCCTGAGCCTGAAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATGTAGTTAGTAGTGGTGAATTGTTTTGTT
Ab11	TCAGCAGCCTGAGCCTGAAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATGTAGTTAGTAGTGGTGAATTGTTTTGTT
Ab12	TCAGCAGCCTGAGCCTGAAAGATGTTGCAACTTATTACTGT	CTAGGCAGTTATGATGTAGTTAGTAGTGGTGAATTGTTTTGCT
Ab13	TCAGCAGCCTGAGCCTGAAAGATGTTGCAACTTATTACTGT	GGAGGCTACAGAAGTGAATGTTGATGTTGATGTTGTTGCT
Ab14	TCAGCAGCCTGAGCCTGAAAGATGTTGCAACTTATTACTGT	CTGGGCAGTTATGATGTAGTTAGTAGTGGTGAATTGTTTTGTT

Figure 4E - Light Chain DNA Sequence

Sequence Name	FR4	Constant Region
Ab1	TTCGGGGGAGGGACCCGAGGTGGTGTCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG
Ab2	TTCGGGGGAGGAACCAAGGTGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG
Ab3	TTCGGGGGAGGGAAACCAAGGTGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG
Ab4	TTCGGGGGAGGGAAACCAAGGTGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG
Ab5	TTCGGGGGAGGGAAACCAAGGTGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG
Ab6	TTCGGGGGAGGGAAACCAAGGTGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG
Ab7	TTCGGGGGAGGGAAACCAAGGTGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG
Ab8	TTCGGGGGAGGGAAACCAAGGTGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG
Ab9	TTCGGGGGAGGGAAACCAAGGTGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG
Ab10	TTCGGGGGAGGGAAACCAAGGTGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG
Ab11	TTCGGGGGAGGGAAACCAAGGTGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG
Ab12	TTCGGGGGAGGGAAACCAAGGTGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG
Ab13	TTCGGGGGAGGGAAACCAAGGTGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG
Ab14	TTCGGGGGAGGGAAACCAAGGTGAAATCAAACGT	ACGGTGGCTGCACCATCTGTCTTCATCTTCCCACATCTGTAGGAGCTTG

Figure 4F - Light Chain DNA Sequence

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

Figure 4G - Light Chain DNA Sequence

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

Figure 4H - Light Chain DNA Sequence

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

Figure 4I - Light Chain DNA Sequence
Sequence

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

Figure 5
Heavy Chain Protein Sequence Features

Antibody	Heavy Chain Protein Sequence Features			SEQ ID NO:	Coordinates	SEQ ID NO:	Coordinates	SEQ ID NO:	Coordinates	SEQ ID NO:
	Variable Region	SEQ ID NO:	CDR1							
Ab1	1-109	2	30-34		4	49-64		6	96-98	8
Ab2	1-111	42	31-35		44	50-65		46	98-100	48
Ab3	1-111	82	31-35		84	50-65		86	98-100	88
Ab4	1-109	122	30-34		124	49-64		126	96-98	128
Ab5	1-111	162	31-35		164	50-65		166	98-100	168
Ab6	1-111	202	31-35		204	50-65		206	98-100	208
Ab7	1-110	242	31-35		244	50-65		246	97-99	248
Ab8	1-111	282	31-35		284	50-65		286	98-100	288
Ab9	1-109	322	30-34		324	49-64		326	96-98	328
Ab10	1-111	362	31-35		364	50-65		366	98-100	368
Ab11	1-109	402	30-34		404	49-64		406	96-98	408
Ab12	1-111	442	31-35		444	50-65		446	98-100	448
Ab13	1-111	482	30-34		484	49-65		486	97-100	488
Ab14	1-111	522	31-35		524	50-65		526	98-100	528

Figure 6
Heavy Chain Protein 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 Coordinates	SEQ ID 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

Antibody	Variable Region Coordinates	SEQ ID NO:	CDR1 SEQ ID NO:	Coordinates	CDR2 SEQ ID NO:	Coordinates	CDR3 SEQ ID NO:	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 Coordinates	SEQ ID NO:	FR2 Coordinates	SEQ ID NO:	FR3 Coordinates	SEQ ID NO:	FR4 Coordinates	SEQ ID NO:	Constant Region Coordinates	SEQ ID 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

Antibody	Variable Region Coordinates	SEQ ID NO:	CDR1 SEQ ID NO:	CDR2 SEQ ID NO:	CDR3 SEQ ID NO:	SEQ ID NO:
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 Coordinates	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:
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

Antibody	FR1 Coordinates	SEQ ID NO: Coordinates					
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

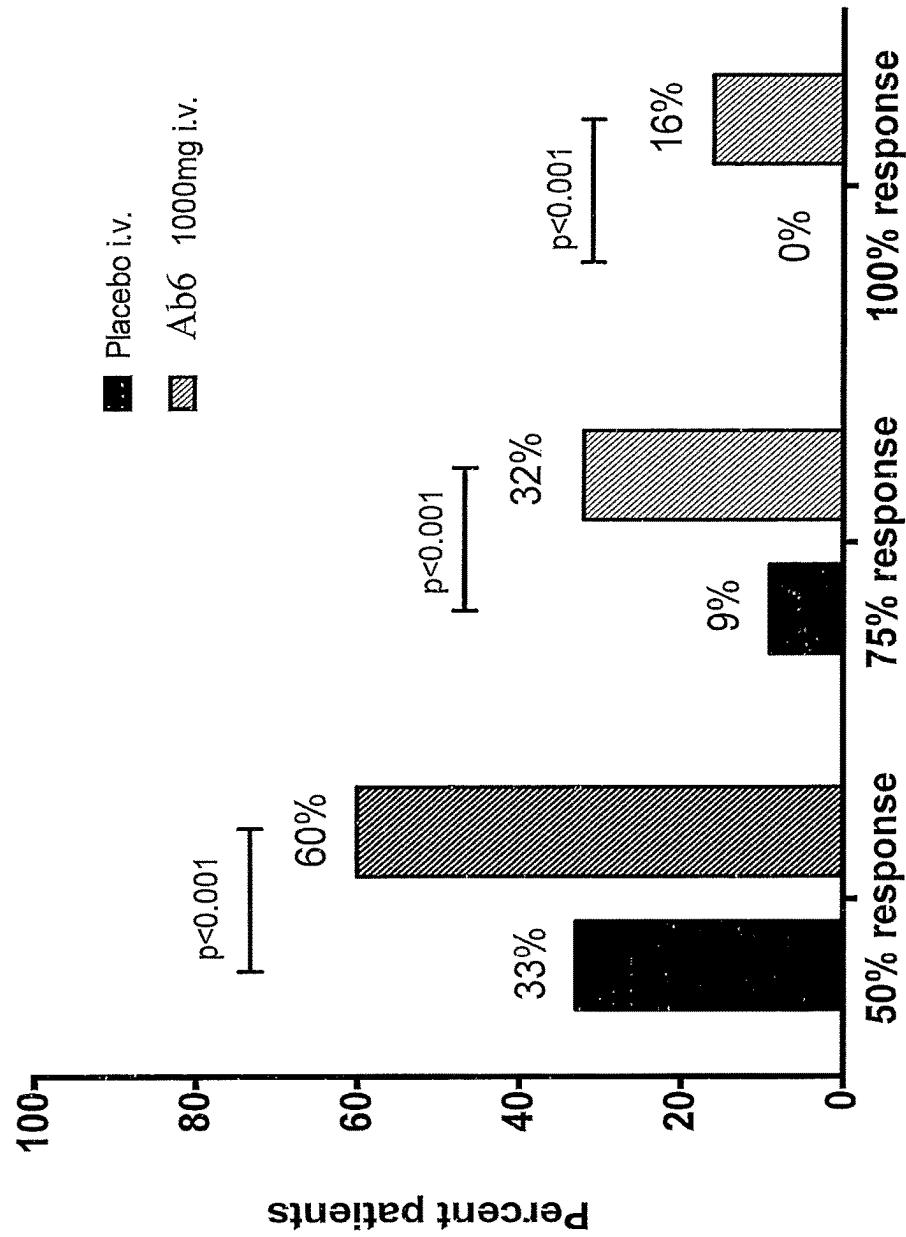


FIG. 14

Median % change from baseline: migraine days per month

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

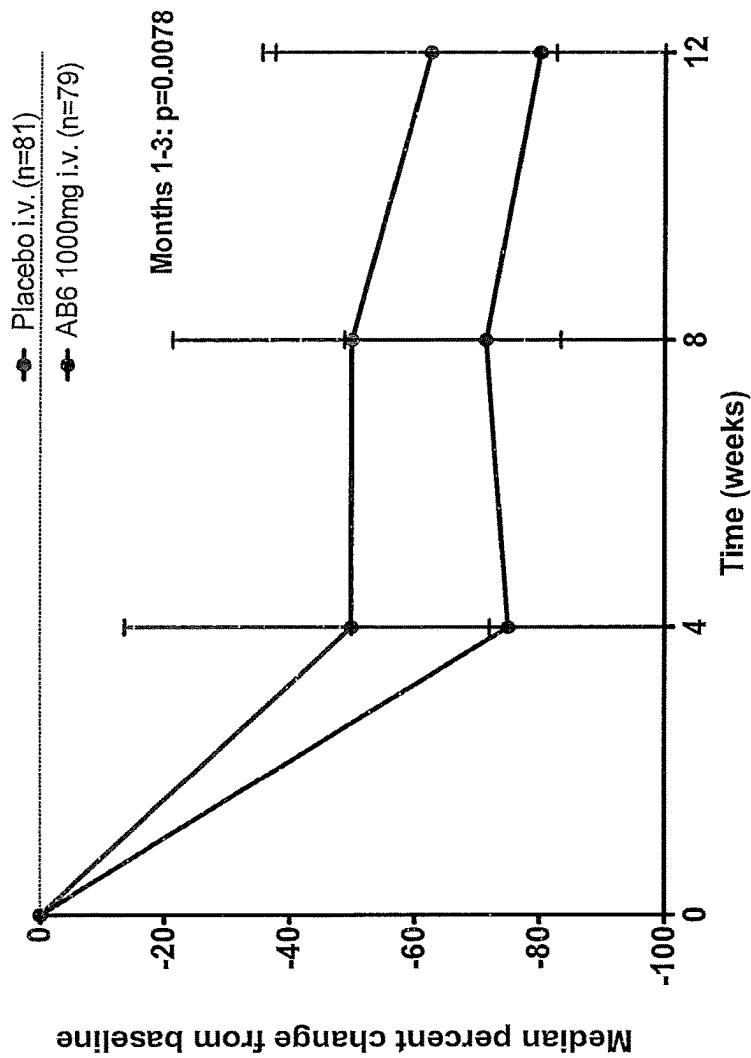


FIG. 15

Median % change from baseline: migraine episodes per month

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

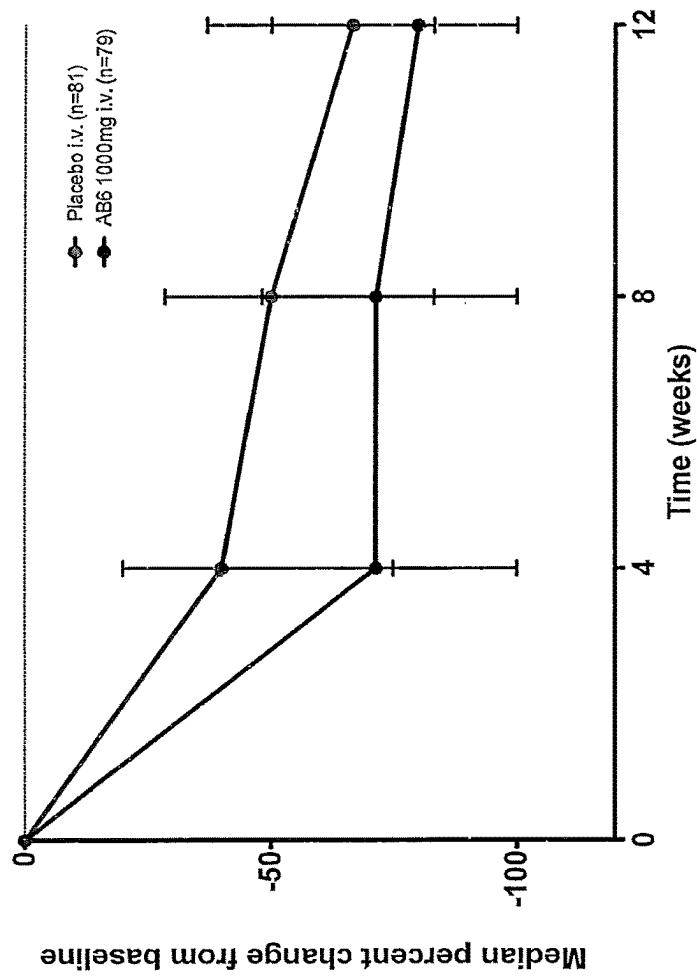


FIG. 16

Median % change from baseline: migraine hours per month

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

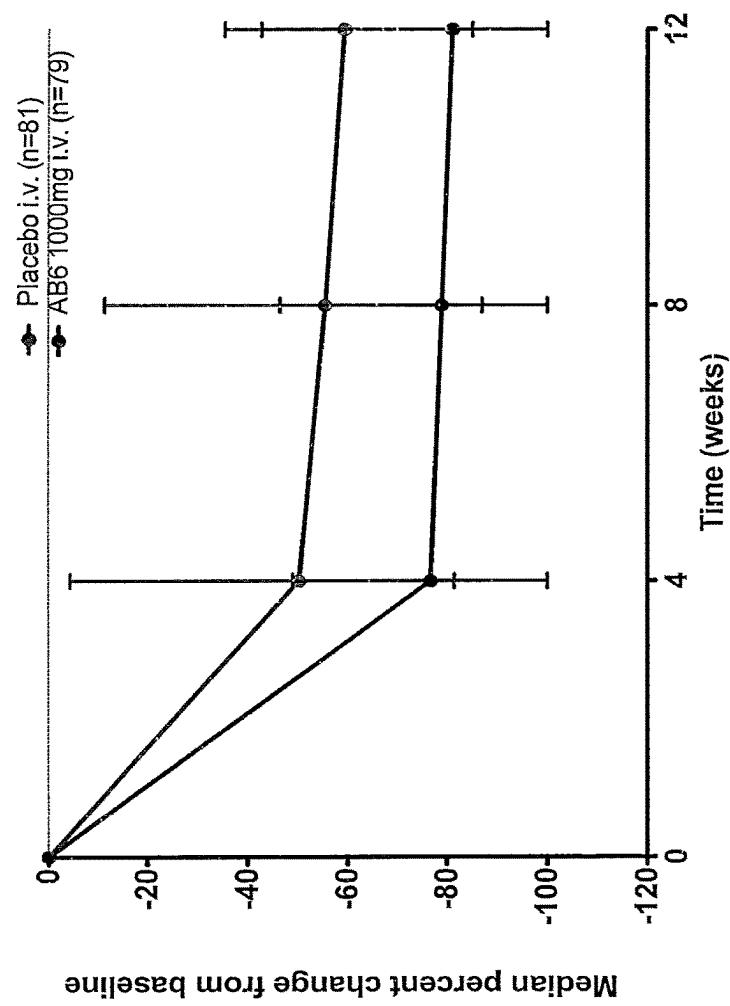
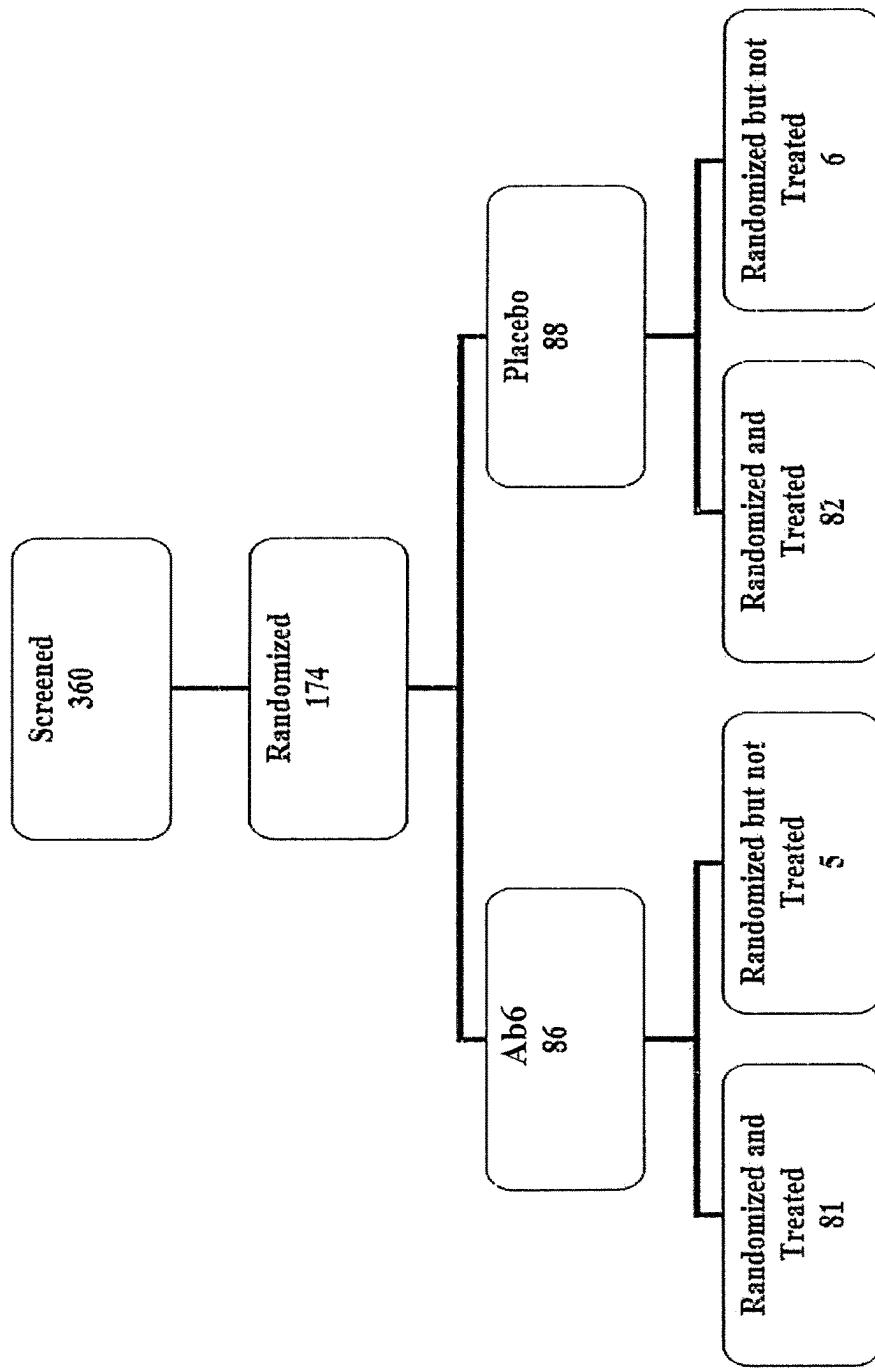


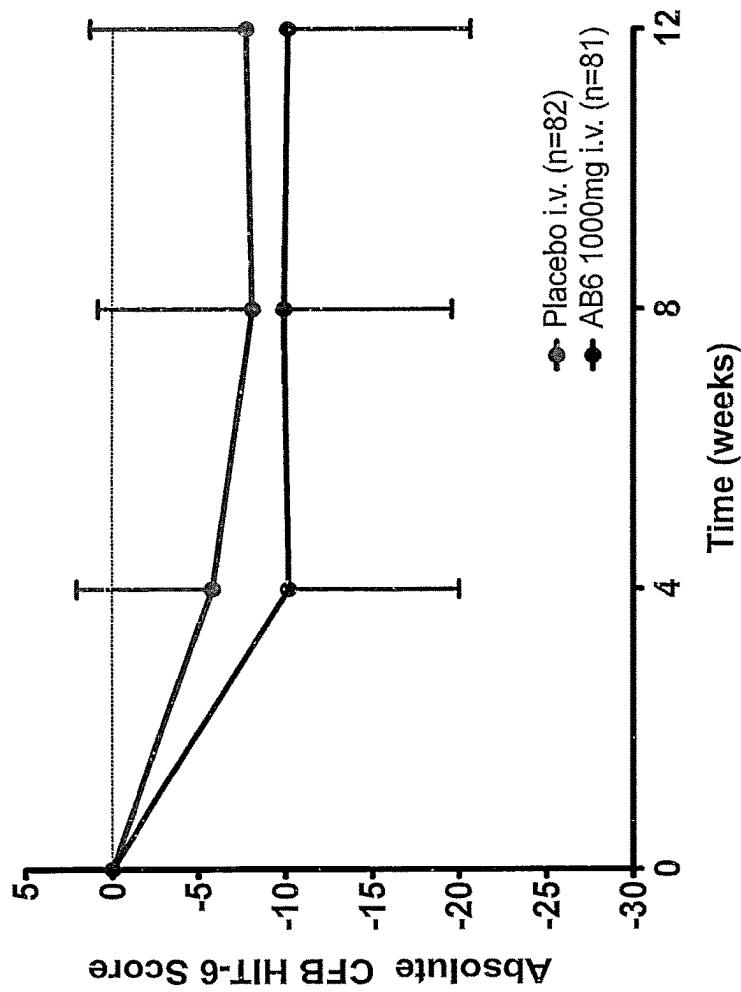
FIG. 17



Mean Change Baseline HIT-6 score

FIG. 18

Mean (\pm SD) absolute change from baseline in Headache Impact Test (HIT-6) Score: AB6 vs Placebo



HIT-6 Responder Analysis

FIG. 19

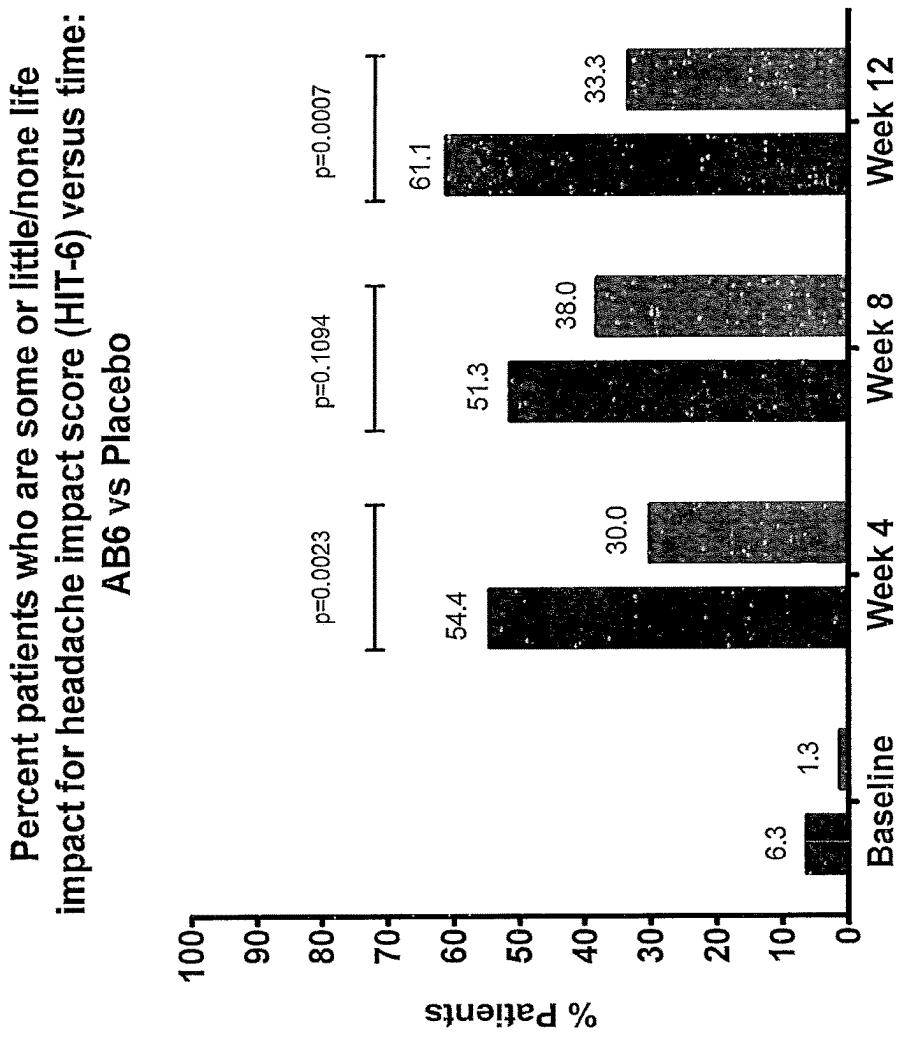


FIG. 20. PK Profile

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

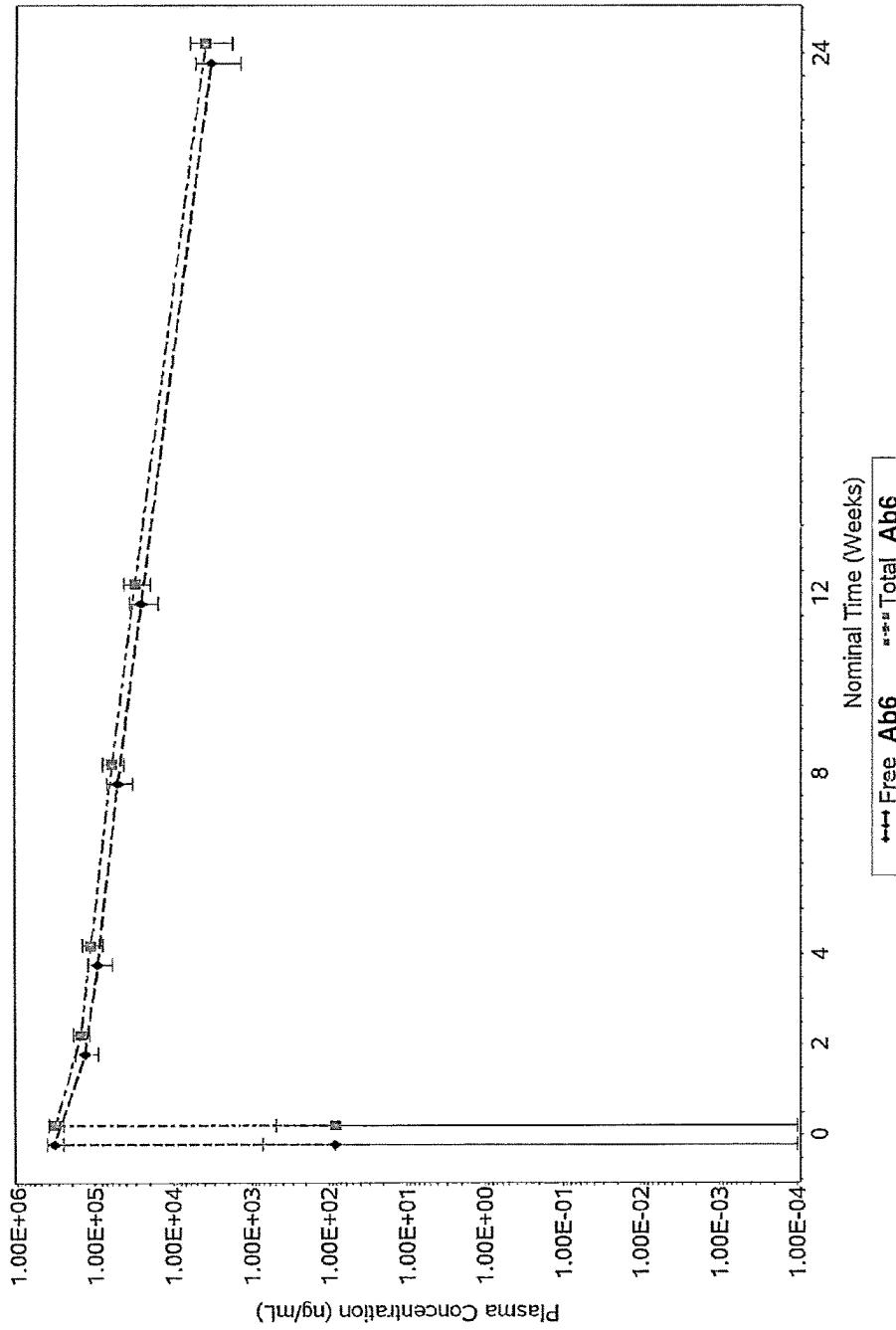


FIG. 21. PK Parameters

Plasma Free Ab6*

	C _{max} (μ g/mL)	AUC _{0-∞} (mg*hr/mL)	Half-Life (Days)	Vz (L)	CL (mL/hr)
N	81	78	78	78	78
Mean	336	219	31	5.2	5.0
SD	80	64	8	2.1	1.5

* - Following 1000 mg Ab6 IV single-dose

FIG. 22

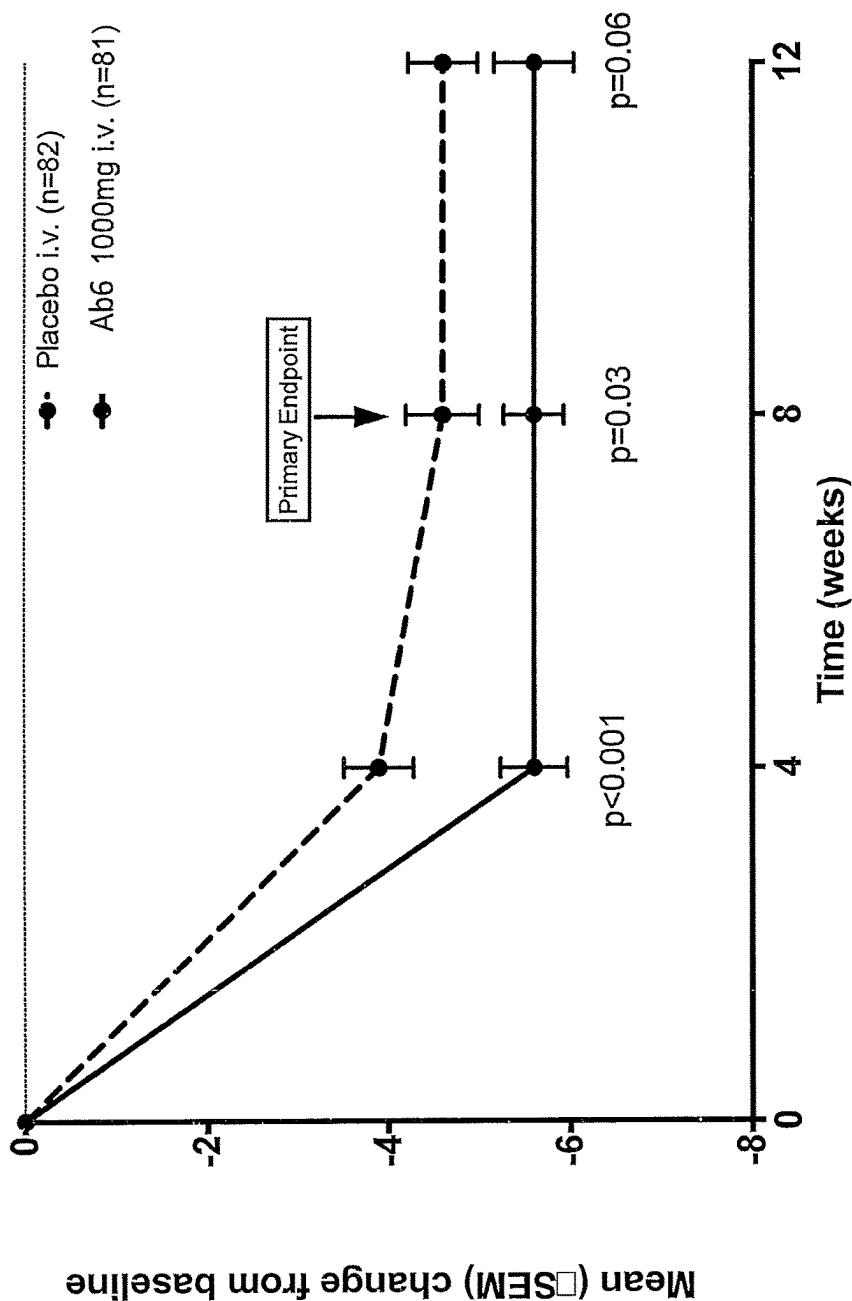


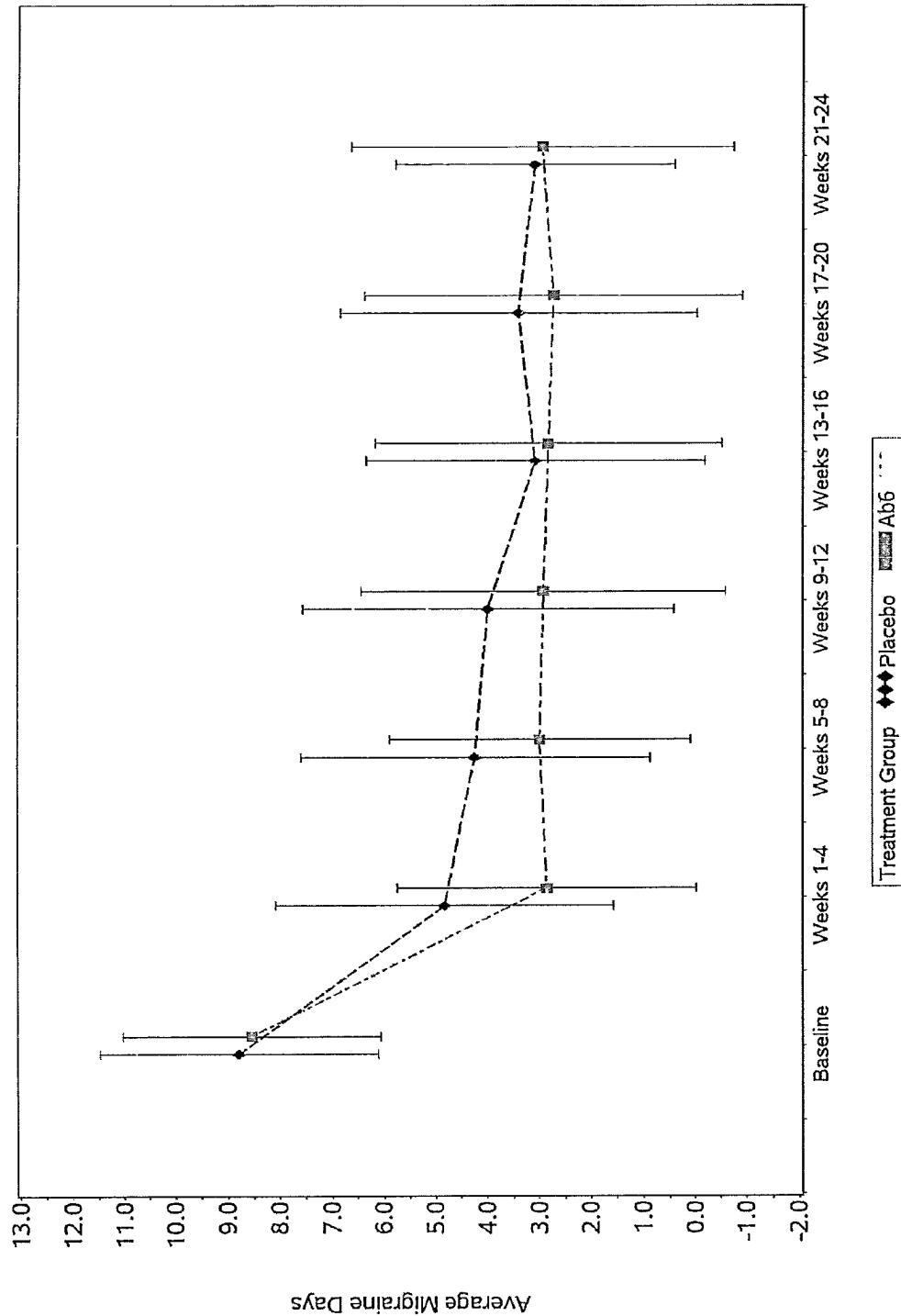
FIG. 23

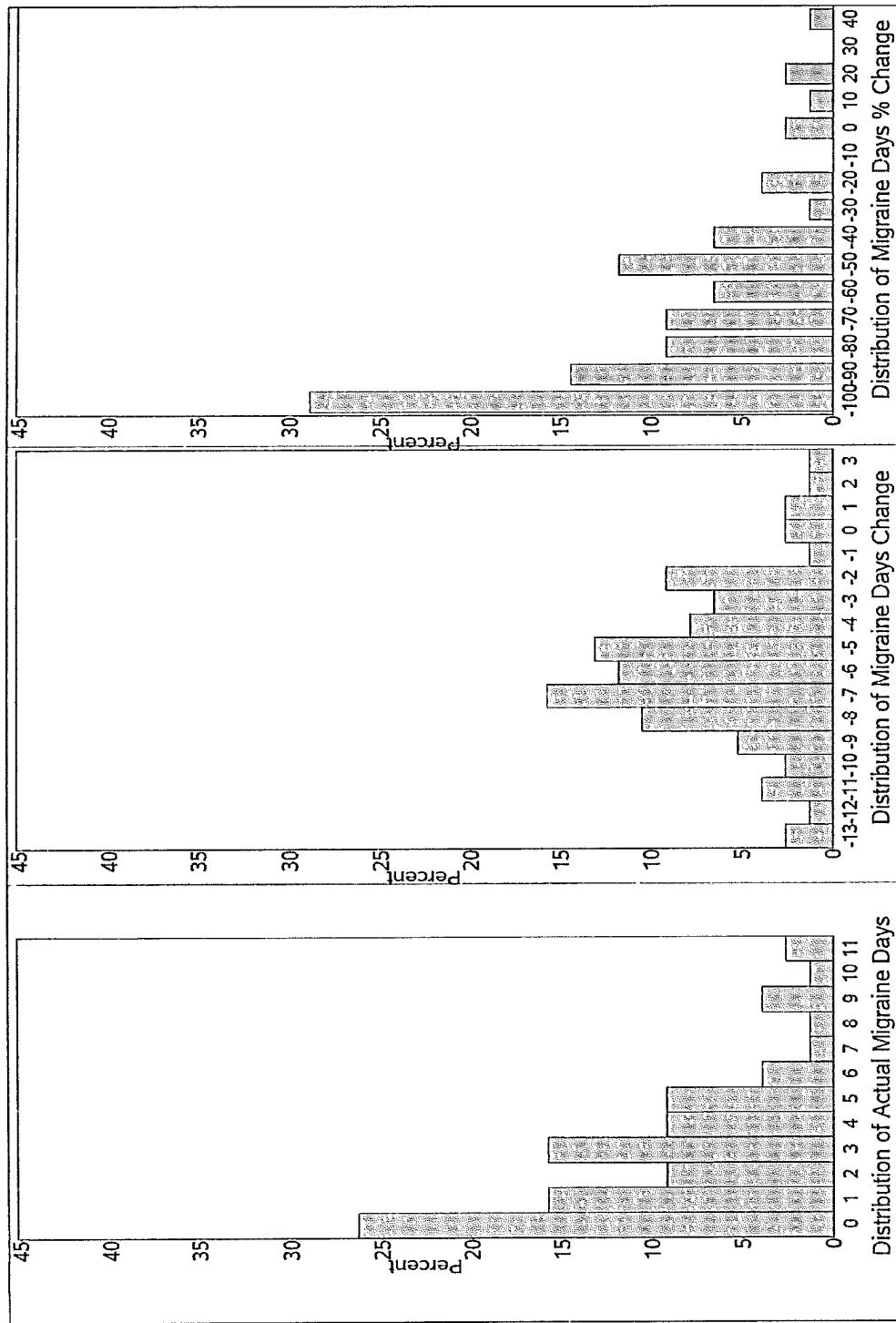
FIG. 24

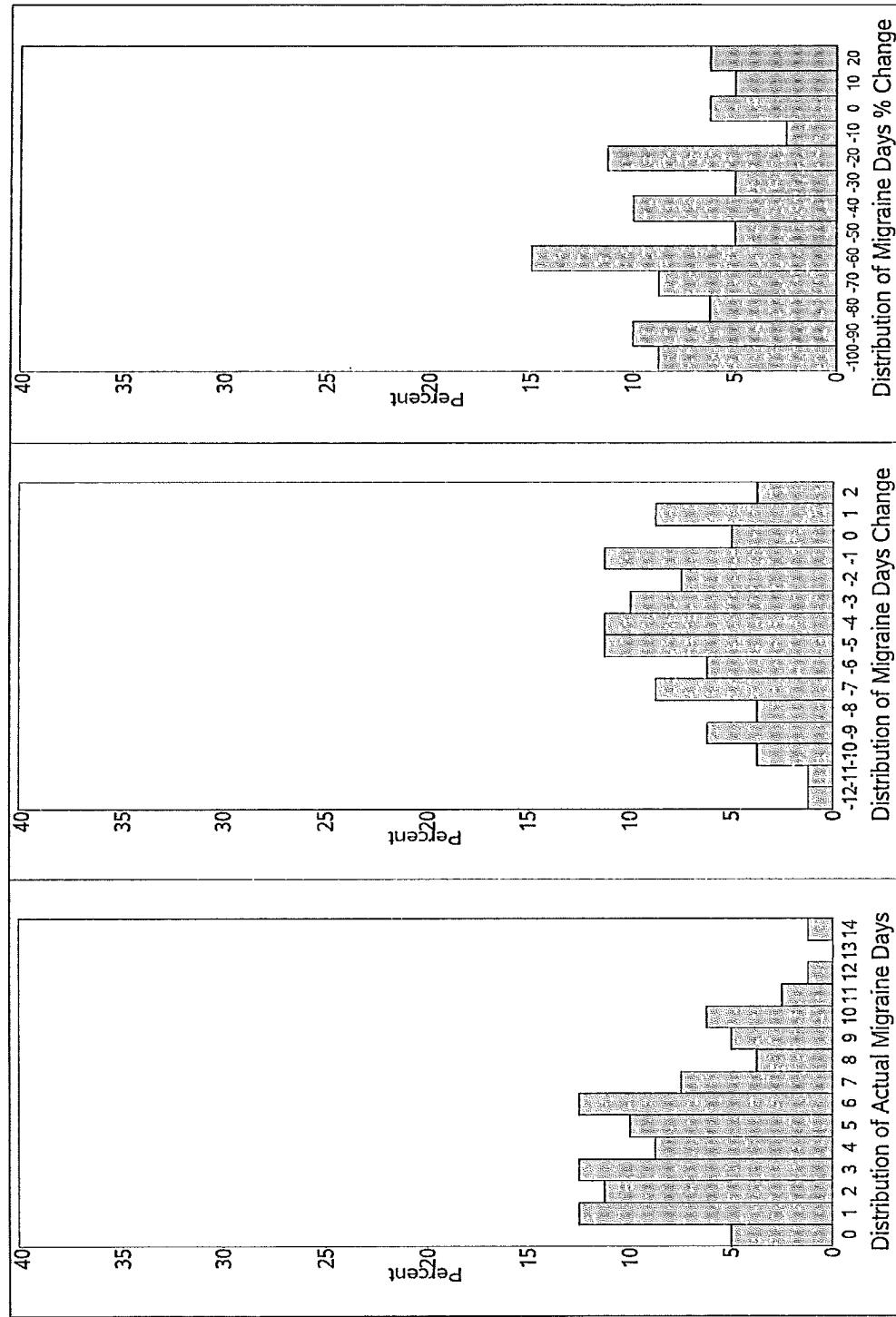
FIG. 25

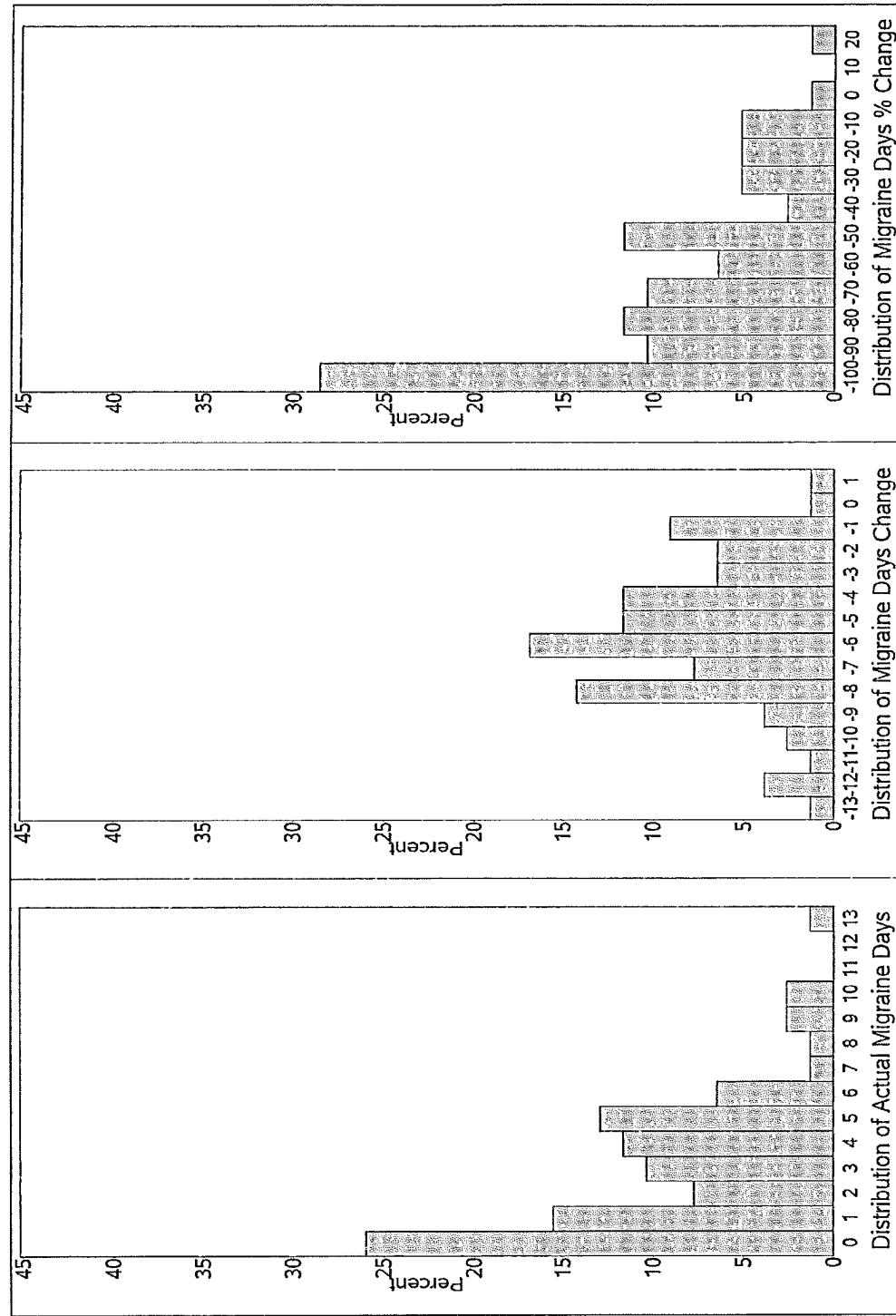
FIG. 26

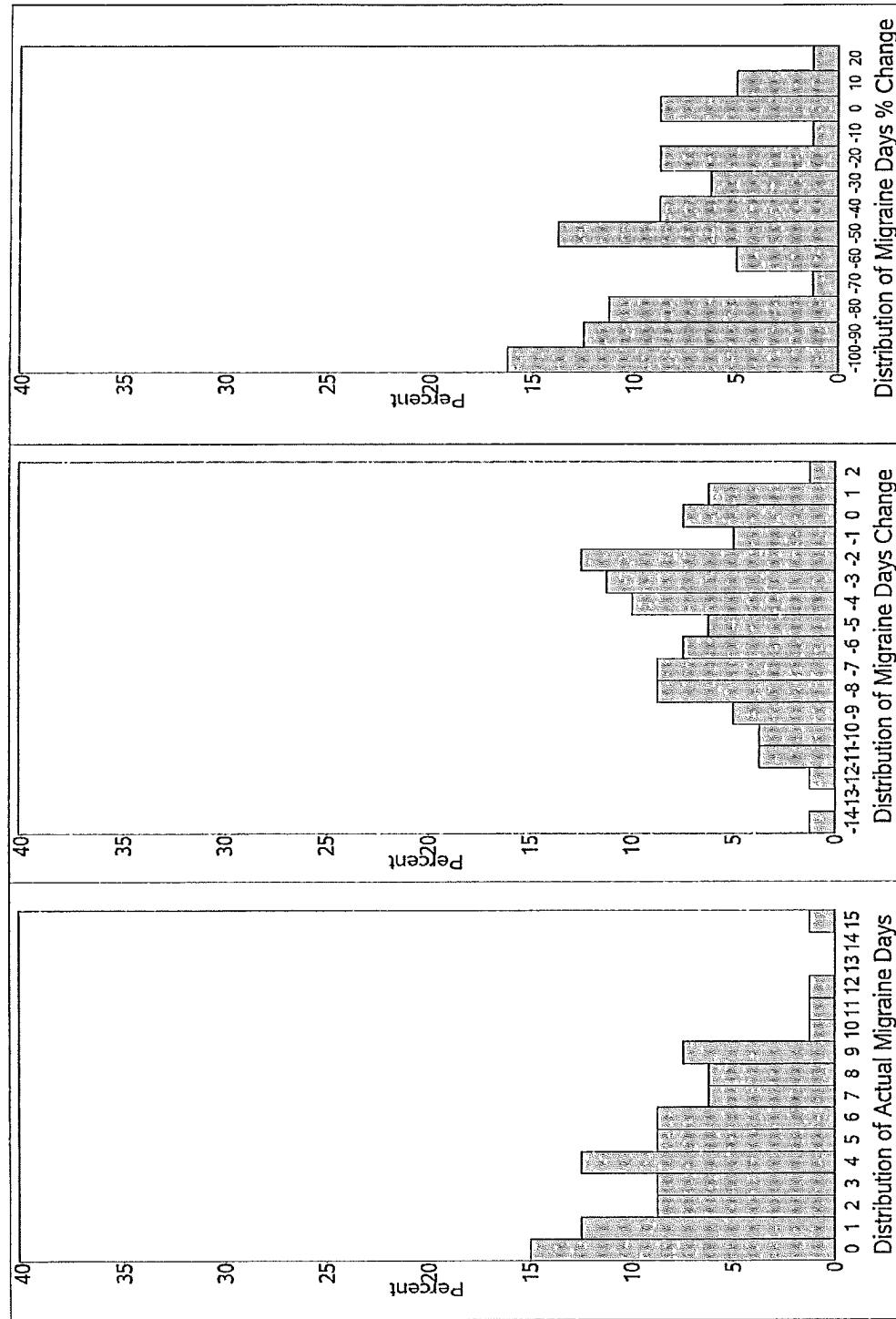
FIG. 27

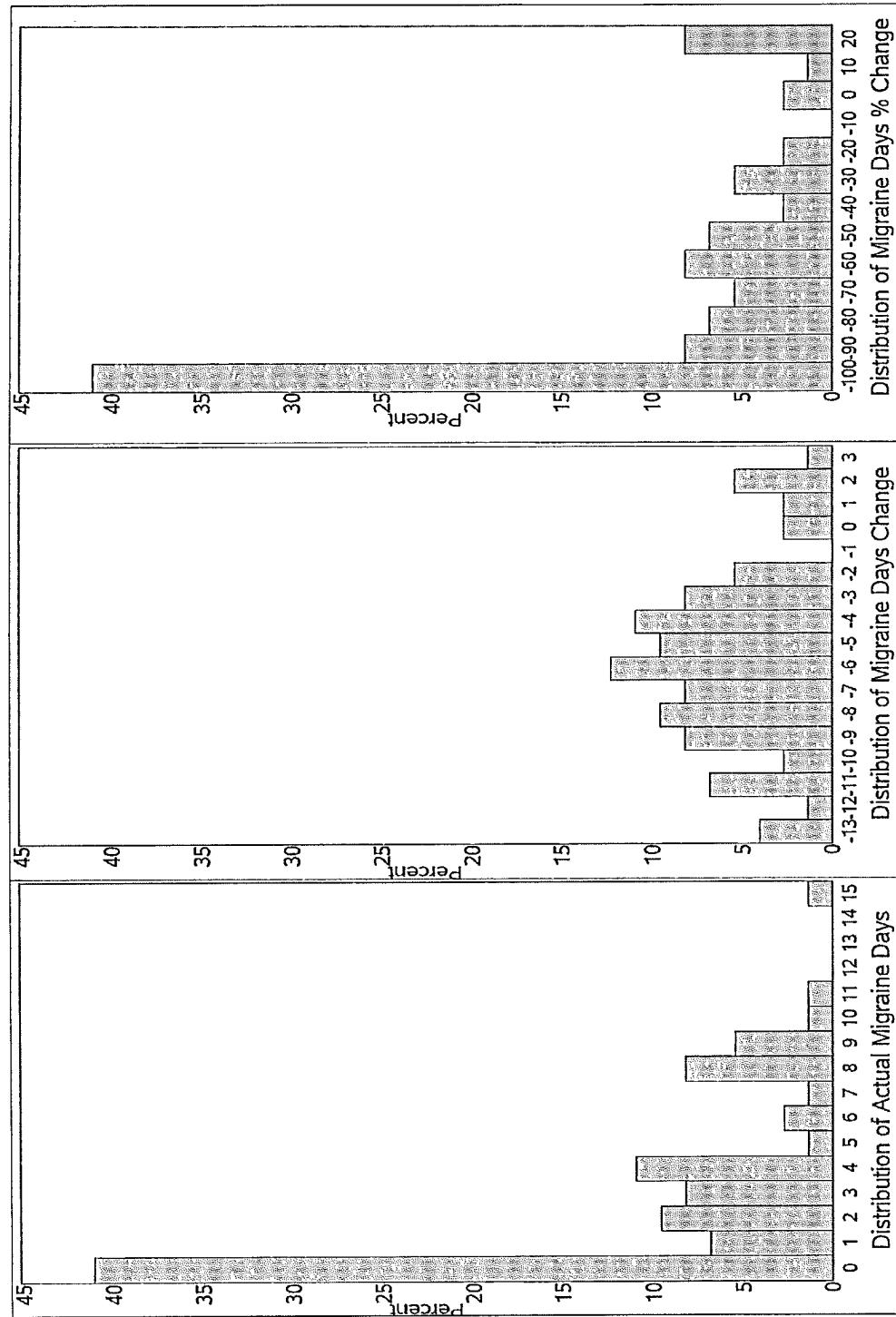
FIG. 28

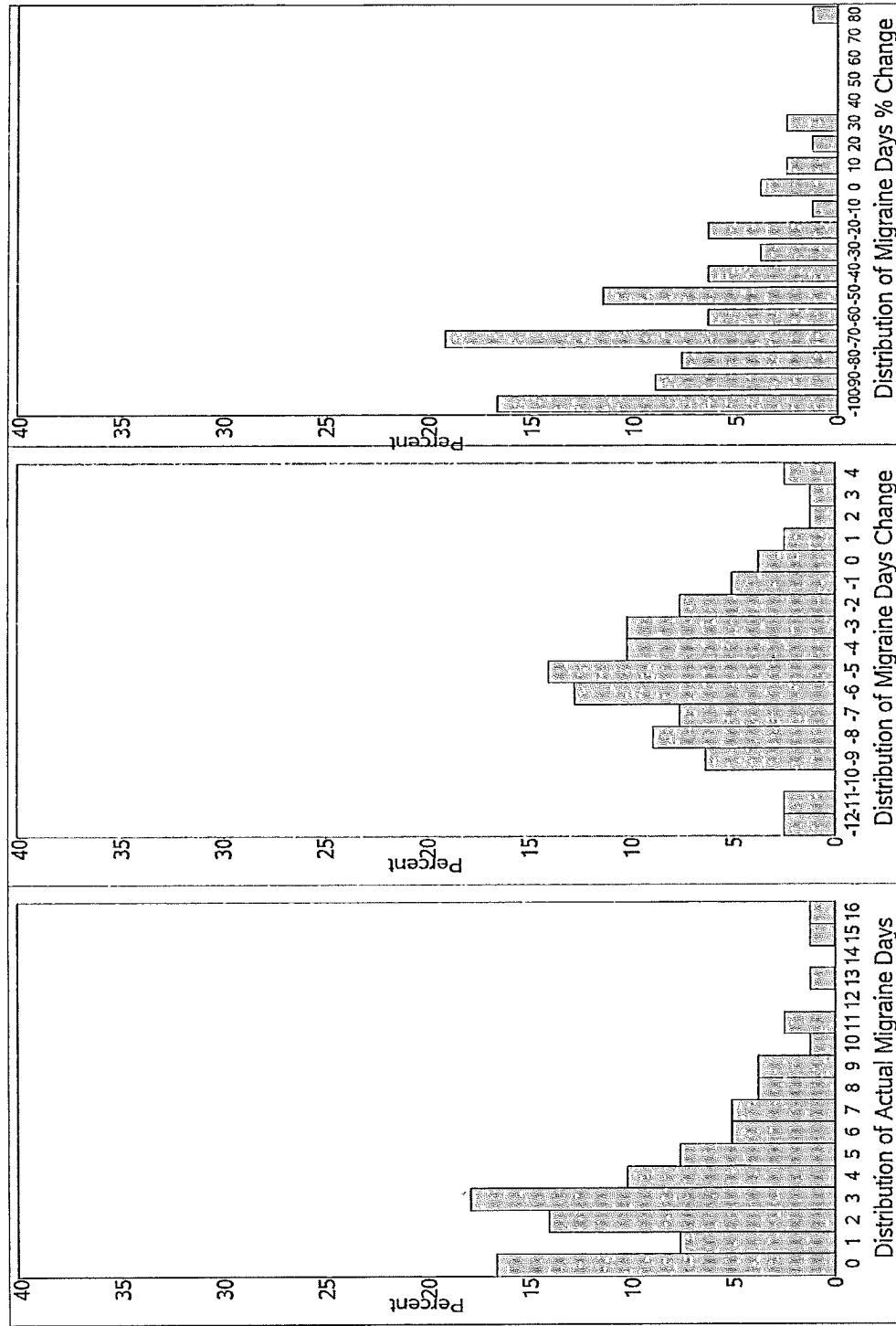
FIG. 29

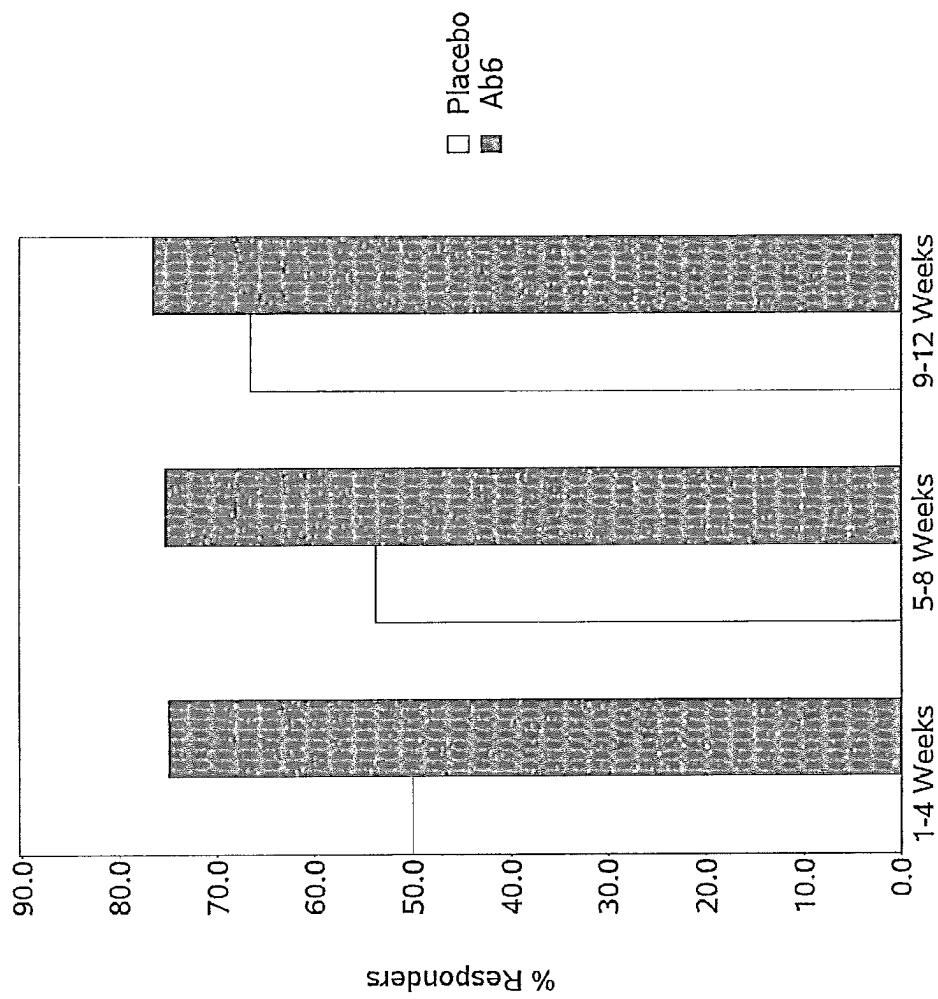
FIG. 30

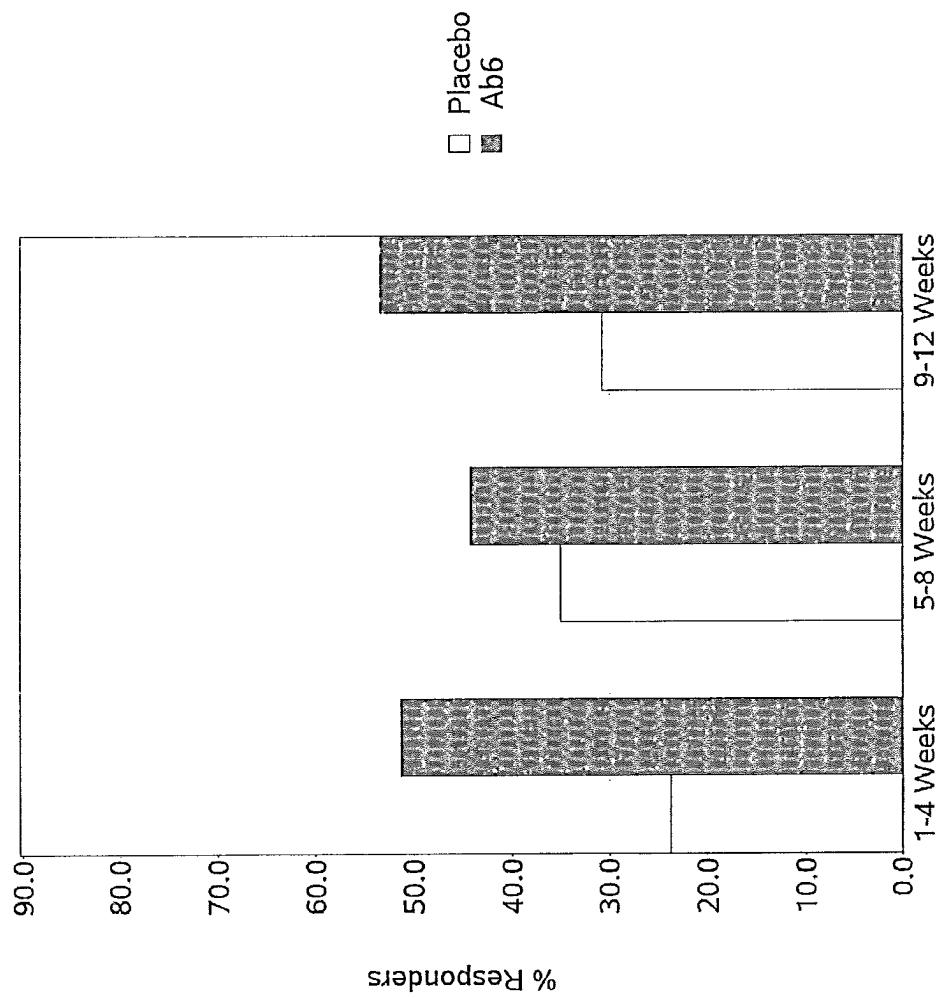
FIG. 31

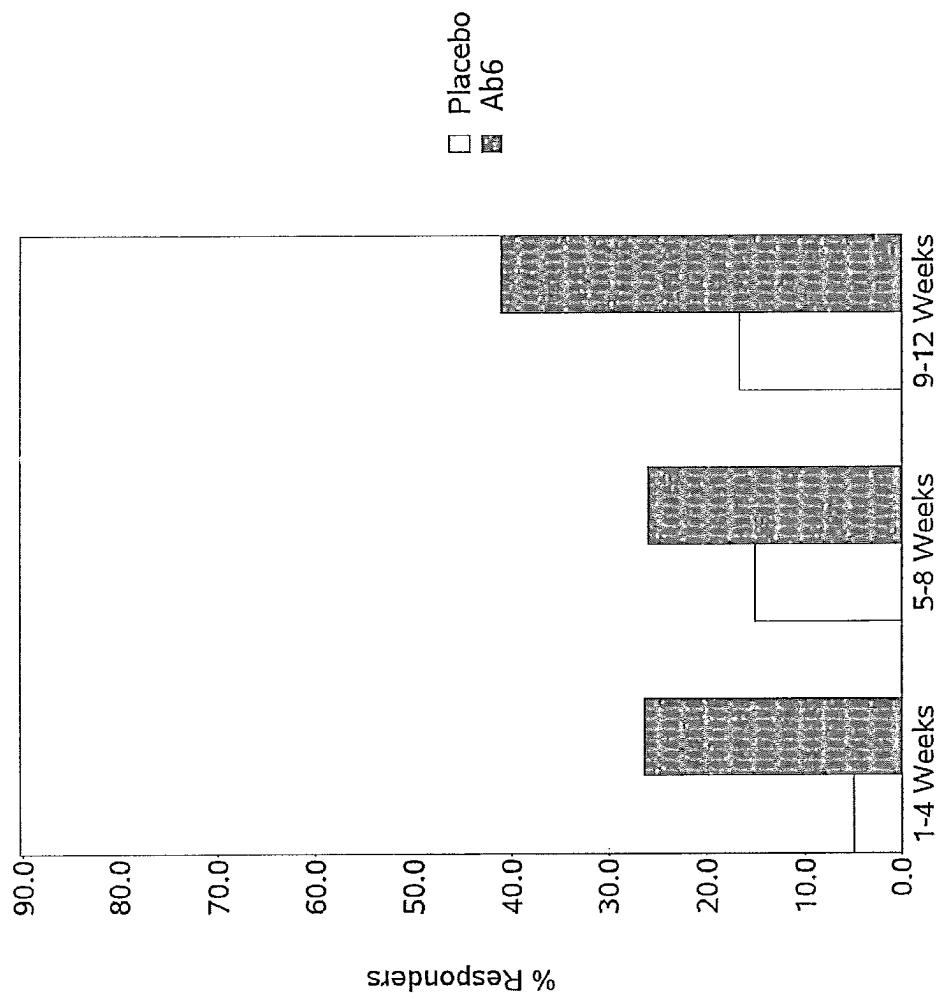
FIG. 32

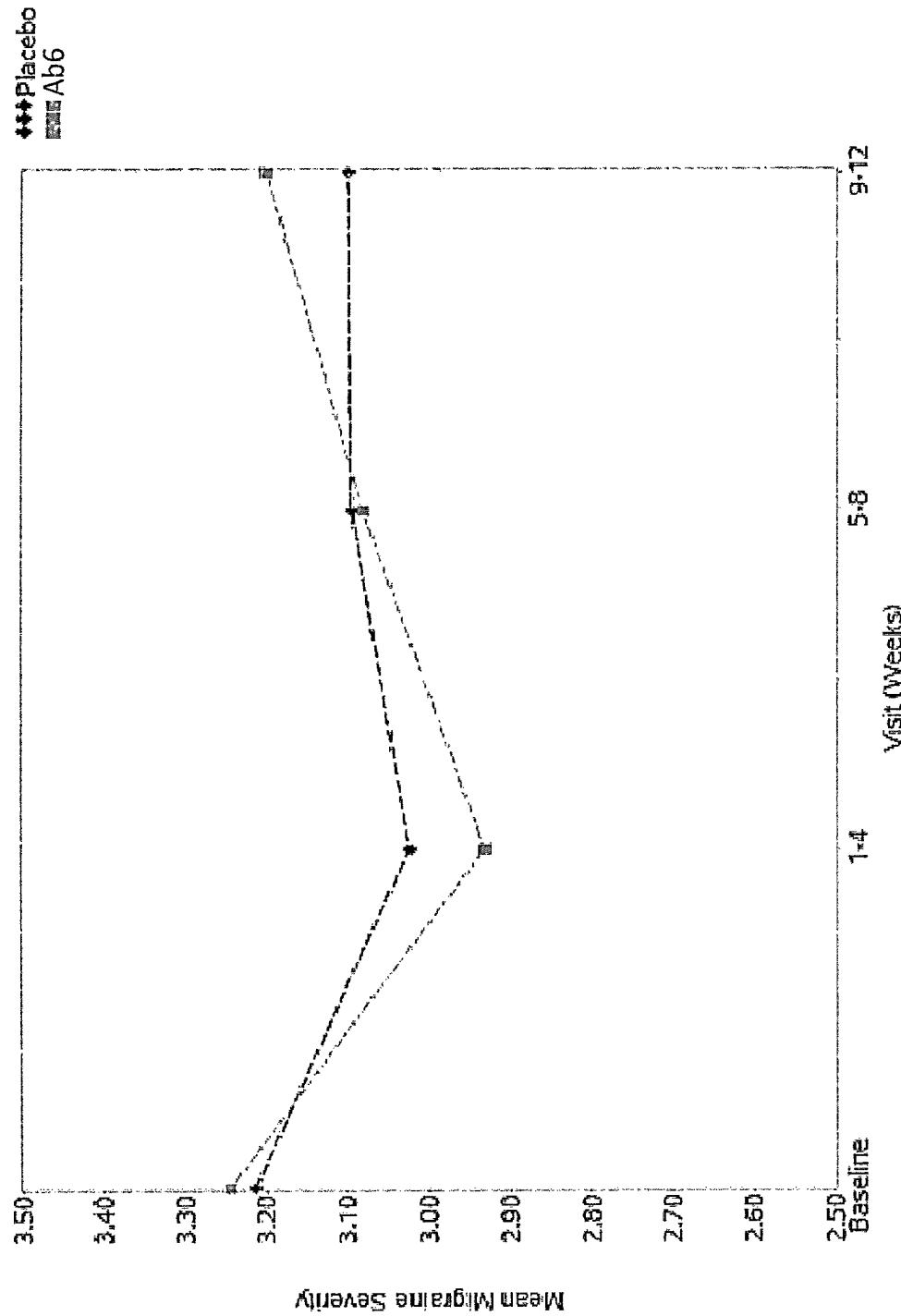
FIG. 33

FIG. 34Mean (\pm SD) Change from Baseline In Study Endpoints

Endpoint	Weeks 1-4			Weeks 5-8			Weeks 9-12		
	Placebo i.v. (n=82)	Ab6 1000mg i.v. (n=81)	Placebo i.v. (n=82)						
Migraine Days	-3.9 (3.5) ^a	-5.6 (3.3) ^b	-4.6 (3.6)	-5.6 (3.0) ^b	-4.6 (3.5)	-5.6 (4.0) ^b	-4.6 (3.5)	-5.6 (4.0) ^b	-4.6 (3.5)
Migraine Episodes	-3.0 (2.7)	-3.7 (2.4)	-3.7 (2.9)	-3.8 (2.2)	-3.7 (2.8)	-3.8 (2.6)	-3.7 (2.8)	-3.9 (2.6)	-3.7 (2.8)
Migraine Hours	-33.7 (41.8)	-58.0 (49.1)	-36.1 (45.9)	-54.4 (48.3)	-37.1 (40.0)	-54.6 (60.5)	-37.1 (40.0)	-54.6 (60.5)	-37.1 (40.0)
Average Migraine Severity ⁴	-0.16 (0.58)	-0.31 (0.58)	-0.10 (0.54)	-0.16 (0.50)	-0.08 (0.54)	-0.08 (0.54)	-0.08 (0.54)	-0.11 (0.43)	-0.08 (0.54)
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)	-5.1 (3.7)	-5.9 (3.8)	-5.1 (3.7)
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)	-7.7 (9.0)	-10.1 (10.6)	-7.7 (9.0)
MSQ RFP	19.9 (23.8)	29.3 (24.3)	25.2 (24.8)	28.8 (24.7)	22.2 (23.1)	28.5 (24.5)	22.2 (23.1)	28.5 (24.5)	22.2 (23.1)
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)	18.0 (20.5)	21.4 (23.1)	18.0 (20.5)
MSQ EEF	19.4 (27.6)	25.1 (28.3)	21.2 (25.1)	23.8 (25.8)	21.1 (25.1)	23.1 (26.8)	21.1 (25.1)	23.1 (26.8)	21.1 (25.1)

^ap<0.001; ^bp=0.03; ^cp=0.06; ^dSeverity measured on a 4 point scale with 1=mild and 4=severe

FIG. 35

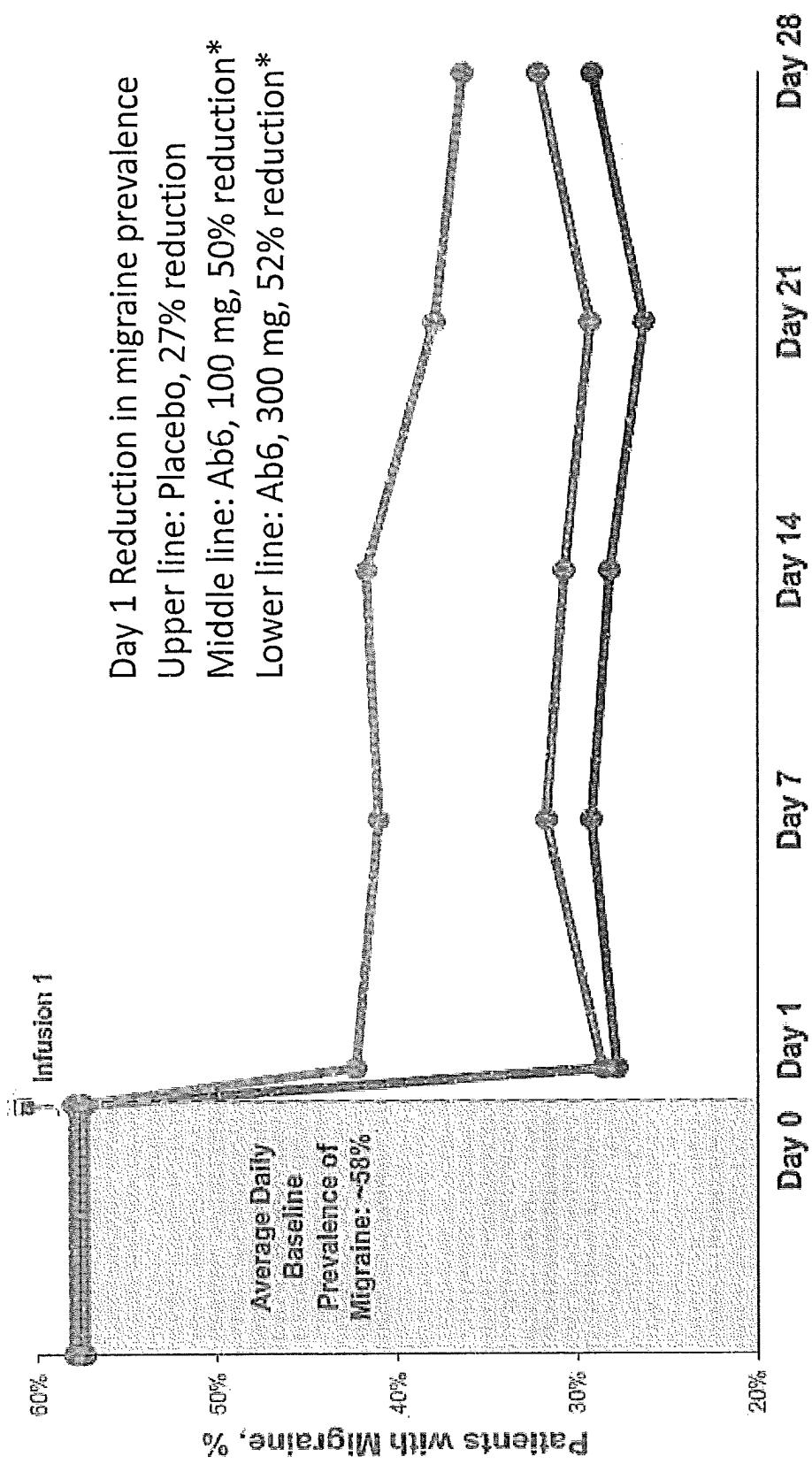


FIG. 36. Chronic migraine $\geq 50\%$ responder rates

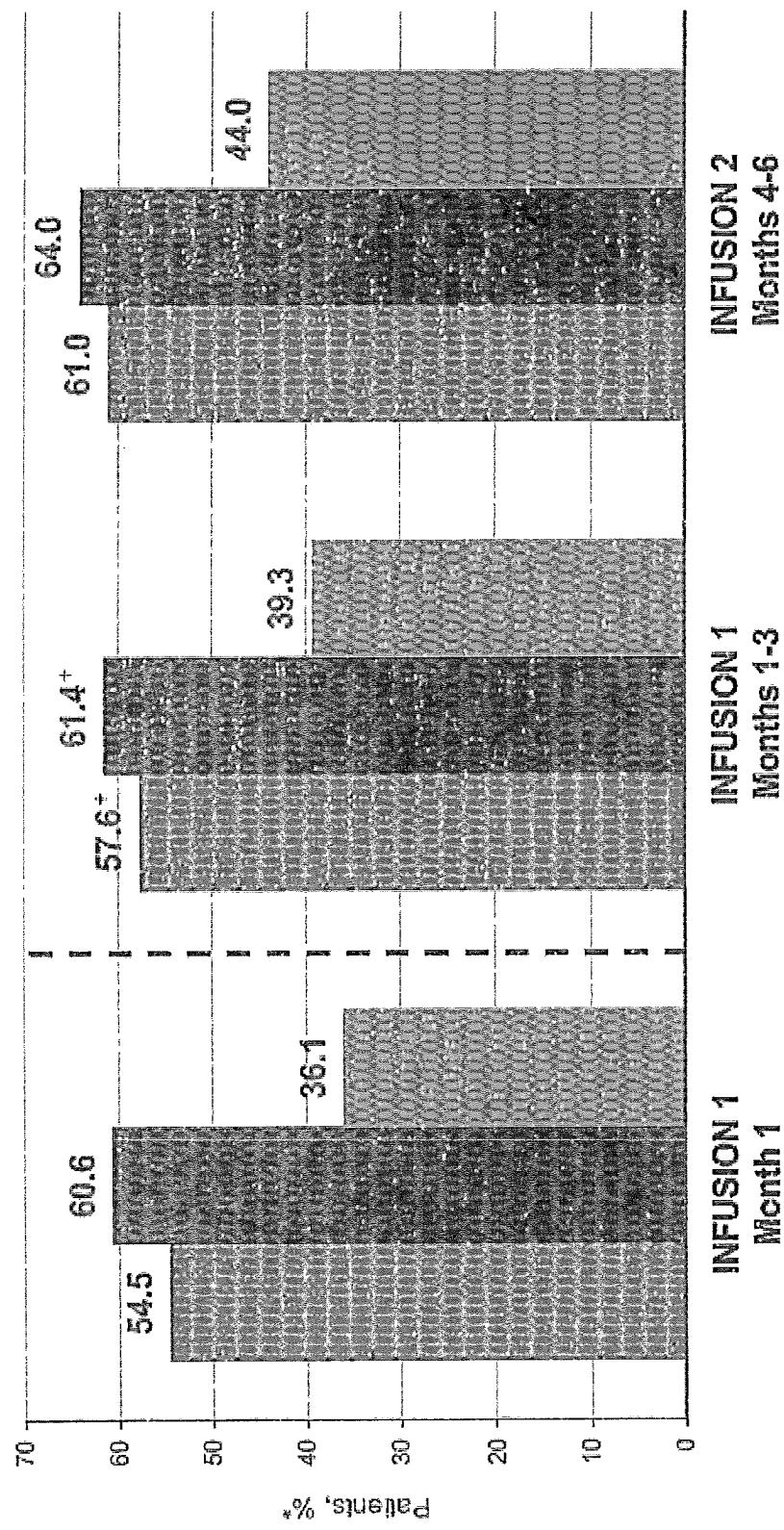


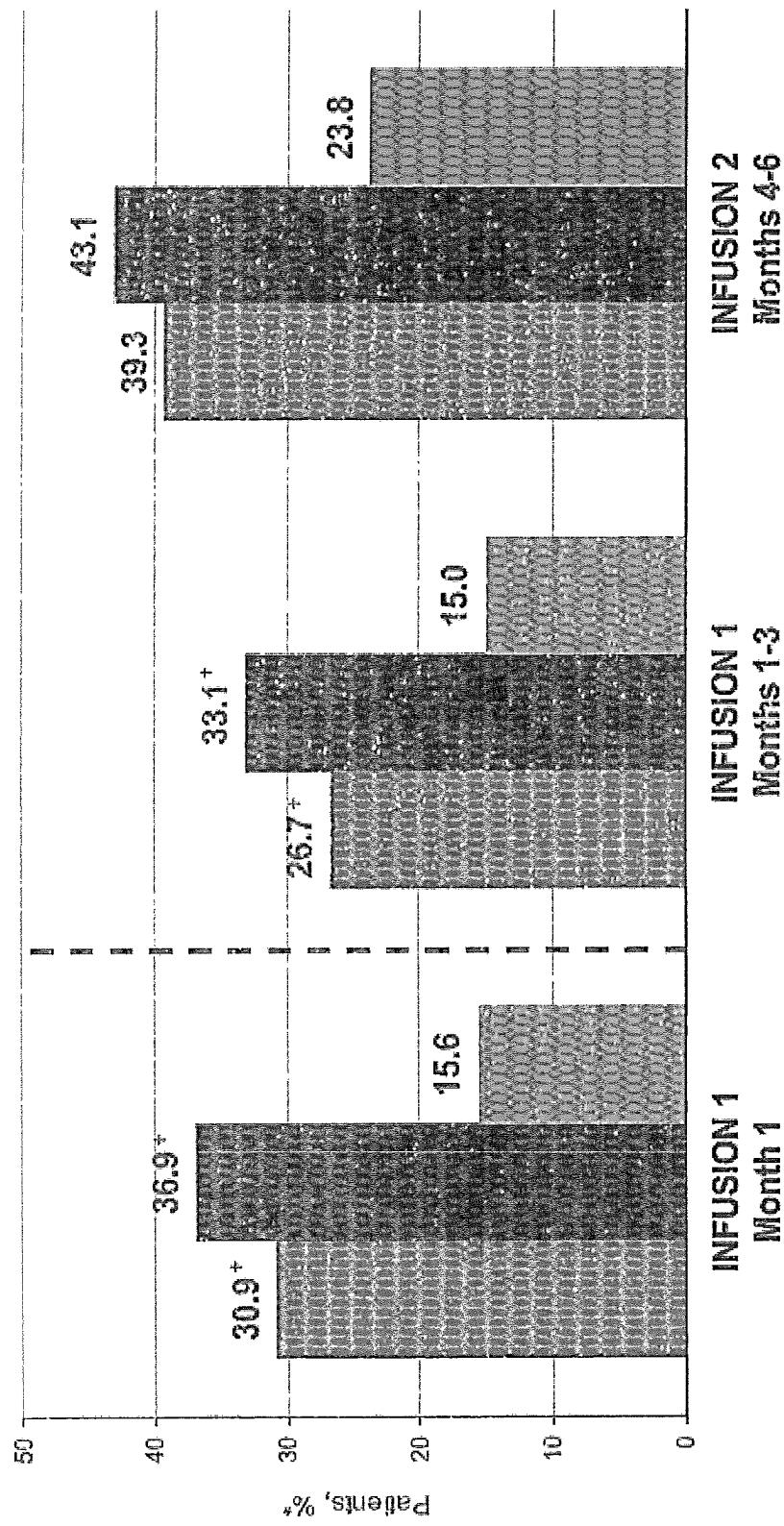
FIG. 37. Chronic migraine $\geq 75\%$ responder rates

FIG. 38. Chronic migraine 100% responder rates

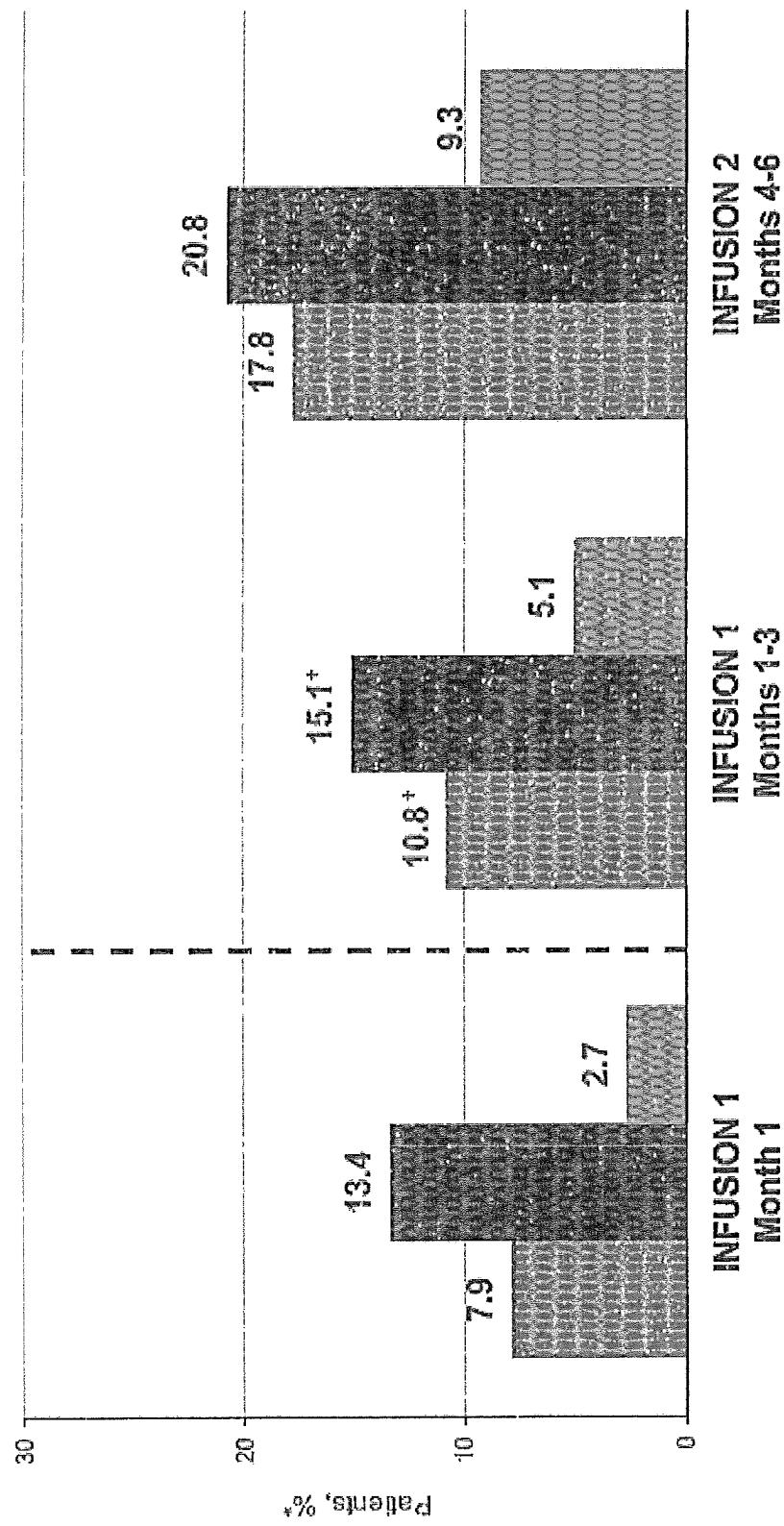


FIG. 39

	100 mg	100 mg	300 mg
Subjects, n	366	356	350
Mean age, years (SD)	39.6 (11.3)	41.0 (11.7)	41.0 (10.4)
Mean BMI, kg/m² (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

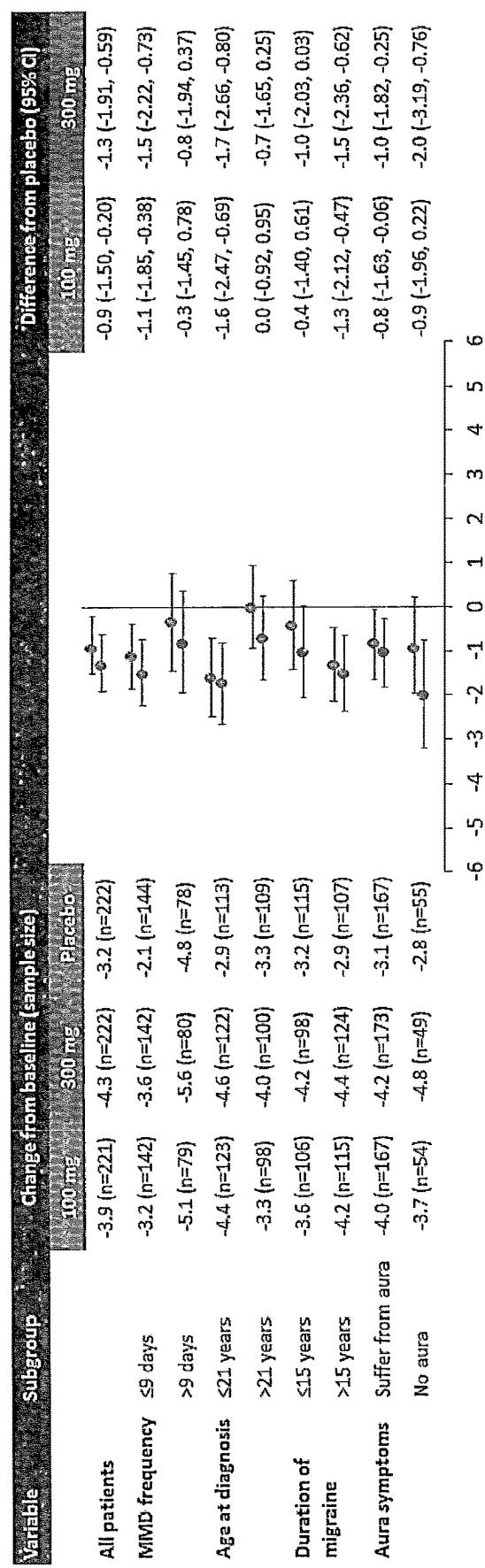


FIG. 41. Difference from placebo in change from baseline in mean migraine days (MMD) over months 1-3 by baseline subgroup

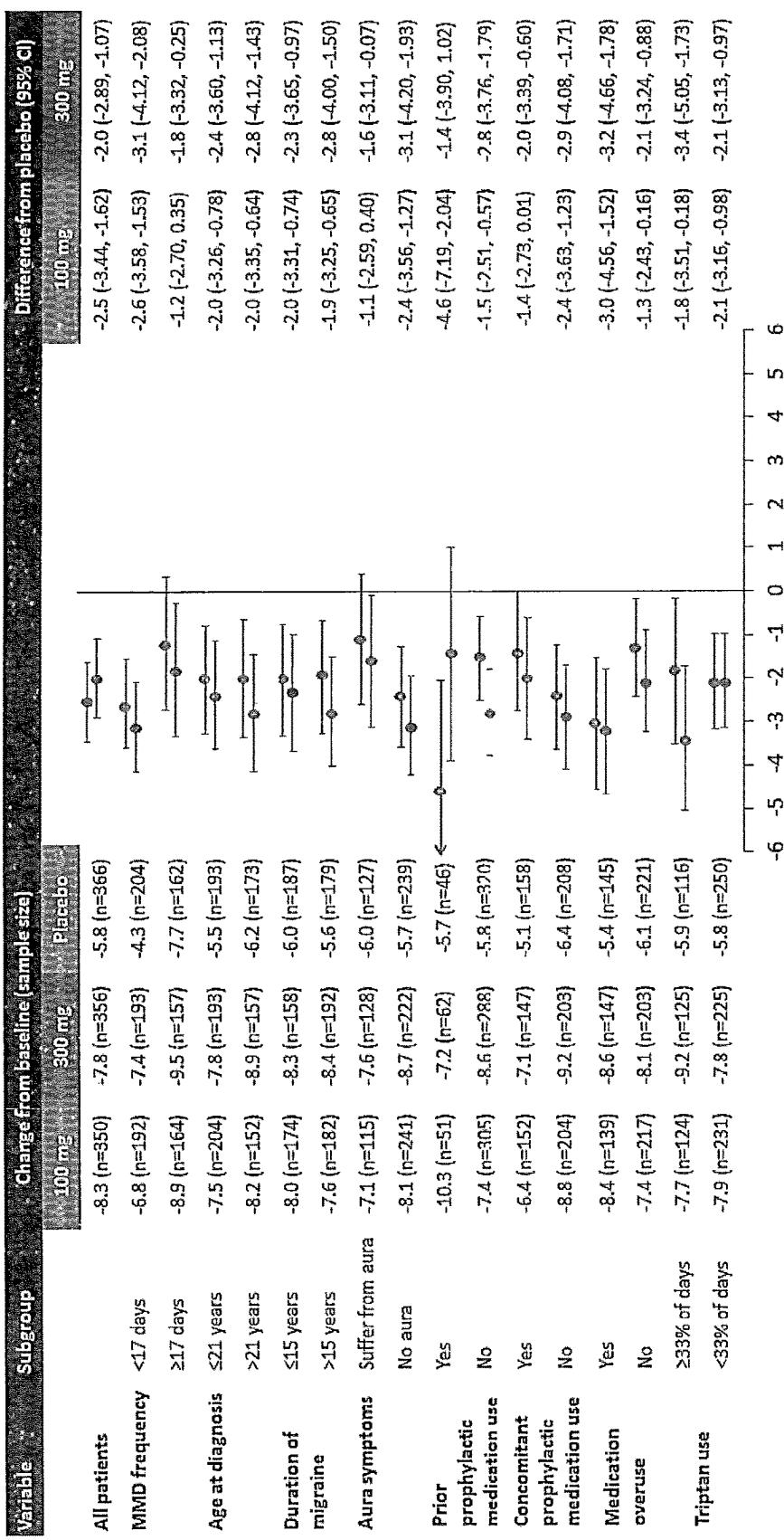


FIG. 42.

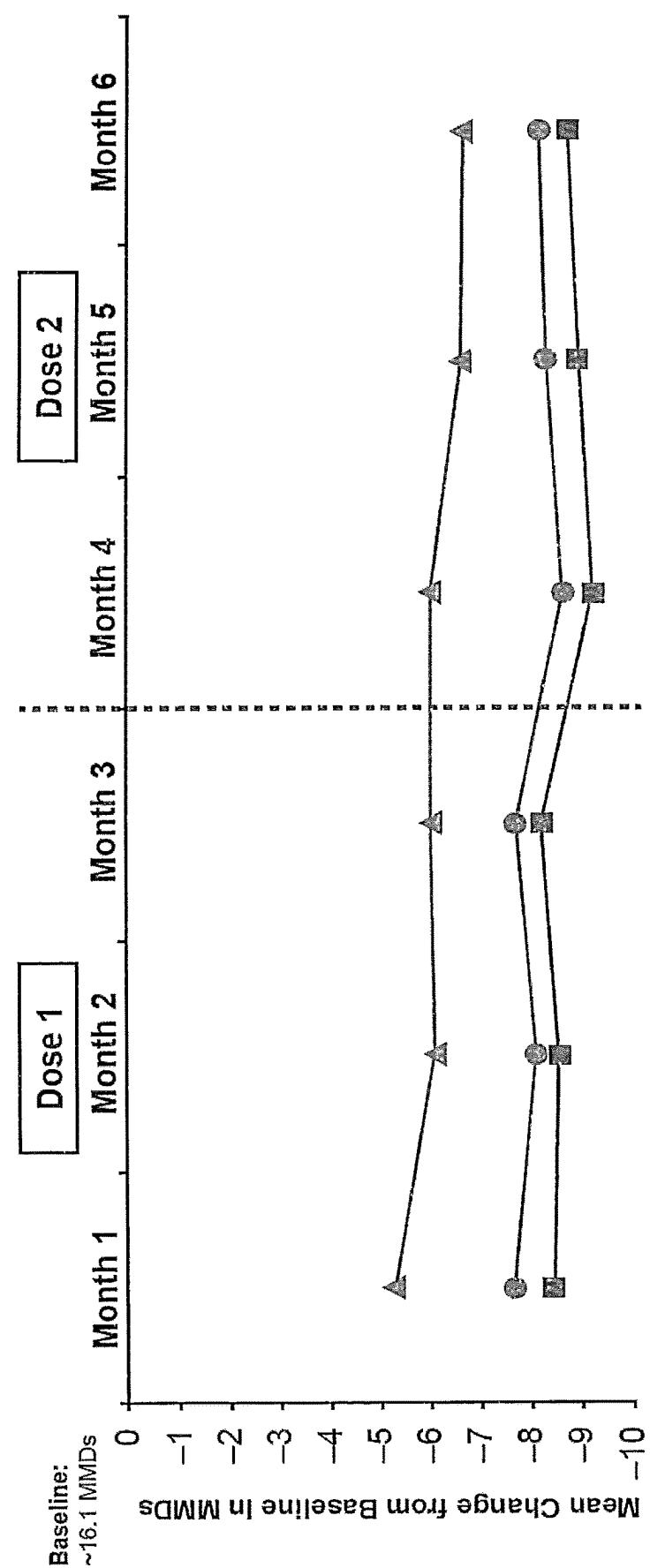


FIG. 43.

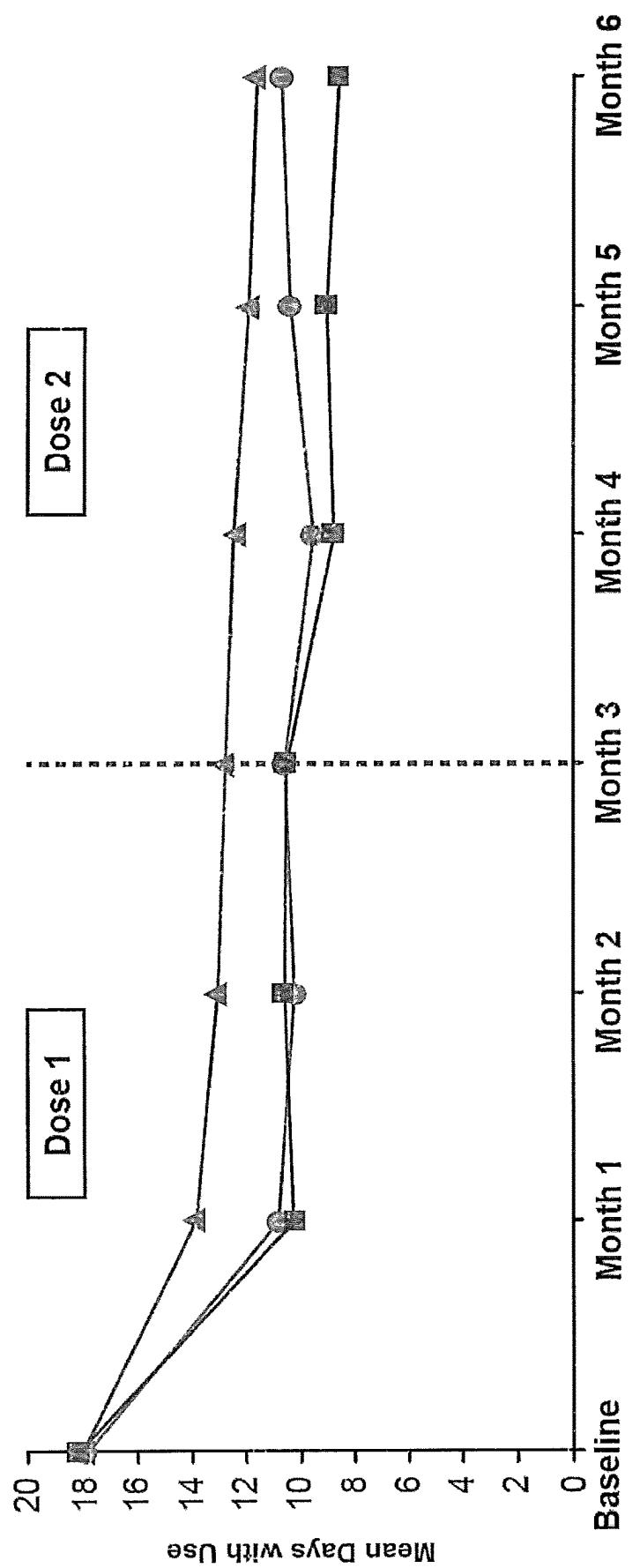


FIG. 44.

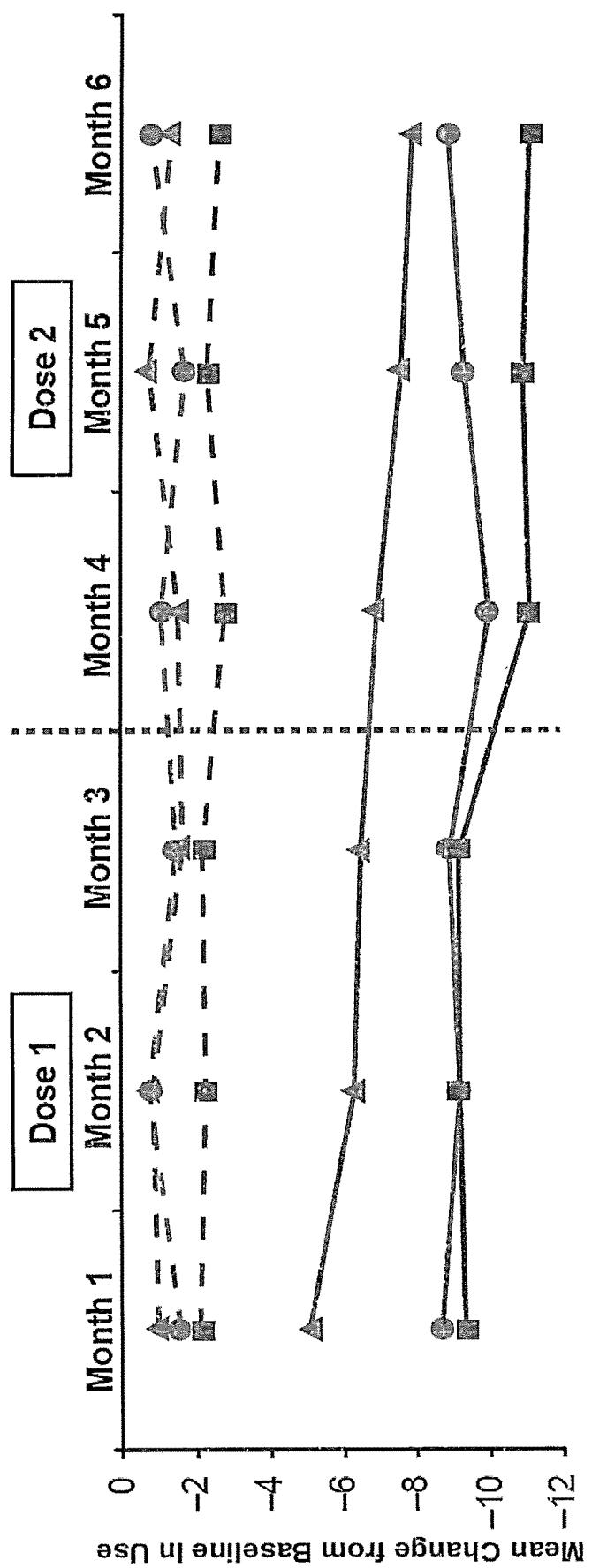


FIG. 45.

	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 (100.52)	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.

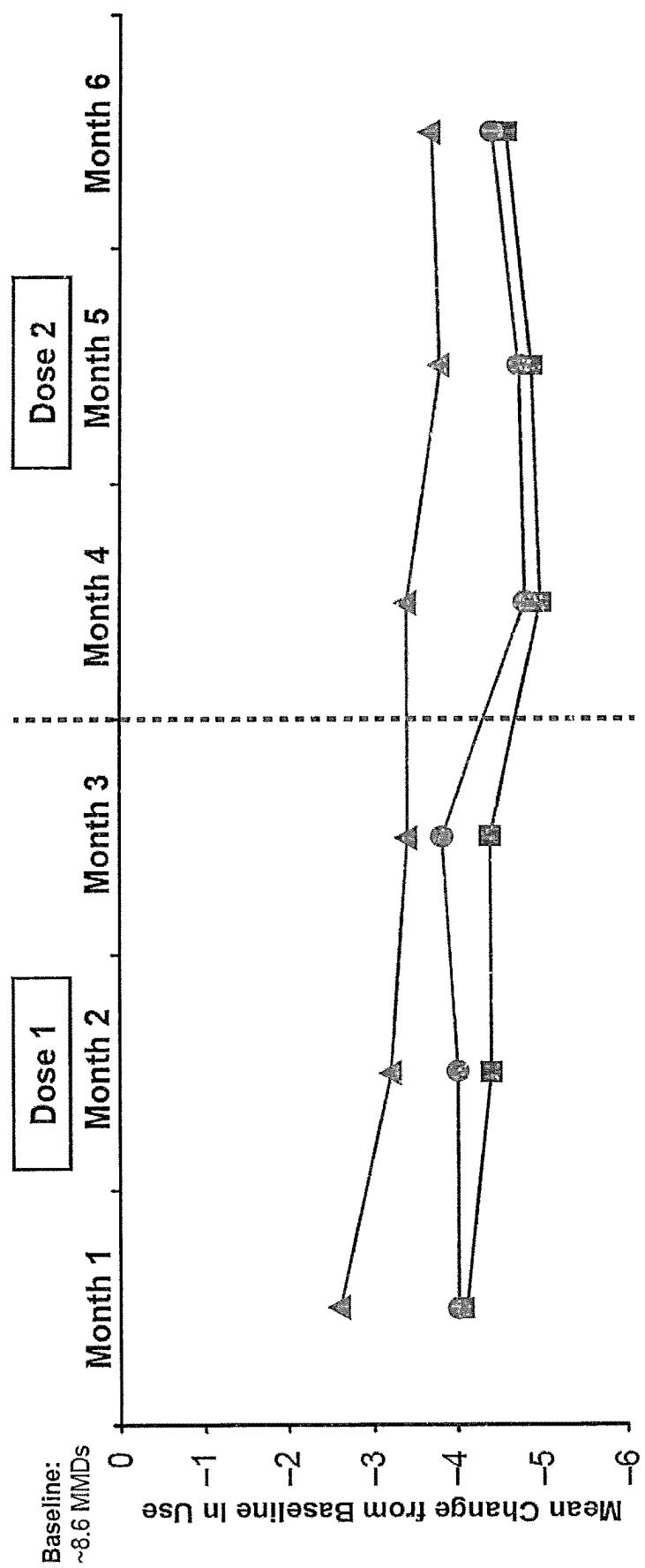


FIG. 47.

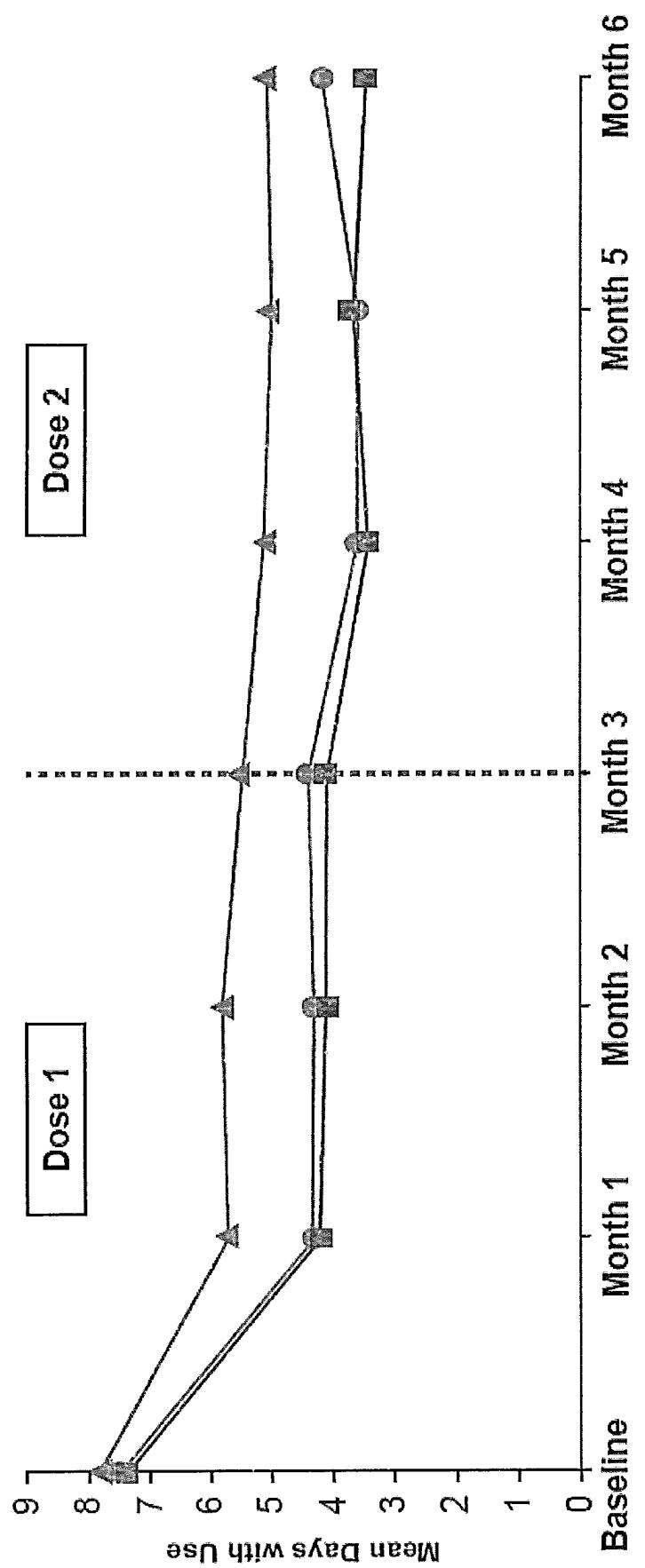


FIG. 48.

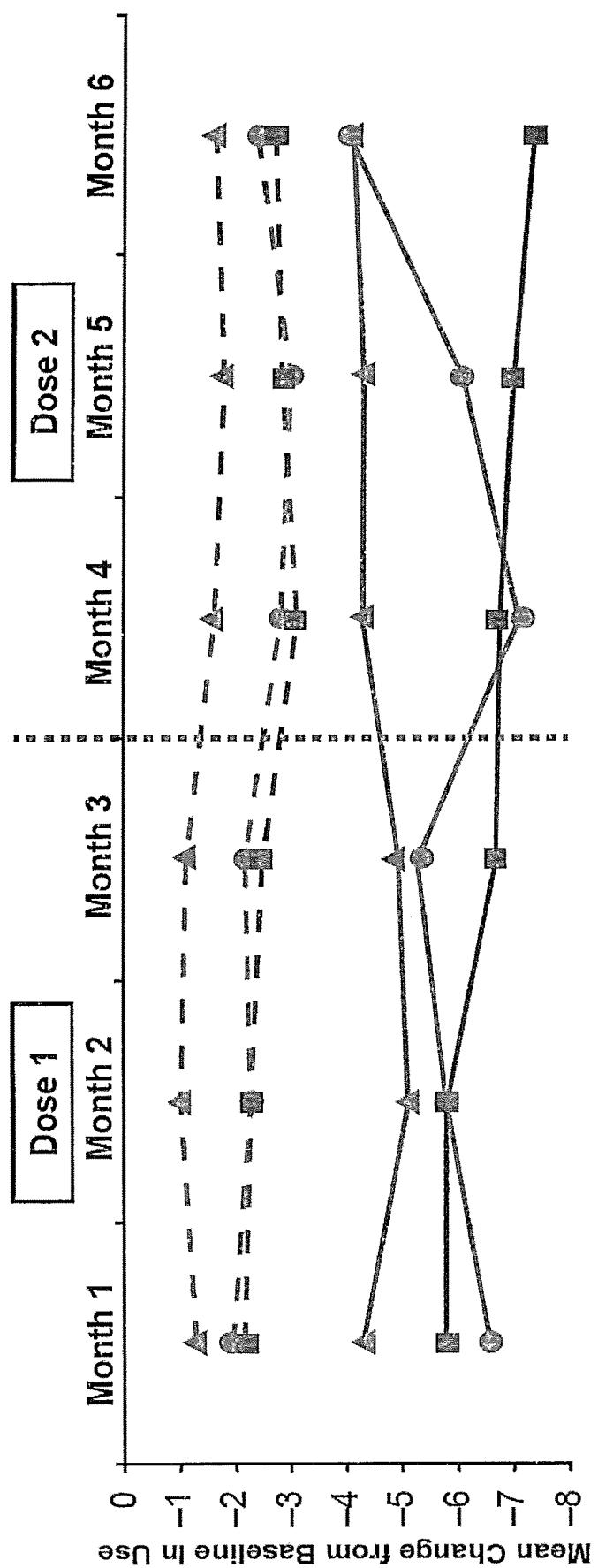
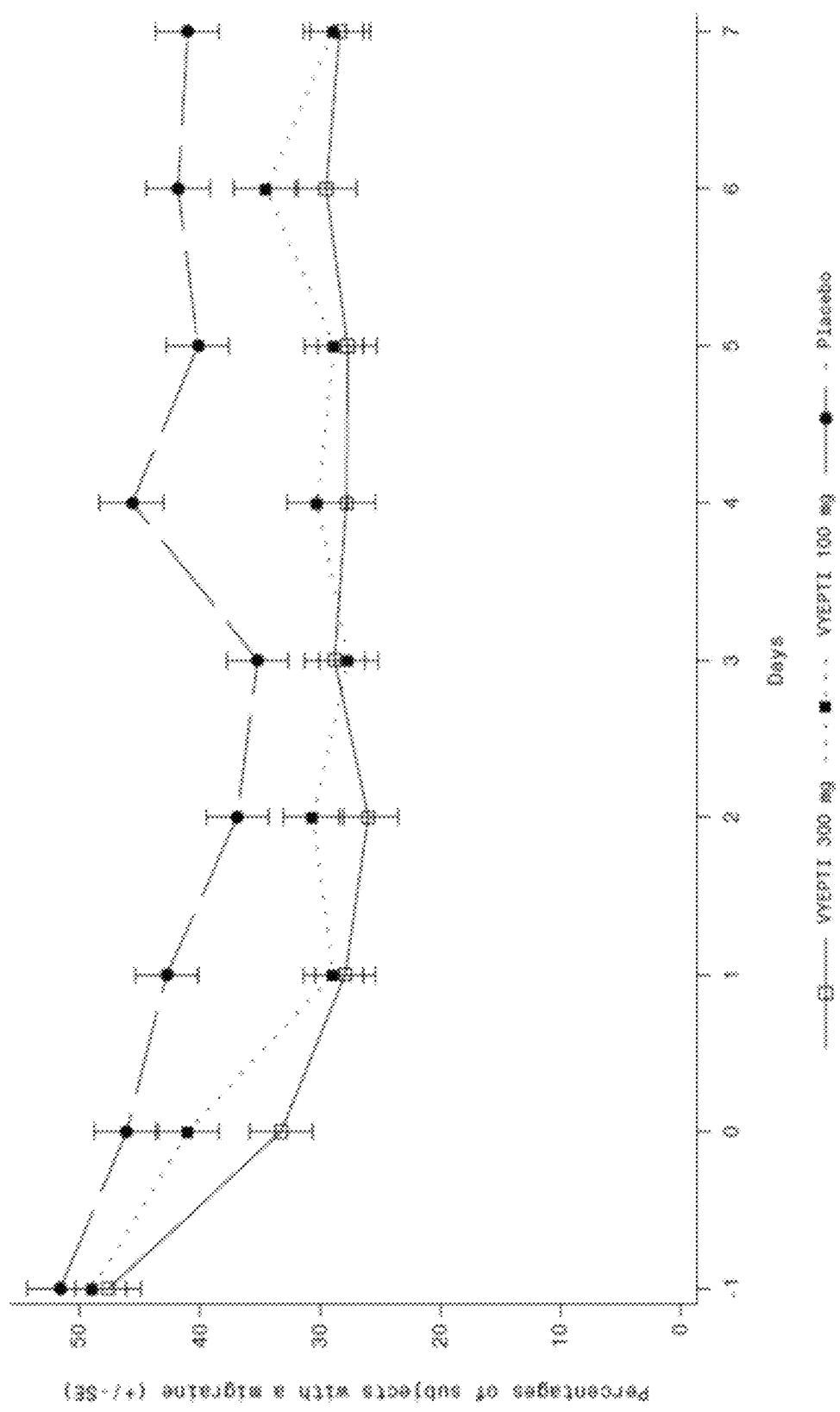


FIG. 49. Summary of Acute Medication Days by Subgroups of Episodic Migraine Patients with Baseline Acute Medication Use

	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)

FIG 50



TREATMENT OF HEADACHE USING ANTI-CGRP ANTIBODIES

RELATED APPLICATIONS

This application is a divisional of U.S. patent application Ser. No. 16/793,208, filed Feb. 18, 2020, which is a Continuation-in-part of Int'l Nat'l Appl. No. PCT/US2020/012781, 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 (1143257.009203.xml; Size: 771,623 bytes; and Date of Creation: Feb. 22, 2023) is herein incorporated by reference in its entirety.

BACKGROUND

Field

This invention pertains to methods of 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 immediate 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 vasodilation, 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

In one aspect, the present disclosure provides a method for treatment of migraine or headache in a patient in the need of immediate relief of migraine or headache symptoms or for prevention of migraine or headache in a patient in need of immediate preventative treatment of migraine or headache, comprising intravenous administering to a patient in need 100 or 300 mg of an anti-CGRP antibody comprising 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.

In some aspects, said patient may exhibit at least one headache and/or migraine symptom at the time of administration.

In some aspects, said at least one headache and/or migraine symptom may comprise one or more of pain, nausea, photophobia, or phonophobia.

In some aspects, said at least one headache and/or migraine symptom may comprise head pain.

In some aspects, the most bothersome symptom may be alleviated after said administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

In some aspects, said patient may no longer have a migraine after said administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

In some aspects, said anti-CGRP antibody may comprise 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.

In some aspects, said anti-CGRP antibody may comprise the variable light chain polypeptide of SEQ ID NO: 222.

In some aspects, said anti-CGRP antibody may comprise the variable light chain polypeptide encoded by SEQ ID NO: 232.

In some aspects, said anti-CGRP antibody may comprise the variable heavy chain polypeptide of SEQ ID NO: 202.

In some aspects, said anti-CGRP antibody may comprise the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

In some aspects, 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.

In some aspects, 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.

In some aspects, said anti-CGRP antibody may comprise the light chain polypeptide of SEQ ID NO: 221.

In some aspects, said anti-CGRP antibody may comprise the light chain polypeptide encoded by SEQ ID NO: 231.

In some aspects, said anti-CGRP antibody may comprise the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

In some aspects, said anti-CGRP antibody may comprise the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

In some aspects, 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.

In some aspects, 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.

In some aspects, said intravenous administration may be infused over a period of approximately 30 min to 60 minutes.

In some aspects, the headache or migraine symptoms may decline or may be abolished immediately after administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

In some aspects, said patient may be headache free 2 hours post-completion of infusion.

In some aspects, said 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.

In some aspects, said 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.

In some aspects, said anti-CGRP antibody may be comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

In some aspects, said formulation may comprise or may consist 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.

In some aspects, said formulation may comprise or may consist of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Poly-

sorbate 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.

In some aspects, said formulation may comprise or may consist 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.

10 In some aspects, said formulation may comprise or may consist 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.

15 In some aspects, said formulation may comprise or may consist 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.

20 In some aspects, said L-Histidine in said formulation comprises a mixture of L-Histidine and L-Histidine monohydrate. Said 3.1 mg of histidine in said formulation may comprise a mixture of L-Histidine (1 mg) and L-Histidine monohydrate (2.8 mg), which in the final formulation sums up to 3.1 mg L-histidine free base.

25 In some aspects, said formulation may be comprised in a 100 mg/mL single-dose vial wherein each mL contains 100 mg anti-CGRP antibody, L-histidine (1 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 80 (0.15 mg), sorbitol (40.5 mg), and Water for Injection, USP, at a pH of 5.8.

30 In some aspects, said formulation may be comprised in a 300 mg/mL single-dose vial wherein each mL contains 300 mg anti-CGRP antibody, L-histidine (1 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 80 (0.15 mg), sorbitol (40.5 mg), and Water for Injection, USP, at a pH of 5.8.

35 In some aspects, said migraine or headache may be selected from the group comprising acute migraine or headache, migraines with or without aura, chronic migraine, episodic migraine, chronic/episodic migraine, hemiplegic migraines, cluster headaches, migraineous neuralgia, chronic headaches, tension headaches, general headaches, headaches due to an underlying structural problem in the head or neck, sinus headaches (such as for example associated with sinusitis), and allergy-induced headaches or migraines.

40 In some aspects, said patient may exhibit a pain level of at least 2 on the VRS-4 at the time of administration of said antibody.

45 In some aspects, said patient may exhibit a pain level of at least 3 on the VRS-4 at the time of administration of said antibody.

50 In some aspects, said patient may exhibit a pain level of at most 2 on the VRS-4 immediately after administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

55 In some aspects, said patient may exhibit a pain level at most 1 on the VRS-4 immediately after administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration

within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

In some aspects, said patient may not be administered any acute migraine medication within a period of time before and after said administration, such as within 15 minutes, within 30 minutes, within 1 hour, within 2 hours, within 3 hours, within 4 hours, within 5 hours, or within 6 hours before and after said administration.

In some aspects, said acute migraine medication may comprise a triptan, an analgesic such as non-opioids or opioids/narcotics, acetaminophen, an NSAID, a combination medication, an ergotamine, or an ergot derivative.

In some aspects, said non-opioid analgesic may comprise paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic; said triptan may comprise use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, or frovatriptan; said opioid may comprise use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone; said combination medication may comprise two drugs with analgesic effects (for example, paracetamol and codeine), an analgesic and an adjuvant (for example, paracetamol and caffeine) and/or said combination-analgesics may comprise at least one opioid (such as tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital, and/or caffeine, and/or said combination-analgesic may comprise acetylsalicylic acid (aspirin), paracetamol and caffeine (EXCEDRIN®, EXCEDRIN MIGRAINE®).

In some aspects, the patient may be receiving or has received additional migraine medication.

In some aspects, the patient may receive additional migraine medication prior, concurrent or after administration of the anti-CGRP antibody.

In some aspects, the patient may receive additional migraine medication within a period of time before and after said anti-CGRP antibody administration, such as within 15 minutes, within 30 minutes, within 1 hour, within 2 hours, within 3 hours, within 4 hours, within 5 hours, or within 6 hours before and after said anti-CGRP antibody administration.

In some aspects, said additional migraine medication may comprise an acute and/or a chronic migraine medication.

In some aspects, said additional migraine medication may comprise a triptan, an analgesic such as non-opioid or opioid/narcotic, acetaminophen, an NSAID, a combination medication, an ergotamine, or an ergot derivative.

In some aspects, said non-opioid analgesic may comprise paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic; said triptan comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, or frovatriptan; said opioid comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone; said combination medication comprises two drugs with analgesic effects (for example, paracetamol and codeine), an analgesic and an adjuvant (for example, paracetamol and caffeine) and/or said combination-analgesics comprises at least one opioid (such as tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital, and/or caffeine, and/or said combination-analgesic comprises acetylsalicylic acid (aspirin), paracetamol and caffeine (EXCEDRIN®, EXCEDRIN MIGRAINE®).

In some aspects, said anti-CGRP antibody may be expressed in or obtained by expression in *Pichia pastoris*.

In some aspects, said anti-CGRP antibody may be expressed in or obtained by expression in CHO cells.

5 In some aspects, said patient may be administered 100 mg or 300 mg of said anti-CGRP antibody every three months.

In some aspects, said method may result in immediate relief of migraine or headache symptoms.

10 In some aspects, said method may result in immediate preventative treatment of migraine or headache.

The present disclosure further provides methods of immediate 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

15 antibody or antibody fragment or one or more formulations comprising said antibody or antibody fragment as disclosed herein. In some aspects, said antibody may be administered while said patient has a headache. In some aspects, said antibody administration may be initiated within 1-6 hours of

20 the onset of said headache. In some aspects, said headache may comprise migraine, e.g., episodic migraine or chronic migraine. Said headache may comprise medication overuse headache. In some aspects, said anti-CGRP antibody or antibody fragment Ab6 or a Fab fragment thereof, 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,

25 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

30 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. In some aspects, said anti-CGRP antibody may

35 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:

40 232 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. In some aspects, said anti-CGRP antibody may comprise the light chain polypeptide encoded by SEQ ID NO:

45 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567. In some aspects, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the variable light chain

50 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

55 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 aspects, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells

60 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

65 some aspects, any of the aforementioned anti-CGRP anti-

bodies 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. In some aspects, said 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. In some aspects, said 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.

In some aspects, 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. In some aspects, 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.

In some aspects, 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. In some aspects, 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. In some aspects, 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.

In some embodiments, 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.

In some aspects, 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.

In some aspects, 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.

In some aspects, 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.

In some aspects, 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.

In some aspects, 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.

In some aspects, 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.

In some aspects, 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.

In some aspects, 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, dipropanoylmorphine, diacetyldihydromorphine, acetylpropionylmorphine, desomorphine, methyldesorphine, dibenzoylmorphine, ethylmorphine, heterocodeine, buprenorphine, etorphine, hydromorphone, oxymorphone, fentanyl, alphamethylfentanyl, alfentanil, sufentanil, remifentanil, carfentanyl, ohmefentanyl, pethidine (meperidine), ketobemidone, MPPP, allylprodine, prodine, PEPAP, promedol, diphenylpropylamine, propoxyphene, dextropropoxyphene, dextromoramide, bezitramide, piritramide, among others.

In some aspects, 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.

In some aspects, 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. In some aspects, said anti-CGRP antibody Ab6, 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. In some aspects, 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. In some aspects, 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. In some aspects, 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.

In some aspects, 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. 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 comprises 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.

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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.

In other exemplary embodiments, 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.

In other exemplary embodiments, 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.

In some embodiments, the 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.

In some embodiments, the 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.

In some embodiments, the patient may have a headache when administered said first dosage.

In some embodiments, the patient may have a migraine, such as a migraine with aura, when administered said first dosage.

In some embodiments, the 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.

In some embodiments, the 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.

In some embodiments, the 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.

In some embodiments, the patient may have a reduction in the number of migraine days by at least 50% in the 12

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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.

In some embodiments, the 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.

In some embodiments, the 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.

In some embodiments, 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.

In some embodiments, 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.

In some embodiments, 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.

In some embodiments, 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.

In some embodiments, 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.

In some embodiments, 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.

In some embodiments, 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.

In some embodiments, 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.

In some embodiments, 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.

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In some embodiments, 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.

In some embodiments, 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.

In some embodiments, 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.

In some embodiments, 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.

In some embodiments, said 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.

In some embodiments, 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.

In some embodiments, said anti-CGRP antibody may be aglycosylated or if glycosylated only may contain only mannose residues.

In some embodiments, 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

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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, 5 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 10 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 15 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, 20 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 25 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, 30 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 35 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 40 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 45 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 50 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 55 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 60 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 65 single formulation or divided into different formulations

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which are administered at a frequency of approximately every 16 weeks or every 4 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 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 aforementioned methods is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 2 years.

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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.

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.

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.

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.

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.

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.

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.

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.

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

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} ($\mu\text{g/mL}$), $AUC_{0-\infty}$ ($\text{mg}^*\text{hr}/\text{mL}$), 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.

FIG. 50. Inclusion of Day -1 in the Migraine Data. Day 0 is defined as the day of the infusion. Thus, the data on Day 0 are indicative of the treatment effect post-infusion

DETAILED DESCRIPTION

Use of anti-CGRP antibodies for treatment of 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 "immediate relief" is intended to mean a relief in headache or migraine symptoms in a patient, e.g., headache or migraine symptoms associated with an acute migraine or chronic/episodic migraine or another headache or migraine condition associated with frequent headache or migraine episodes, wherein said relief of symptoms is experienced rapidly or immediately after anti-CGRP antibody treatment, e.g., relief of one or more symptoms is experienced by the patient within a short time period post-infusion with Ab6, such as within minutes or a few hours, such as within 10 minutes, 20 minutes, 30 minutes, 60 minutes, 1 hour, 2 hours or 6 hours, up to e.g. a day.

As used herein, the term "immediate preventative treatment" is intended to mean prevention of headache or migraine symptoms in a patient, e.g., prevention of headache or migraine symptoms associated with an acute migraine or chronic/episodic migraine or another headache or migraine condition. In this context, "immediate preventative treatment" refers to the prophylactic treatment of a subject who is at risk of developing migraine or headache, resulting in a

decrease in the probability that the subject will develop headache or migraine. Typically, due to a patient history of headache or migraine episodes, there is a high risk of a new headache or migraine episode in the patient. Typically the prevention of symptoms is experienced rapidly or immediately after anti-CGRP antibody treatment, e.g., prevention of one or more symptoms is experienced by the patient within a short time period post-infusion with Ab6, such as within minutes or a few hours, such as within 10 minutes, 20 minutes, 30 minutes, 60 minutes, 1 hour, 2 hours or 6 hours, up to e.g. a day.

As used herein, the terms “4-point scale” or “4 point pain scale” or “VRS” or “VRS-4” refer to the 4-point verbal rating scale (VRS) used to measure pain (VRS-4) (see “The International Classification of Headache Disorders, 3rd edition”, Cephalgia, 2018, Vol. 38(1) 1-211, at pg. 210 (“intensity of pain”)). In the VRS the patient is asked to rate the pain verbally on a 4 point scale (between 0 and 3), with 3 being severe, 2 being moderate, 1 being mild, and 0 being no pain. It may also be scored on a verbal rating scale expressed in terms of its functional consequence: 0, no pain; 1, mild pain, does not interfere with usual activities; 2, moderate pain, inhibits but does not wholly prevent usual activities; 3, severe pain, prevents all activities.

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-NH₂ (SEQ ID NO: 561), wherein the terminal phenylalanine is amidated; CGRP-beta: ACNTATCVTHR-LAGLLSRSGGMVKSNFVPTNVGSKAF-NH₂ (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 (mutiens), 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 nutri-

ents not available from complex media. Exemplary vectors and methods for transformation of yeast are described, for example, in Burke, D., Dawson, D., & Stearns, 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, nobodies, IgNAR (single-chain antibodies derived from sharks), small-modular immunopharmaceuticals (SMIPs), and antibody fragments such as Fabs, Fab', F(ab')₂ and the like. See Streltsov 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. Epub 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 animal-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. 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 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 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, 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 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 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 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 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 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 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 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 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 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 trans-

formation 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 F_c 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

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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.

"C_{max}" 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 C_{max} 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

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CGRP and possessing a variable light chain sequence comprising the sequence set forth below:

(SEQ ID NO: 222)

5 QVLTQSPSSLASAVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIY
DASTLASGVPSRSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCTNGDC
FVFGGGTKVEIKR .

10 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)

15 QVLTQSPSSLASAVGDRVTINCQASQSVYHNTYLAWYQQKPGKVPKQLIY
DASTLASGVPSRSGSGSGTDFTLTISSLQPEDVATYYCLGSYDCTNGDC
FVFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAK
20 VQWKVDNALQSGNSQESVTEQDSKDSTYLSSTTLSKADYEKHKVYACE
VTHQGLSSPVTKSFNRGEC .

25 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)

30 EVQLVESGGGLVQPGGSLRLSCAVSGIDLGSYYMNWVRQAPGKGLEWVG
IGINGATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDI
WGQGTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
35

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)

40 EVQLVESGGGLVQPGGSLRLSCAVSGIDLGSYYMNWVRQAPGKGLEWVG
IGINGATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDI
WGQGTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
45 SWNSGALTSGVHTFPAPLQSSGLYSLSSVTVPSLGTQTYICNVNHP
SNTKVDARVEPKSCDKTHTCPCCPAPELLGGPSVFLPPPKPKDTLMISRT
PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTPREEQYASTYRVVSL
50 TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMEHALHNHYTQKSLSLSPGK .

55 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:

(SEQ ID NO: 566)

60 EVQLVESGGGLVQPGGSLRLSCAVSGIDLGSYYMNWVRQAPGKGLEWVG
IGINGATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARGDI
WGQGTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT
65 SWNSGALTSGVHTFPAPLQSSGLYSLSSVTVPSLGTQTYICNVNHP

-continued

SNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
 PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVSVL
 TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE
 EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL
 YSKLTVDKSRWQQGNVFSCSVMHEALJNHYTQKSLSLSPG.

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.

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.

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.

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 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)
 TVAAPSVFIFPPSDEQLKSGTASVVCCLNNFPREAKVQWKVDNALQSGN
 SQESVTEQDSKDSTYLSSTLTSKADYEKHKVYACEVTHQGLSSPVTKS
 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)
 ASTKGPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVWSWNSGALTSGV
 HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEP
 KSCDKTHTCPPCPAPEELLGGPSVFLFPPKPDKTLMSRTPEVTCVVVDVS
 HEDPEVKFNWYVGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
 LVKGFYPSDIAVEWESNGQPENNYKTPVLDSDGSFFLYSKLTVDKSRW
 QQGNVFSCSVMHEALHNHYTQKSLSLSPKG.

(SEQ ID NO: 565)
 ASTKGPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPVTVWSWNSGALTSGV
 HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEP
 KSCDKTHTCPPCPAPEELLGGPSVFLFPPKPDKTLMSRTPEVTCVVVDVS
 HEDPEVKFNWYVGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGK
 EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
 LVKGFYPSDIAVEWESNGQPENNYKTPVLDSDGSFFLYSKLTVDKSRW
 QQGNVFSCSVMHEALHNHYTQKSLSLSPKG.

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: 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 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, 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-galactosidase and luciferase. Further exemplary fluorescent materials include, but are not limited to, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin 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, amionopterin, 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, mytotoxine (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, nobodies, 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 poly-

peptide 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 Ab 14 as ascertained by epitopic mapping using overlapping linear peptide fragments which span the full length of the native human CGRP polypeptide.

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, Ab 11, 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 aglycosylated 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 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 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 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, 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

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specificity to CGRP, may also be described by their strength of binding or their affinity for CGRP. In one embodiment of 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 (KD) of less than or equal to 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} 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, the anti-CGRP antibodies and fragments thereof bind CGRP with a dissociation constant of less than or equal to 10^{-11} M, 5×10^{-12} 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 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 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 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)
 CAAGTGCTGaccaggactccatcctccctgtcatctgttaggagacag
 agtcaccatcATTgcCAGGCCAGTCAGAGTGTATCATAACACCTACC
 TGGCCTggtatcagcagaaccaggaaagttcttaagCAActgtatctat
 GATGCATCCACTCTGGCATCTgggtccatctcggtcagtggcagtgg
 atctggacagatttactctaccatcagcagcctgcagcctgaagatg
 ttgcaacttattactgtCTGGCAGTTATGATTGACTAATGGTGATTGT
 TTGTTTcggcgaggaaaccaggaaatcaaacgt.

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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)
 CAAGTGCTGaccaggactccatcctccctgtcatctgttaggagacag
 agtcaccatcATTgcCAGGCCAGTCAGAGTGTATCATAACACCTACC
 TGGCCTggtatcagcagaaccaggaaagttcttaagCAActgtatctat
 GATGCATCCACTCTGGCATCTgggtccatctcggtcagtggcagtgg
 atctggacagatttactctaccatcagcagcctgcagcctgaagatg
 ttgcaacttattactgtCTGGCAGTTATGATTGACTAATGGTGATTGT
 TTGTTTcggcgaggaaaccaggaaatcaaacgtACGGTGGCTGC
 ACCATCTGTCTTCATCTCCGCCATCTGATGAGCAGTTGAATCTGGAA
 CTGCCTCTGTTGTGCGCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA
 GTACAGTGGAAAGGTGGATAACGCCCTCAAATCGGTAACCTCCAGGAGAG
 TGTCACAGCAGGACAGCACAGAACAGCACCTACAGCCTCAGCAGCACCC
 TGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAA
 GTCACCCATCAGGGCTGAGCTGCCGTACAAAGAGCTTCAACAGGGG
 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)
 gaggtgcagctTgtggagtctggggaggcttggtcagcctgggggtc
 cctgagactctctgtgcaGTCTctggaATCGACCTCagtggtACTACA
 TGAACTgggtccgtcaggctccaggaaagggtggagttgggtcGGAGTC
 ATTGGTATTAATGGTGCCACATACTACCGCAGCTGGCGAAAGGCcgatt
 caccatctccagagacaattccaagACCACGGTGtatcttcaaata
 gcctgagagctgaggacactgtgttatTTctgtGCTAGAGGGGACATC
 tggggccaaggggaccctcgtaaccgtTCGAGCGCCTCCACCAAGGGCCC.

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:

(SEQ ID NO: 211)
 gaggtgcagctTgtggagtctggggaggcttggtcagcctgggggtc
 cctgagactctctgtgcaGTCTctggaATCGACCTCagtggtACTACA
 TGAACTgggtccgtcaggctccaggaaagggtggagttgggtcGGAGTC
 ATTGGTATTAATGGTGCCACATACTACCGCAGCTGGCGAAAGGCcgatt
 caccatctccagagacaattccaagACCACGGTGtatcttcaaata
 gcctgagagctgaggacactgtgttatTTctgtGCTAGAGGGGACATC
 tggggccaaggggaccctcgtaaccgtTCGAGCGCCTCCACCAAGGGCCC
 ATCGGTCTCCCCCTGGCACCCCTCCACCAAGGGCAG.

- continued

CGGCCCTGGGCTGCCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG
 TCGTGGAACTCAGGCGCCCTGACCAGCGCGTGCACACCTTCCCGCTGT
 CCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTACCGTGCCT
 CCAGCAGCTGGCACCCAGACCTACATCTGAAACGTGAATACAAGCCC
 AGCAACACCAAGGTGGACGGAGAGTTGAGCCAAATCTTGTGACAAAAC
 TCACACATGCCAACCGTGCCTGACCTGAACTCCCTGGGGGACCGTCAG
 TCTTCCTTCCCCCAAACCCAAGGACACCCCATGATCTCCCgGACC
 CCTGAGGTACATGCGTGGTGGAGCTGAGCCACGAGACCCCTGAGGT
 CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAA
 AGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTACGGCCTC
 ACCGTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTCAAGGT
 CTCCAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCAAAGCCA
 AAGGGCAGCCCCAGAACCACAGGTGTACACCTGCCCCATCCGGGAG
 GAGATGACCAAGAACCGAGTCAGCCTGACCTGGTCAAGGCTTCTA
 TCCCAGCGACATGCCGTGGAGTGGAGAGCAATGGCAGCCGAGAACAA
 ACTACAAGACCAAGCCTCCGTGTGGACTCCGACGGCTCTTCTCC
 TACAGCAAGCTACCGTGGACAAGAGCAGGTGGCAGCAGGGAACGTCTT
 CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACCGCAGAAGA
 GCCTCTCCCTGTCCTGGTAAATGA.

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:

(SEQ ID NO: 567)

gaggtgcagctTgtggagtctggggaggcttggccagcctgggggtc
 cctgagactctctgtgcaGTCTctggaATCGACCTCAGtGGCTACTACA
 TGAACTgggtccgtcaggctcaggaaagggctggagtggtttcGGAGTC
 ATTGGTATTAATGGTGCACATACAGCGAGCTGGCGAAAGGCcgatt
 caccatctccagagacaattccaaagACCACGGTGtatcttcaaata
 gacca
 gcctgagagctgaggacactgtgttatTTctgtGCTAGAGGGACATC
 tggggccaaggaccctcgtaccgtcTCGAGCGCCTCCACCAAGGGCCC
 ATCGGTCTTCCCCCTGGCAcCCTCCTCCAGACGGCTCTGGGGCACAG
 CGGCCCTGGGCTGCCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG
 TCGTGGAACTCAGGCGCCCTGACCAGCGCGTGCACACCTTCCCGCTGT
 CCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTACCGTGCCT
 CCAGCAGCTGGCACCCAGACCTACATCTGAAACGTGAATACAAGCCC
 AGCAACACCAAGGTGGACGGAGAGTTGAGCCAAATCTTGTGACAAAAC
 TCACACATGCCAACCGTGCCTGACCTGAACTCCCTGGGGGACCGTCAG
 TCTTCCTTCCCCCAAACCCAAGGACACCCCATGATCTCCCgGACC
 CCTGAGGTACATGCGTGGTGGAGCTGAGCCACGAGACCCCTGAGGT
 CAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAA

- continued

AGCCGGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTC
 ACCGTCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTCAAGGT
 5 CTCCAACAAAGCCCTCCAGCCCCATCGAGAAAACCATCTCAAAGCCA
 AAGGGCAGCCCCAGAACCACAGGTGTACACCTGCCCCATCCGGGAG
 GAGATGACCAAGAACCGAGTCAGCCTGACCTGGTCAAAGGCTTCTA
 10 TCCCAGCGACATGCCGTGGAGTGGAGAGCAATGGCAGCCGAGAACAA
 ACTACAAGACCAAGCCTCCGTGTGGACTCCGACGGCTCTTCTCC
 TACAGCAAGCTACCGTGGACAAGAGCAGGTGGCAGCAGGGAACGTCTT
 15 CTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGA
 GCCTCTCCCTGTCCTGGTTGA.

In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to 20 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 40 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.

10 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 20 the genus *Pichia*.

Methods of Producing Antibodies and Fragments Thereof

25 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 30 thereof in mammalian cells, e.g., CHO cells are further well known in the art.

35 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 40 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); Boulian, G. L. et al., *Nature*, 312:643-46 (1984), the disclosures of each of which are herein incorporated by 45 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 50 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); Verhoeven, M. et al, *Science*, 239:1534-36 (1988), the disclosures of each of which are 55 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; phenylheptylamines; phenylpiperidines; morphinans; and benzomorphans, all of which are within the scope of the term. Exemplary opioid analgesics include codeine, dihydrocodeine, 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 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 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 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 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 pathophysiological 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 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 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 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 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 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 0.1% 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 polypeptides 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

S1. Use of an anti-CGRP antibody for the manufacture of a medicament for treating migraine or headache in a patient in the need of immediate relief of migraine or headache symptoms or for prevention of migraine or headache in a patient in need of immediate preventative treatment of migraine or headache, wherein said medicament is for intravenous infusion in a dosage of 100 or 300 mg of said anti-CGRP antibody, 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.

S2. Use of the anti-CGRP antibody of embodiment S1, wherein said medicament is for use in a patient that patient exhibits at least one headache and/or migraine symptom at the time of administration.

S3. Use of the anti-CGRP antibody of embodiment S2, wherein said at least one headache and/or migraine symptom comprises one or more of pain, nausea, photophobia, or phonophobia.

S4. Use of the anti-CGRP antibody of embodiment S3, wherein said pain is head pain.

S5. Use of the anti-CGRP antibody of any one of embodiments S2-S4, wherein the most bothersome symptom is alleviated after said administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

S6. Use of the anti-CGRP antibody of any one of embodiments S2-S5, wherein said patient no longer has a migraine after said administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

S7. 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.

S8. 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.

S9. 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.

S10. 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.

S11. 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.

S12. 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.

S13. 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.

S14. 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.

S15. 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.

S16. 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.

S17. 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.

S18. 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.

S19. 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.

S20. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said intravenous administration is infused over a period of approximately 30 min to 60 minutes.

S21. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the headache or migraine symptoms decline or are abolished immediately after administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

S22. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient is headache free 2 hours post-completion of infusion.

S23. 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

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anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

S24. Use of the anti-CGRP antibody of any one of embodiments S1-S22, 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.

S25. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

S26. Use of the anti-CGRP antibody of embodiment S25, 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.

S27. Use of the anti-CGRP antibody of embodiment S25, 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.

S28. Use of the anti-CGRP antibody of embodiment S25, 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.

S29. Use of the anti-CGRP antibody of embodiment S25, 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.

S30. Use of the anti-CGRP antibody of embodiment S25, 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.

S31. Use of the anti-CGRP antibody of any one of embodiments S25-S30, wherein said L-Histidine in said formulation comprises a mixture of L-Histidine and L-Histidine monohydrate.

S32. Use of the anti-CGRP antibody of any one of embodiments S25-S30, wherein said 3.1 mg of histidine in said formulation comprises a mixture of L-Histidine (1 mg) and L-Histidine monohydrate (2.8 mg), which in the final formulation sums up to 3.1 mg L-histidine free base.

S33. Use of the anti-CGRP antibody of any one of embodiments S26-S32, wherein said formulation is comprised in a 100 mg/mL single-dose vial wherein each mL contains 100 mg anti-CGRP antibody, L-histidine (1 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 80 (0.15 mg), sorbitol (40.5 mg), and Water for Injection, USP, at a pH of 5.8.

S34. Use of the anti-CGRP antibody of any one of embodiments S26-S32, wherein said formulation is comprised in a 300 mg/mL single-dose vial wherein each mL contains 300 mg anti-CGRP antibody, L-histidine (1 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 80 (0.15 mg), sorbitol (40.5 mg), and Water for Injection, USP, at a pH of 5.8.

S35. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said migraine or headache is selected from the group comprising acute migraine or

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headache, migraines with or without aura, chronic migraine, episodic migraine, chronic/episodic migraine, hemiplegic migraines, cluster headaches, migrainous neuralgia, chronic headaches, tension headaches, general headaches, headaches due to an underlying structural problem in the head or neck, sinus headaches (such as for example associated with sinusitis), and allergy-induced headaches or migraines.

S36. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is for administration to a patient that exhibits a pain level of at least 2 on the VRS-4 at the time of administration of said antibody.

S37. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is for administration to a patient that exhibits a pain level of at least 3 on the VRS-4 at the time of administration of said antibody.

S38. Use of the anti-CGRP antibody of any one of embodiments S1-S37, wherein said medicament is for administration to a patient that exhibits a pain level of at most 2 on the VRS-4 immediately after administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

S38. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is for administration to a patient that exhibits a pain level at most 1 on the VRS-4 immediately after administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

S40. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is for administration to a patient that is not administered any acute migraine medication within a period of time before and after said administration, such as within 15 minutes, within 30 minutes, within 1 hour, within 2 hours, within 3 hours, within 4 hours, within 5 hours, or within 6 hours before and after said administration.

S41. Use of the anti-CGRP antibody of embodiment S40, wherein said acute migraine medication comprises a triptan, an analgesic such as non-opioids or opioids/narcotics, acetaminophen, an NSAID, a combination medication, an ergotamine, or an ergot derivative.

S42. Use of the anti-CGRP antibody of embodiment S41, wherein said non-opioid analgesic comprises paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic; said triptan comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, or frovatriptan; said opioid comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone; said combination medication comprises two drugs with analgesic effects (for example, paracetamol and codeine), an analgesic and an adjuvant (for example, paracetamol and caffeine) and/or said combination-analgesics comprises at least one opioid (such as tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital, and/or caffeine, and/

or said combination-analgesic comprises acetylsalicylic acid (aspirin), paracetamol and caffeine (EXCEDRIN®, EXCEDRIN MIGRAINE®).

S43. Use of the anti-CGRP antibody of any one of embodiments S1-S39, wherein the patient is receiving or has received additional migraine medication.

S44. Use of the anti-CGRP antibody of any one of embodiments S1-S39 or S43, wherein the patient receives additional migraine medication prior, concurrent or after administration of the anti-CGRP antibody.

S45. Use of the anti-CGRP antibody of any one of embodiments S1-S39 or S43-S44, wherein the patient receives additional migraine medication within a period of time before and after said anti-CGRP antibody administration, such as within 15 minutes, within 30 minutes, within 1 hour, within 2 hours, within 3 hours, within 4 hours, within 5 hours, or within 6 hours before and after said anti-CGRP antibody administration.

S46. Use of the anti-CGRP antibody of any one of embodiments S44 or S45, wherein said additional migraine medication comprises an acute and/or a chronic migraine medication.

S47. Use of the anti-CGRP antibody of any one of embodiments S44-S46, wherein said additional migraine medication comprises a triptan, an analgesic such as non-opioid or opioid/narcotic, acetaminophen, an NSAID, a combination medication, an ergotamine, or an ergot derivative.

S48. Use of the anti-CGRP antibody of embodiment S47, wherein said non-opioid analgesic comprises paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic; said triptan comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, or frovatriptan; said opioid comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone; said combination medication comprises two drugs with analgesic effects (for example, paracetamol and codeine), an analgesic and an adjuvant (for example, paracetamol and caffeine) and/or said combination-analgesics comprises at least one opioid (such as tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital, and/or caffeine, and/or said combination-analgesic comprises acetylsalicylic acid (aspirin), paracetamol and caffeine (EXCEDRIN®, EXCEDRIN MIGRAINE®).

S49. 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*.

S50. Use of the anti-CGRP antibody of any of any one of embodiments S1-S48, wherein said anti-CGRP antibody is expressed in or obtained by expression in CHO cells.

S51. Use of the anti-CGRP antibody of any of any one of the foregoing embodiments, wherein said patient is administered 100 mg or 300 mg of said anti-CGRP antibody every three months.

S52. Use of the anti-CGRP antibody of any of any one of the foregoing embodiments, wherein said method results in immediate relief of migraine or headache symptoms.

S53. Use of the anti-CGRP antibody of any of any one of the foregoing embodiments, wherein said method results in immediate preventative treatment of migraine or headache.

FURTHER EXEMPLARY EMBODIMENTS

E1. An anti-CGRP antibody for use in treating migraine or headache in a patient in the need of immediate relief of

migraine or headache symptoms or for use in preventing migraine or headache in a patient in need of immediate preventative treatment of migraine or headache, wherein said anti-CGRP antibody is for intravenous infusion in a dosage of 100 or 300 mg of said anti-CGRP antibody, 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.

E2. The anti-CGRP antibody for use according to embodiment E1, wherein said anti-CGRP antibody is for use in a patient that patient exhibits at least one headache and/or migraine symptom at the time of administration.

E3. The anti-CGRP antibody for use according to embodiment E2, wherein said at least one headache and/or migraine symptom comprises one or more of pain, nausea, photophobia, or phonophobia.

E4. The anti-CGRP antibody for use according to embodiment E3, wherein said pain is head pain.

E5. The anti-CGRP antibody for use according to any one of embodiments, E2-E4, wherein the most bothersome symptom is alleviated after said administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

E6. The anti-CGRP antibody for use according to any one of embodiments E2-E5, wherein said patient no longer has a migraine after said administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

E7. The anti-CGRP antibody for use according to 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.

E8. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

E9. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

E10. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

E11. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

E12. The anti-CGRP antibody for use according to 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.

E13. The anti-CGRP antibody for use according to 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.

E14. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

E15. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

E16. The anti-CGRP antibody for use according to 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.

E17. The anti-CGRP antibody for use according to 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.

E18. The anti-CGRP antibody for use according to 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.

E19. The anti-CGRP antibody for use according to 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.

E20. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said intravenous administration is infused over a period of approximately 30 min to 60 minutes.

E21. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein the headache or migraine symptoms decline or are abolished immediately after administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

E22. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said patient is headache free 2 hours post-completion of infusion.

E23. The anti-CGRP antibody for use according to 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.

E24. The anti-CGRP antibody for use according to any one of embodiments E1-E22, 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 every 11-13 weeks, more preferably every 12 weeks.

E25. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

E26. The anti-CGRP antibody for use according to embodiment E25, 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.

E27. The anti-CGRP antibody for use according to embodiment E25, 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.

E28. The anti-CGRP antibody for use according to embodiment E25, 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.

E29. The anti-CGRP antibody for use according to embodiment E25, 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.

E30. The anti-CGRP antibody for use according to embodiment E25, 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.

E31. The anti-CGRP antibody for use according to any one of embodiments E25-E30, wherein said L-Histidine in said formulation comprises a mixture of L-Histidine and L-Histidine monohydrate.

E32. The anti-CGRP antibody for use according to any one of embodiments E25-E30, wherein said 3.1 mg of histidine in said formulation comprises a mixture of L-Histidine (1 mg) and L-Histidine monohydrate (2.8 mg), which in the final formulation sums up to 3.1 mg L-histidine free base.

E33. The anti-CGRP antibody for use according to any one of embodiments E26-E32, wherein said formulation is comprised in a 100 mg/mL single-dose vial wherein each mL contains 100 mg anti-CGRP antibody, L-histidine (1 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 80 (0.15 mg), sorbitol (40.5 mg), and Water for Injection, USP, at a pH of 5.8.

E34. The anti-CGRP antibody for use according to any one of embodiments E26-E32, wherein said formulation is comprised in a 300 mg/mL single-dose vial wherein each mL contains 300 mg anti-CGRP antibody, L-histidine (1 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 80 (0.15 mg), sorbitol (40.5 mg), and Water for Injection, USP, at a pH of 5.8.

E35. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said migraine or headache is selected from the group comprising acute migraine or headache, migraines with or without aura, chronic migraine, episodic migraine, chronic/episodic migraine, hemiplegic migraines, cluster headaches, migrainous neuralgia, chronic headaches, tension headaches, general headaches, headaches due to an underlying structural

problem in the head or neck, sinus headaches (such as for example associated with sinusitis), and allergy-induced headaches or migraines.

E36. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody is for administration to a patient that exhibits a pain level of at least 2 on the VRS-4 at the time of administration of said antibody.

E37. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody is for administration to a patient that exhibits a pain level of at least 3 on the VRS-4 at the time of administration of said antibody.

E38. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody is for administration to a patient that exhibits a pain level of at most 2 or 3 on the VRS-4 immediately after administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

E39. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody is for administration to a patient that exhibits a pain level at most 1 on the VRS-4 immediately after administration, such as within the first day after administration, within 12 hours after administration, within 6 hours after administration within 5 hours after administration, within 4 hours after administration, within 3 hours after administration, within 2 hours after administration, or within 1 hour of after administration, within 30 minutes after administration, or such as between 1-6 hours after administration.

E40. The anti-CGRP antibody for use according to any one of the foregoing embodiments, wherein said anti-CGRP antibody is for administration to a patient that is not administered any acute migraine medication within a period of time before and after said administration, such as within 15 minutes, within 30 minutes, within 1 hour, within 2 hours, within 3 hours, within 4 hours, within 5 hours, or within 6 hours before and after said administration.

E41. The anti-CGRP antibody for use according to embodiment E40, wherein said acute migraine medication comprises a triptan, an analgesic such as non-opioids or opioids/narcotics, acetaminophen, an NSAID, a combination medication, an ergotamine, or an ergot derivative.

E42. The anti-CGRP antibody for use according to embodiment E41, wherein said non-opioid analgesic comprises paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic; said triptan comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, or frovatriptan; said opioid comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone; said combination medication comprises two drugs with analgesic effects (for example, paracetamol and codeine), an analgesic and an adjuvant (for example, paracetamol and caffeine) and/or said combination-analgesics comprises at least one opioid (such as tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital, and/or caffeine, and/or said combination-analgesic comprises acetylsalicylic acid (aspirin), paracetamol and caffeine (EXCEDRIN®, EXCEDRIN MIGRAINE®).

E43. Use of the anti-CGRP antibody of any one of embodiments E1-E39, wherein the patient is receiving or has received additional migraine medication.

E44. Use of the anti-CGRP antibody of any one of embodiments E1-E39 or E43, wherein the patient receives additional migraine medication prior, concurrent or after administration of the anti-CGRP antibody.

E45. Use of the anti-CGRP antibody of any one of embodiments E1-S39 or E43-E44, wherein the patient receives additional migraine medication within a period of time before and after said anti-CGRP antibody administration, such as within 15 minutes, within 30 minutes, within 1 hour, within 2 hours, within 3 hours, within 4 hours, within 5 hours, or within 6 hours before and after said anti-CGRP antibody administration.

E46. Use of the anti-CGRP antibody of any one of embodiments E44 or E45, wherein said additional migraine medication comprises an acute and/or a chronic migraine medication.

E47. Use of the anti-CGRP antibody of any one of embodiments E44-E46, wherein said additional migraine medication comprises a triptan, an analgesic such as non-opioid or opioid/narcotic, acetaminophen, an NSAID, a combination medication, an ergotamine, or an ergot derivative.

E48. Use of the anti-CGRP antibody of embodiment E47, wherein said non-opioid analgesic comprises paracetamol (acetaminophen), acetylsalicylic acid (aspirin), another NSAID, or another non-opioid analgesic; said triptan comprises use of one or more of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, or frovatriptan; said opioid comprises use of one or more of oxycodone, tramadol, butorphanol, morphine, codeine, and hydrocodone; said combination medication comprises two drugs with analgesic effects (for example, paracetamol and codeine), an analgesic and an adjuvant (for example, paracetamol and caffeine) and/or said combination-analgesics comprises at least one opioid (such as tramadol, butorphanol, morphine, codeine, hydrocodone, or any combination thereof), barbiturate such as butalbital, and/or caffeine, and/or said combination-analgesic comprises acetylsalicylic acid (aspirin), paracetamol and caffeine (EXCEDRIN®, EXCEDRIN MIGRAINE®).

E49. The anti-CGRP antibody for use according to any of any one of the foregoing embodiments, wherein said anti-CGRP antibody is expressed in or obtained by expression in *Pichia pastoris*.

E50. The anti-CGRP antibody for use according to any of any one of embodiments E1-E39, wherein said anti-CGRP antibody is expressed in or obtained by expression in CHO cells.

E51. Use of the anti-CGRP antibody of any of any one of the foregoing embodiments, wherein said patient is administered 100 mg or 300 mg of said anti-CGRP antibody every three months.

E52. Use of the anti-CGRP antibody of any of any one of the foregoing embodiments, wherein said method results in immediate relief of migraine or headache symptoms.

E53. Use of the anti-CGRP antibody of any of any one of the foregoing embodiments, wherein said method results in immediate preventative treatment of migraine or headache.

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.

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.

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 \leq 50 years of age (ICHD-II, 2004 Section 1), and further had a history of migraine \geq 12 months with \geq 5 and \leq 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 \leq 14 days per 28 day period and, within those days, \leq 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

Baseline Demographics and Clinical Characteristics		
Characteristic	Placebo iv (n = 82)	Ab6 1000 mg iv (n = 81)
Mean \pm SD Age (years)	39.0 (9.6)	38.6 (10.8)
Mean \pm 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 \pm SD Migraine Days	8.8 (2.7)	8.4 (2.1)
Mean \pm SD Migraine Episodes	6.7 (2.4)	6.0 (2.2)
Mean \pm SD Headache Frequency	9.6 (2.8)	9.2 (2.6)
Mean \pm SD Migraine Hours	72.2 (51.0)	80.1 (49.1)
Mean \pm SD HIT-6 Score	64.5 (4.44)	63.8 (5.21)

TABLE 1-continued

Characteristic	Placebo iv (n = 82)	Ab6 1000 mg iv (n = 81)
Mean \pm SD MSQ RFP Score	49.0 (17.9)	49.5 (21.2)
Mean \pm SD MSQ RFR Score	61.9 (22.7)	63.9 (24.0)
Mean \pm 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

Responder analysis for migraine days

Time period	% reduction migraine days	Placebo iv	Ab6 1000 mg iv	P value
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, 31% 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} (μg/mL), AUC₀₋₂₈ (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 results include analysis of the change (mean +/-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 ≥50% reduction in migraine frequency were considered to be a 50% responder. Subjects with ≥75% reduction in migraine frequency were considered

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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, migraine hours, 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

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, 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

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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, 10 50%, 75%, and 100% reduction in migraine days in month 1, over months 1-3 (after the 1st infusion), and over months 15 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).

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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).

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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 medication 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

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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.

¹⁰ Migraine Treatment Optimization Questionnaire-6 (mTOQ-6) is assessed as the change from baseline of the total score and is summarized and compared between the treatment groups in the study.

¹⁵ 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.

²⁰ 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.

²⁵ The study shows that Ab6 is effective and safe for acute migraine treatment.

Example 7

In the pivotal clinical studies the patients received Ab6 as 100 mg or 300 mg dosages, as described in Example 3. ³⁰ Including day -1 (post infusion of Ab6) in the statistical analysis shows that an apparent treatment effect is present immediately after infusion when the treatment effect is assessed (FIG. 50). In the Figure Day 0 is defined as the day of the infusion and Day -1 data represent the pre-infusion condition. A substantial decrease in the percentage of migraines from Day -1 (baseline, the day prior to infusion) to Day 0 is apparent. Moreover, the magnitude of the effect is greater with the 300 mg dosage than the 100 mg dosage, and both show a greater effect than the placebo group.

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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

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source          1..106
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 30
TVAAAPSVIF 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
caagtgtga cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
aattgccagg ccagtccagg tggttatgt aacaactacc tagcctggta tcagcagaaa 120
ccaggccagg ctcccaagca actgtatcat tctacatcca ctctggatc tggggctca 180
tcgcgggtca aaggcagttg atctggaca cagttcactc tcaccatcag cgacctggag 240
tgtgcccgtat ctgcacttca ctactgtcta ggcagttatg atttgtatgt tggtgatgt 300
tttgttttcg gggggggc cgagggtgtg gtcaaacgtg cgggtggc accatctgtc 360
ttcatcttccg cggccatcgta tgacgttgc aatctggaa ctgcctctgt tggtgctg 420
ctgaataact ttatcccaag agggccaaa gtacagtgg aagtgatcaa cgcctccaa 480
tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagctc 540
agcagcaccc tgacgcttag caaaggcagac tacgagaaac acaaagtcta cgcctcgaa 600
gtcaccatc agggccttag ctcggccgtc acaaaggtc 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
caagtgtga cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
aattgccagg ccagtccagg tggttatgt aacaactacc tagcctggta tcagcagaaa 120
ccaggccagg ctcccaagca actgtatcat tctacatcca ctctggatc tggggctca 180
tcgcgggtca aaggcagttg atctggaca cagttcactc tcaccatcag cgacctggag 240
tgtgcccgtat ctgcacttca ctactgtcta ggcagttatg atttgtatgt tggtgatgt 300
tttgttttcg gggggggc cgagggtgtg gtcaaacgtg 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
caggccactc 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
tggtatcagg agaaaccagg 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

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-continued

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 aggcaagtgg a tctgggacac agttcaactt caccatcagc 60
gacctggagt gtgcggatgc 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
ctaggcagg t atgattttag tagtggtat 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
ttcggcgag 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
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 40
acgtgtggctt caccatctgt ctcatcttc ccgcgcattgtt atgaggcagg t gaaatctgg 60
actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
aagggtggata acggccatccca atcgggttaac tcccaggaga gtgtcacaga gcaggacagc 180
aaggacagaca ctacagccct cagcagcacc ctgacgcgtt gcaaaaggaga ctacgagaaa 240
cacaaggatctt acggctgtca agtaccccat cagggtgtt gctcgccgtt cacaaggagc 300
ttcaacacagg gagagtgtt a 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
EVQLVESGGG LVQPGGSLRL SCAVSGLDLS SYYMOWVRQA PGKGLEWVGIGINDNTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
TVPSSSLGTO TYICCNVNHKP SNTKVDKRV PKSCDKTHTCPPCPAPELLG GPSVPLFPPK 240
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVSLSVL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
CLVKGFYPSD IAVEWESNGQ PENNYKTTTPP VLSDGSFFL 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
EVQLVESGGG LVQPGGSLRL SCAVSGLDLS SYYMOWVRQA PGKGLEWVGIGINDNTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS S 111

SEQ ID NO: 43 moltype = AA length = 30

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FEATURE REGION	Location/Qualifiers 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 REGION	Location/Qualifiers 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 REGION	Location/Qualifiers 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 REGION	Location/Qualifiers 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	
FEATURE REGION	Location/Qualifiers 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 REGION	Location/Qualifiers 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 REGION	Location/Qualifiers 1..330 note = Engineered antibody sequence	
source	1..330 mol_type = protein organism = synthetic construct	
SEQUENCE: 50		
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYPPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKPNW YVDGVDEVHNA KTKPREEQYA STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTFIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESENQGP ENNYKTTPPV LDSDGSSFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK		60 120 180 240 300 330
SEQ ID NO: 51	moltype = DNA length = 1326	

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FEATURE	Location/Qualifiers
misc_feature	1..1326
	note = Engineered antibody sequence
source	1..1326
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 51	
gagggtgcagc ttgtggagtc tgggggaggo ttgggtccagc ctggggggtc cctgagactc	60
tccctgtcgag tctctggact cgacactcagt agctactaca tgcaatgggt ccgtcaggct	120
ccagggaagg ggctggagtg ggtcgaggatc attggtatca atgataaacat atactacgct	180
agctggcgca aaggccgatt caccatctcc agagacaat ccaagaccac ggtgtatctt	240
caaataaaca gctgtggagc tgaggacact gctgtgtatt tctgtgttag aggggacatc	300
tggggcacaag ggaccctcgat caccgtctcg agccgcctcca ccaaggccc atcggtctc	360
ccccctggcaac cctctccaa gacgacact gggggcacac cggccctggg ctgcgtggc	420
aaggactact tccccaaacc ggtgtacgggt tcgtggact cagggccct gaccaggccg	480
gtgcacacct tcccggtgt cctacagtcc tcaggactct actcccttag cagcgtgg	540
accgtgcacc ctccggatc gggcacccag acctacatctt gcaacgtgaa tcacaaggcc	600
agecaacacca aagggtggacaa gagatggtag cccaaatctt gtgacaaaatc tcacacatc	660
ccaccgtgcc cagcacctgact cttctgggg ggaccgtcag ttttcttccc ccccccaaaa	720
cccaaggaca ccctcatgtat ctcgggacc cctgaggta catgcgttgt ggtggacgt	780
agccacgaaag accctggatc caagttaacd tggtaacgtgg acggcgtgaa ggtgcataat	840
gccaagacaa aggccgggaa ggacgttacatc gccagcacgt accgtgttgt cagcgtctc	900
accgtctcgc accaggactg cgtaatggc aagggtgtaca agtgcgttgtt ctccaaacaaa	960
gcccctccag ccccccattca gaaaaccatc tccaaagccca aaggccagcc ccgagaacca	1020
cagggttaca cccctggccca atccgggag aagatgtacca agaaccaggat cagcgtgacc	1080
tgcctggatc aaggcttcta tcccggcgtc atcgccgtgg agtggggagag caatgggag	1140
ccggagaaaca actacaagac caccgttccc gtgtgtggact ccgacggctc cttttctc	1200
taacagcaagc tcaccgtggc caagagcagg tggcagcagg ggaacgttctt ctcatgtcc	1260
gtgtatgtcgat aggctctgca caaccactac acgcagaaga gcctctccct 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	
gagggtgcagc ttgtggagtc tgggggaggo ttgggtccagc ctggggggtc cctgagactc	60
tccctgtcgag tctctggact cgacactcagt agctactaca tgcaatgggt ccgtcaggct	120
ccagggaagg ggctggagtg ggtcgaggatc attggtatca atgataaacat atactacgct	180
agctggcgca aaggccgatt caccatctcc agagacaat ccaagaccac ggtgtatctt	240
caaataaaca gctgtggagc tgaggacact gctgtgtatt tctgtgttag aggggacatc	300
tggggcacaag ggaccctcgat 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	
gagggtgcagc ttgtggagtc tgggggaggo ttgggtccagc ctggggggtc cctgagactc	60
tccctgtcgag tctctggact cgacactcagt	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

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misc_feature      1..48
                  note = Engineered antibody sequence
source           1..48
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 56
gtcattggta tcaatgataa cacatactac gcgagctggg 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 accacggtgt atcttcaa at gaacagctg 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 ggaccctcggt 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
SEQUENCE: 60
gcctccacca agggcccate ggtttcccc ctggcacccct cctccaagag cacctctggg 60
ggcacacggg ccctggctg cctggtaag gactacttc ccgaaccgg gacgggtcg 120
tggaaacttag ggcctctgac cagcggctgtg cacaccttc cggctgtctt acagtcc 180
ggactctact ccctcagcag cgtggtgacc gtgccttcca gcagcttggg caccctgacc 240
tacatctgca acgttaatca caagccccc aaccaacaagg tggacaagg agtggggcc 300
aaatcttggc aaaaaactca ccatggccca cctgtggccag actctgaact cctggggg 360
ccgtcagtct ttcttctccc cccaaaaccc aaggacaccc tcatgtatcc ccggaccct 420
gagggtcacat gctgtgggtt ggacgtgago cacggaaaccc ctgagggtcaa gttcaactgg 480
taacgtggacg gctgtggggat gcataatgcc aagacaaaccc cgcggggagg gcaatggcc 540
agcaacgtacc gttgtggatcg cgtcttacc cgtctgacc aggactggct gaatggcaag 600
gagttacaatg gcaagggtctc caacaaaggcc ctccccagccc ccateggaaa aaccatctcc 660
aaagccaaag ggcagccccg agaaccacag gtgtacacc tgccccatc ccggggaggag 720
atgaccacca accagggtcg cctgacatcg ctgtcaatgg gtttatcc cagcgacatc 780
gcccgtggagt gggagggcaa tggcagccg gagaacaact acaagaccac gcctcccgtg 840
cttgacttcg accggctctt cttecttac agcaaggtca ccgtggacaa gagcagggtgg 900
cagcaggggg acgttttctc atgctccgt atgcatgagg ctctgcacaa ccactacacg 960
cagaagagcc ttccctgtc 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 NCQASQSVD NNYLAWYQQK PKVVKQLIY STSTLASGVP 60
SRFSRSGSGGT DFTLTISSLQ PEDVATYYCL GSYDCSSGDC FVFGGGTKVE IKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 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

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-continued

SEQUENCE: 62
 QVLTQSPSSL SASVGDRVTI NCQASQSVYD NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISLQ PEDVATYYCL GSYDCSSGDC FVFGGGTKVE IKR 113

SEQ ID NO: 63 moltype = AA length = 22
 FEATURE Location/Qualifiers
 REGION 1..22
 source note = Engineered antibody sequence
 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
 source note = Engineered antibody sequence
 1..13
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 64
 QASQSVYDNN YLA 13

SEQ ID NO: 65 moltype = AA length = 15
 FEATURE Location/Qualifiers
 REGION 1..15
 source note = Engineered antibody sequence
 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
 source note = Engineered antibody sequence
 1..7
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 66
 STSTLAS 7

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

SEQUENCE: 67
 GVPSRFSG SGTDFTLTIS SLQPEDVATY YC 32

SEQ ID NO: 68 moltype = AA length = 13
 FEATURE Location/Qualifiers
 REGION 1..13
 source note = Engineered antibody sequence
 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
 source note = Engineered antibody sequence
 1..11
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 69
 FGGGTKEIK R 11

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

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mol_type = protein
organism = synthetic construct

SEQUENCE: 70
TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSS LTLSKADYEK HKVYACEVTH 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
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccagg ccagtcatcgat tggttatgt aacaactacc tagcctggta tcagcagaaaa 120
ccagggaaag ttccataagca actgtatctat tctacatcca ctctggatc tgggtccca 180
tctcggttca gtggcagttg atctgggaca gatttcactc teacatcag cagcctgcag 240
cctgaagatg ttgcactta ttactgtcta ggcagttatg attgtatgt tggtgatgt 300
tttgtttcg gcggaggaac caagggtggaa atcaaacgtg cgggtggctgc accatctgtc 360
ttcatcttcc cggccatctca tgacgttg aaatctgttgc ctgcctctgt tgggtgcctg 420
ctgaataact tctatcccg agaggccaa gtacagtggaa aggtggataa cgccctccaa 480
tcgggttaact cccaggagag tgtcacagag caggacacgca ctacagcctc 540
agcagcaccc tgacgttag caaacgcac tacgagaaac acaaagtcta cgcctgcgaa 600
gtcacccatc agggccttag ctcggccgtc acaaaggtc 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
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccagg ccagtcatcgat tggttatgt aacaactacc tagcctggta tcagcagaaaa 120
ccagggaaag ttccataagca actgtatctat tctacatcca ctctggatc tgggtccca 180
tctcggttca gtggcagttg atctgggaca gatttcactc teacatcag cagcctgcag 240
cctgaagatg ttgcactta ttactgtcta ggcagttatg attgtatgt tggtgatgt 300
tttgtttcg gcggaggaac caagggtggaa atcaaacgtg 339

SEQ ID NO: 73      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: 73
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgc 66

SEQ ID NO: 74      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: 74
caggccagtc agagtgttta tgataacaac tacctagcc 39

SEQ ID NO: 75      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: 75
tggtatcaggc agaaaaccagg gaaaagttct aagcaactga tctat 45

SEQ ID NO: 76      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

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SEQUENCE: 76
tctacatcca ctctggcatc t 21

SEQ ID NO: 77 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: 77
gggttccat ctcgtttcag tggcagtggaa tctgggacag atttcactt caccatcaggc 60
agcctgcaggc ctgaagatgt tgcaacctat tactgt 96

SEQ ID NO: 78 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: 78
ctaggcagtt atgattgttag tagtggtat tgttttgtt 39

SEQ ID NO: 79 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: 79
ttcggcgagg gaaccaaggt ggaaaatcaaa cgt 33

SEQ ID NO: 80 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: 80
acggtgttgcg caccatctgt cttcatcttc ccgcacatctg atgagcaggta gaaatctgg 60
actgcctctg ttgtgtgcct gctaataac ttcataccca gagaggccaa agtacagtgg 120
aagggtggata acggccatcca atcgggttaac tcccaggaga gtgtcacaga gcaggacagc 180
aaggacacga octacagccct cagcagcacc ctgacgcgtga gcaaaggaga ctacgagaaa 240
cacaaggatct acgcctgcga atcaccatc caggcgcgtga gtcgcggcgt cacaaggagc 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
EVQLVESGGG LVQPGGSLRL SCAVGLDLS SYYMQWVRQA PGKGLEWVGIGINDNTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
PLAPSSKSTS CGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSVV 180
TVPSSSLGTQ TYICCNVNHPK SNTKVNDARVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK 240
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVVSVL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSR EMTKNQVSLT 360
CLVKGFYPSD IAVEWESNQQ PENNYKTTPPP VLDSDGSSLF 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
EVQLVESGGG LVQPGGSLRL SCAVGLDLS SYYMQWVRQA PGKGLEWVGIGINDNTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS S 111

SEQ ID NO: 83 moltype = AA length = 30
FEATURE Location/Qualifiers

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REGION	1..30	
source	note = Engineered antibody sequence	
	1..30	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 83		
EVQLVESGGG LVQPGGSLRL SCAVSGLDLS		30
SEQ ID NO: 84	moltype = AA length = 5	
FEATURE	Location/Qualifiers	
REGION	1..5	
source	note = Engineered antibody sequence	
	1..5	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 84		
SYYMQ		5
SEQ ID NO: 85	moltype = AA length = 14	
FEATURE	Location/Qualifiers	
REGION	1..14	
source	note = Engineered antibody sequence	
	1..14	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 85		
WVRQAPGKGL BWVG		14
SEQ ID NO: 86	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
REGION	1..16	
source	note = Engineered antibody sequence	
	1..16	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 86		
VIGINDNTYY ASWAKG		16
SEQ ID NO: 87	moltype = AA length = 32	
FEATURE	Location/Qualifiers	
REGION	1..32	
source	note = Engineered antibody sequence	
	1..32	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 87		
RFTISRDN SK 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	
source	note = Engineered antibody sequence	
	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	
source	note = Engineered antibody sequence	
	1..330	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 90		
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYPPEPVTVS WNSGALTSGV HTFPAVLQSS	60	
GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDARVEP KSCDKTHTCP PCPAPELLGG	120	
PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA	180	
STYRVRVSVLT VLHQDWLNGE EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPSPREE	240	
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW	300	
QQGNVFSCSV MHEALHNHYT QKSLSLSPKG	330	
SEQ ID NO: 91	moltype = DNA length = 1326	
FEATURE	Location/Qualifiers	

-continued

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misc_feature          1..1326
                      note = Engineered antibody sequence
source               1..1326
                      mol_type = other DNA
                      organism = synthetic construct
SEQUENCE: 91
gaggtgcagc ttgtggagtc tgggggaggo ttgggtccagc ctggggggtc cctgagactc 60
tccctgtcag tctctggact cgacctcagt agctactaca tgcaatgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggctggagtc attggtatca atgataaac acatacgcg 180
agctggcaga aaggccgatt caccatctc agagacaattt ccaagaccac ggtgtatctt 240
caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgtctag aggggacatc 300
tggggcgaag ggacctctgt caccgtctcg agcgccctcca ccaaggccc atcggtttc 360
ccacctggcac cctctccca gaggacctt gggggcacac cggccctggg ctgctgttc 420
aaggactact tcccccaacc ggtgacggty tctgtggactt caggccctt gaccaggcc 480
gtgcacacct tcccgctgt cctacagtcc tcaggactctt actccctcag cagcgtgtc 540
accgtgeccct ccagcagctt gggccacccag acctacatctt gcaacgtgaa tcacaagccc 600
agcaacacca aagggtggacgc gagagtgttgg cccaaatctt gtgacaaaac tcacacatgc 660
ccacccgtgcc cagcaccttca actectgggg ggacccgtcaq tttctctt ccccccaaaa 720
cccaaggaca ccctcatgtat ctcgggacc cctgaggctca catcgctgtt ggtggacgt 780
agccacgaag accctggaggt caagttaac tggtagctgg acggcggtt ggtgcataat 840
gccaagacaa accggcggggaa ggagcagttt gccagcagctt accgtgttgtt cagcgtctc 900
accgtctctgc accaggactt gctgaatggc aaggagtactt aagtgtcaatggtt ctccaaacaaa 960
ggccctccccc ccccatctgaa gaaaaccatc tccaaagccca aaggccggcc cccgagaacca 1020
cagggttaca ccctggcccccc atccgggag gagatgacca agaaccagg tccgtgtt 1080
tgccctgttca aagggttcttca tcccgagcgtt atccgggttgg aatggggcag 1140
ccggagaaca actacaagac cacgttccca gttgtgttggactt ccggacggctc cttttcttc 1200
tacagcaacgc tcaccgttgcgaa agagcagggttggcaggcggg ggaacgttctt ctcatgttcc 1260
gtgtatgttca agggttcttca caaccactac acgcagaaga gtccttccctt gtctccgggt 1320
aaatga                                              1326

SEQ ID NO: 92          moltype = DNA length = 333
FEATURE
misc_feature          Location/Qualifiers
1..333
                      note = Engineered antibody sequence
source               1..333
                      mol_type = other DNA
                      organism = synthetic construct
SEQUENCE: 92
gaggtgcagc ttgtggagtc tgggggaggo ttgggtccagc ctggggggtc cctgagactc 60
tccctgtcag tctctggact cgacctcagt agctactaca tgcaatgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggctggagtc attggtatca atgataaac acatacgcg 180
agctggcaga aaggccgatt caccatctc agagacaattt ccaagaccac ggtgtatctt 240
caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgtctag aggggacatc 300
tggggcgaag ggacctctgt caccgtctcg accgtctcgtt 333

SEQ ID NO: 93          moltype = DNA length = 90
FEATURE
misc_feature          Location/Qualifiers
1..90
                      note = Engineered antibody sequence
source               1..90
                      mol_type = other DNA
                      organism = synthetic construct
SEQUENCE: 93
gaggtgcagc ttgtggagtc tgggggaggo ttgggtccagc ctggggggtc cctgagactc 60
tccctgtcag tctctggact cgacctcagt 90

SEQ ID NO: 94          moltype = DNA length = 15
FEATURE
misc_feature          Location/Qualifiers
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
misc_feature          Location/Qualifiers
1..42
                      note = Engineered antibody sequence
source               1..42
                      mol_type = other DNA
                      organism = synthetic construct
SEQUENCE: 95
tgggtccgtc aggctccagg gaaggggctg gatgtgggtc ga                                              42

SEQ ID NO: 96          moltype = DNA length = 48
FEATURE
misc_feature          Location/Qualifiers
1..48

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-continued

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source          note = Engineered antibody sequence
                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
misc_feature      Location/Qualifiers
1..96
note = Engineered antibody sequence
source            1..96
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 97
cgattccacca tctccagaga caattccaag accacgggt atcttcaa at gaacagcctg  60
agagctgagg acactgctgt gtatctgt gctaga                         96

SEQ ID NO: 98      moltype = length =
SEQUENCE: 98
000

SEQ ID NO: 99      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: 99
tggggccaag ggaccctcg taccgtctcg agc                           33

SEQ ID NO: 100     moltype = DNA  length = 993
FEATURE
misc_feature      Location/Qualifiers
1..993
note = Engineered antibody sequence
source            1..993
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 100
gcctccacca agggcccatc ggtttcccc ctggcaccc cctccaagag cacctctggg  60
ggcacacggg ccctggctg cctgttcaag gactacttc cccgaaccggt gacggtgtcg 120
tggaaacttag cgcgcctgac cagcggctg cacacccccc cggctgtctt acagtccca 180
ggactctact ccctcagcag cgtgttgacc gtgcctccca gcagcttggg caccaggacc 240
tacatctgca acgtgaatca caagcccagg aacaccaagg tggacgctg agttgagccc 300
aatcttgtg aaaaaactca cacatggccca ccgtgccccg caccctgaaact cctgggggg 360
ccgtcagtctt ccttccccc cccaaaaccc aaggacaccc tcatgatctc ccggaccct 420
gaggtcacat ggtgtgtgtt ggacgtgago cacaagaccc ctgaggctaa gttcaactgg 480
tacgtggacg cgtgtggaggt gcataatgcc aagacaaagg cgccggggg gcaatggcc 540
agcacgtacc gtgtgtgtcg cgttccacc gtcctgaccagg actgtgtt gatgtggcaag 600
gagtacaatg gcaagggtctc caaaaaaggcc ctcccaaggcc ccatcgagaa aaccatctcc 660
aaaggccaaag ggcagccccg agaaccacag gtgtacacc tgccccccatc ccgggaggag 720
atgaccaaga accagggtcag cctgacccctc ctggtcaaa gcttctatcc cagcgacatc 780
gcgggtggagt gggagagccat tggggagccg gagaacaactt acaagaccac gcctccctg 840
ctggacttcc accggcttccat cttccctac agcaagctca ccgtggacaa gagcagggtgg 900
cagcagggggaa acgttccatc atgtccctgt atgcattggg ctctgcacaa ccactacacg 960
cagaagaccc tctccctgtc tccgggtaaa tga                           993

SEQ ID NO: 101      moltype = AA  length = 219
FEATURE
REGION            Location/Qualifiers
1..219
note = Engineered antibody sequence
source            1..219
mol_type = protein
organism = synthetic construct
SEQUENCE: 101
QVLTQSPPSSL SASVGDRVTI NCQASQSVYD NNYLAWYQQK PGKVPQLIY STSTLASGVP  60
SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSSGDC FVFGGGTKVE IKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRRGEC                         219

SEQ ID NO: 102      moltype = AA  length = 113
FEATURE
REGION            Location/Qualifiers
1..113
note = Engineered antibody sequence
source            1..113
mol_type = protein
organism = synthetic construct
SEQUENCE: 102

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QVLTQSPSSL SASVGDRVTI NCQASQSVYD NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
SRFSGSGSGT DFTLTISLQ PEDVATYYCL GSYDCSSGDC 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

SEQUENCE: 106 STSTLAS 7

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 FGGGGTKEIK 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

-continued

organism = synthetic construct

SEQUENCE: 110
 TVAAPSVFIF PPSDEQLKSG TASVVCLNN 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
 caagtgtgaa cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
 aattgcagg ccagtcagag tgtttatgtt aacaactacc tagcctggta tcagcagaaa 120
 ccagggaaag ttccctaagca actgatctat tctacatcca ctctggcatc tgggttccca 180
 ttcgcgttca gtggcagtgg atctgggaca gatttcactc tcaccatcg cagcctgcag 240
 cctgaagatg ttgcaacttatactgttca ggcagttatg attgttagtag tggtgtatgt 300
 ttgttttcg gcccggaaac caagggtggaa atcaaacgttca cgggtgttc accatctgtc 360
 ttcatcttcc cgccatctga tgacgcgttg aaatctggaa ctgcctctgt tgggtgtctg 420
 ctgaaataact ttatccccag agaggccaaa gtacagtggaa aggtggataa cgccttccaa 480
 tcgggttca cccaggagatg tgcacagac cggacacagcac ctacagcctc 540
 agcagcacc cttacgcgttca aaaaatgttca cgcctgcgaa 600
 gtcacccatc agggccttagt ctcggccgtc acaaagatgttca acacagggg 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
 caagtgtgaa cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
 aattgcagg ccagtcagag tgtttatgtt aacaactacc tagcctggta tcagcagaaa 120
 ccagggaaag ttccctaagca actgatctat tctacatcca ctctggcatc tgggttccca 180
 ttcgcgttca gtggcagtgg atctgggaca gatttcactc tcaccatcg cagcctgcag 240
 cctgaagatg ttgcaacttatactgttca ggcagttatg attgttagtag tggtgtatgt 300
 ttgttttcg gcccggaaac caagggtggaa atcaaacgttca 339

SEQ ID NO: 113 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: 113
 caagtgtgaa cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
 aattgc 66

SEQ ID NO: 114 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: 114
 caggccagtc agagtgttta tgataacaac taccttagcc 39

SEQ ID NO: 115 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: 115
 tggtatcagc agaaaccagg gaaagttctt aagcaactgttca totat 45

SEQ ID NO: 116 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: 116

-continued

tctacatcca ctctggcatc t	21
SEQ ID NO: 117	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: 117	
gggggtcccat ctcgtttcag tggcagtggaa tctggggacag atttcactct caccatcagc	60
agcctgcagc ctgaagatgt tgcaacctat tactgt	96
SEQ ID NO: 118	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: 118	
ctaggcagtt atgattttag tagtggtgtat tgttttgtt	39
SEQ ID NO: 119	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: 119	
ttcggcggag gaaccaaggt ggaaaatcaaa cgt	33
SEQ ID NO: 120	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: 120	
acgggtggctt caccatctgt ctteatcttc cccgcatctg atgaggcagtt gaaatctggaa	60
actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg	120
aagggtggata acggccctca atcggttaac tcccaggaga gtgtcacaga gcaggacagc	180
aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaaggcaga ctacgagaaa	240
cacaaggctt acggctgcga agtcacccat cagggcctga gctcgccctgt cacaaggagc	300
ttcaacacaggg gagatgttta 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	
QSLEESGGRL VTPGTPLTLT CSVSGIDLSSG YYMNWVRQAP GKGLEWIGVI GINGATYYAS	60
WAKGRFTISK TSSTTVDLKM TSLTTEDTAT YFCARGDIWG PGTLVTVSSA STKGPSVFPL	120
APSSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVT	180
PSSSLGTQTY ICNVNHPKSN TKVDKRVEPK SCDKTHTCPPK CPAPELLGGP SVFLPPPKPK	240
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYAS TYRVSVLTV	300
LHQDWLNKE YKCKVSNKAL PAPIEKTISK AKQQPREGQV YTLPPSREEM TKNQVSLTCL	360
VKGFYPSDIA VEWESNGQPE NNYKTTPPPVL 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	
QSLEESGGRL VTPGTPLTLT CSVSGIDLSSG YYMNWVRQAP GKGLEWIGVI GINGATYYAS	60
WAKGRFTISK TSSTTVDLKM TSLTTEDTAT YFCARGDIWG PGTLVTVSS	109
SEQ ID NO: 123	moltype = AA length = 29
FEATURE	Location/Qualifiers
REGION	1..29

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source          note = Engineered antibody sequence
1..29
mol_type = protein
organism = synthetic construct

SEQUENCE: 123
QSLEESGGRL 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
note = Engineered antibody sequence
source          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
WGPGLTVTVS 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 DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKPK KDTLMISRTP EVTCVVVDVS HEDPEVKFNV YVDGVEVHNA KTKPREEQYA 180
STYRVVSVLT VLHQDWLNKG EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPP LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK                                330

SEQ ID NO: 131      moltype = DNA  length = 1320
FEATURE          Location/Qualifiers
misc_feature    1..1320

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source note = Engineered antibody sequence
1..1320
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 131
cagtcgtgg aggagtccgg gggtcgcctg gtcacgcctg ggacaccccct gacactcacc 60
tggccgtct ctggcatcga cctcagtggc tactacatga actgggtccg ccaggctcca 120
ggaaaggggc tggaatggat cggagtctgg ggttataatg gtgccacata ctacgcgagc 180
tggcgaaag gocgattcac catctccaaa acctcgtcga ccacgggtgg a tctgaaaatg 240
accagtctga caaccggaga cacggccacc tatttctgtg ccagagggga catctggggc 300
ccgggcaccc tcgtcaccgt ctcgagcgc tccaccaagg gcccacatggg ctteccctcg 360
geaccctct ccaagagcac ctctgggggc acagcggcc ac tgggtctgc ggtcaaggac 420
taacttccccc aaccgggtgac ggtgtcggtg aacttcaggcc ctctgaccag cggcggtcgc 480
acccatccccgg ctgtctaca gtctcaggaa ctctactccc tcagcagggt ggtgaccctg 540
ccctccacga gttgggcac ccacgactac atctgcaccc tgaatcacaa gcccacac 600
accaagggtgg acaagagagt tgagccaaa tcttgcata aaactcacac atgcccacccg 660
tgcccgacac ctgaactctc ggggggaccc tcagtcctcc tcttcccccc aaaacccaag 720
gacacccctcg tggatctca gaccatctgg gtcacatgcg tgggtggta cgtgacccac 780
gaagacccctg aggtcaagtt caacttggtaa gtggacccgg tggagggtca taatgccaag 840
acaaggccgc gggaggagca gtacggccago acgtaccgtg tggcagcgtg cctcaccgtc 900
ctgcaccagg actgggtgaa tggcaaggaa tacaatgtcga aggtctccaa caaaggccctc 960
ccagcaggaaac catctccaaa gccaaggggc agcccccggaa accacagggtg 1020
tacacccctgc ccccatccccgg gggaggatg accaagaaccc aggtcagctt gacctgcctg 1080
gtcaaaggct tctatccccgg cgacatcgcg gtggagtggg agagcaatgg gcacccggag 1140
aacaactaca agaccacggc tccctgtctg gactccggac gtccttctt cctctacacg 1200
aagctcaccg tggacaagag cagggtggcag cagggtggac tcttctcatg ctccgtatg 1260
catgaggcgc tgcacaacca aagacccctc ccctgtctcc gggtaaatga 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 ggacaccccct gacactcacc 60
tggccgtct ctggcatcga cctcagtggc tactacatga actgggtccg ccaggctcca 120
ggaaaggggc tggaatggat cggagtctgg ggttataatg gtgccacata ctacgcgagc 180
tggcgaaag gocgattcac catctccaaa acctcgtcga ccacgggtgg a tctgaaaatg 240
accagtctga caaccggaga cacggccacc tatttctgtg ccagagggga catctggggc 300
ccgggcaccc tcgtcaccgt ctcgagcgc tccaccaagg gcccacatggg ctteccctcg 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 ggacaccccct gacactcacc 60
tggccgtct ctggcatcga cctcagtggc tactacatga actgggtccg ccaggctcca 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
tgggtccggc aggctccagg gaaggggctg 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

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mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 136
 gtcattggta ttaatggtgc cacatactac gcgagctggg cgaaaaggc 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 tgaaaaatgac cagtctgaca 60
 accgaggaca 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 gacccctcg taccgtctcg 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 aggggccatc ggtcttccc ctggcacccct cctccaagag caccctctggg 60
 ggacacagccg ccctgggctg cctggtcaag gactacttc cccgaacccggt gacgggtgtcg 120
 tggaaacttag cggccctgac cagcggcggtg cacaccttc cggctgtctt acagtctca 180
 ggactctact ccctcagtg cgtgtggatc gtggcccttca gcagcttggg caccggacc 240
 tacatctgca acgtgaatca caagggccagc aacaccaagg tggacaagag agttgagccc 300
 aaatcttgtc acaaaaactca cacatggcca cccgtggccagc caccctgaaact cctggggggg 360
 cccgtcgtct tccttccc cccaaaaccc aaggacaccc tcatgtatc cccggccccct 420
 gaggtcacat ggtgtggatc ggacgtgacg caccggatc cttgggtccaa gttcaactgg 480
 tacgtggacg cgtgtggatc gacataatgc aagacaaaggc cgggggggg gcatgtacgccc 540
 agcacgtacc gtgtggtcaag cgtcttccac gtctgtcacc aggactgggt gaatggcaag 600
 gagaataactg gcaaggatc caacaaagcc ctcccaagcc ccatcgagaa aaccatctcc 660
 aaaggccaaag ggcaccccg agaaggccacg gtgtacaccc tgccccatc cccggggggg 720
 atgaccaaga accaggatc cttggatc cttggatc cttggatc cttggatc cttggatc 780
 gccgtggatc gggagagcaa tggggatc gagaacaaact acaagaccac gcctccctgt 840
 ctggactccg acggcttccctt cttctctac agaagatca ccgtggacaa gaggatc 900
 cagcaggggaa acgttccctc atgtccgtg atgcatgagg ctctgcacaa ccactacacg 960
 cagaagaccc tctccctgtc tccgggtaaa 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
 QVLQTQTPSPV SAAVGSTVTI NCQASQSVYH NTYLAWYQQK PGQPPKQLIY DASTLASGVP 60
 SRFSGSGSGBT QFTLTISGVQ CNDAAAAYYCL GSYDCTNGDC FVFGGGTEVV VKRTVAAPSV 120
 FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWVKVDNALQ SGNSQESVTE QDSKDSTYSL 180
 STSTTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 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
 QVLQTQTPSPV SAAVGSTVTI NCQASQSVYH NTYLAWYQQK PGQPPKQLIY DASTLASGVP 60
 SRFSGSGSGBT QFTLTISGVQ CNDAAAAYYCL GSYDCTNGDC FVFGGGTEVV VKR 113

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SEQ ID NO: 143	moltype = AA length = 22
FEATURE	Location/Qualifiers
REGION	1..22
source	note = Engineered antibody sequence
	1..22
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 143	
QVLQTQTPSPV SAAVGSTVTI NC	22
SEQ ID NO: 144	moltype = AA length = 13
FEATURE	Location/Qualifiers
REGION	1..13
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	1..7
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 146	
DASTLAS	7
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	

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TVAAPSVFIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
 KDSTYSLSSLT 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 ccagtccatcgatgtttatcat aacacctacc tggctctgtta tcagcagaaaa 120
 ccaggccagg ctcccaaaaca actgtatcat gatgcattca ctctggcgtc tggggtccca 180
 tccgggttca gcccggatgg atctgggaca cagttcactc tcaccatcag cggcgtcag 240
 tctaactatgttgcgttca ctactgtctg ggcagttatg attgtactaa tggtgattgt 300
 tttttttccg gcccggggac cgagggtgttgc gtcacaaactcgatgttgcgtc accatgttc 360
 ttcatcttcg cggccatctgtatgagcgttgcgaaatctggaa ctgcctctgt tggtgccctg 420
 ctgaataact tctatccccag agaggccaaa gtacagtggaa aggtggataa cgcctcccaa 480
 tccgggttcaatgttgcgttca ctactgtctg ggcagttatg attgtactaa tggtgattgt 540
 agcaggcacccttgcacgttgcgaaatgttgcgttca ctacacgttgcgatgttgcgttgc 600
 gtcacccatc agggccgttgcgaaatgttgcgttca ctacacgttgcgatgttgcgttgc 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 ccagtccatcgatgtttatcat aacacctacc tggctctgtta tcagcagaaaa 120
 ccaggccagg ctcccaaaaca actgtatcat gatgcattca ctctggcgtc tggggtccca 180
 tccgggttca gcccggatgg atctgggaca cagttcactc tcaccatcag cggcgtcag 240
 tctaactatgttgcgttca ctactgtctg ggcagttatg attgtactaa tggtgattgt 300
 tttttttccg gcccggggac cgagggtgttgc gtcacaaactcgatgttgcgtc accatgttc 360
 ttcatcttcg cggccatctgtatgagcgttgcgaaatctggaa ctgcctctgt tggtgccctg 420
 ctgaataact tctatccccag agaggccaaa gtacagtggaa aggtggataa cgcctcccaa 480
 tccgggttcaatgttgcgttca ctactgtctg ggcagttatg attgtactaa tggtgattgt 540
 agcaggcacccttgcacgttgcgaaatgttgcgttca ctacacgttgcgatgttgcgttgc 600
 gtcacccatc agggccgttgcgaaatgttgcgttca ctacacgttgcgatgttgcgttgc 660

SEQ ID NO: 153 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: 153
 caagtgtcga cccagactcc atccccctgt tctgcagctg tgggaagcac agtcaccatc 60
 aattgc 66

SEQ ID NO: 154 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: 154
 caggccaggc agagtgttta tcataaacacc tacctggcc 39

SEQ ID NO: 155 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: 155
 tggtatcagg agaaaccagg gcagcctccc aaacaactga tctat 45

SEQ ID NO: 156 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: 156
 gtgcattcca ctctggcgtc t 21

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SEQ ID NO: 157 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: 157
 ggggtcccat cgcggttcag cggcagtggta tctgggacac agttcactct caccatcaggc 60
 ggctgtcagt gtaacgatgc tgccgcttac tactgt 96

SEQ ID NO: 158 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: 158
 ctgggcaggat atgattgtac taatggtgat tgttttgtt 39

SEQ ID NO: 159 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: 159
 ttccggcgagg ggaccggagggt ggtggtcaaaa cgt 33

SEQ ID NO: 160 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: 160
 acggtgttgcg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga 60
 actgcctctt ttgtgtcg gctgaataac ttttatccca gagaggccaa agtacagttt 120
 aagggttgcata acggcttcata atccggtaaac tccccaggaga gtgtcacaga cgaggacagc 180
 aaggacacgca cctacagcct cagcagcacc ctgacgcgtga gcaaaagcaga ctacgagaaa 240
 cacaaggatct acgcctgcga agtcacccat cagggctgtga gtcgcggcgt cacaaggagc 300
 ttcaacaggggagatgtttagt 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
 EVOLVESGGG LVQPGGSSLRL SCAVSGIDL GYYMNWVRQA PGKGLEWVGV IGINATYYA 60
 SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
 PLAPSSKSTS GGTAALGCLV KDYPPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
 TVPSSSLGTP TYICCNVNHKP SNTKVDKRV PKSCDKTHTC PPCPABELLG GPSVLFPPK 240
 PKDTLMISRT PEVTCVVVDW SHDEPEVKFN WYVDGVVEHVN AKTKPREEQY ASTYRVSVL 300
 TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
 CLVKGFYPSD IAVEWESENQ PENNYKTPPP VLDSDGSSFL YSKLTVDKSR WQQGNVFSCS 420
 VMHEALHHY TQKSSLSPG 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
 EVOLVESGGG LVQPGGSSLRL SCAVSGIDL GYYMNWVRQA PGKGLEWVGV IGINATYYA 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

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mol_type = protein
organism = synthetic construct

SEQUENCE: 163
EVQLVESGGG LVQPGGSLRL SCAVSGIDLS 30

SEQ ID NO: 164      moltype = AA length = 5
FEATURE
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
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
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
REGION          1..32
note = Engineered antibody sequence
source           1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 167
RFTISRDNISK TTVYIQLQMNSL 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
source           1..11
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
source           1..330
mol_type = protein
organism = synthetic construct

SEQUENCE: 170
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPPKP KDLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIK 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
source           1..1326

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mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 171
 gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60
 tcctgtgcag tctctggaat cgacacctcg ggctactaca tgaactgggt ccgtcaggct 120
 ccagggaaagg ggctggagtg ggtcgaggatc attggattata atgggtgcac atatacgcg 180
 agctggcaga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
 caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgttag aggggacatc 300
 tggggccaag ggaccctcg caccgtctcg aeggcctccc ccaaggggccc atcggcttc 360
 cccttggcac ctcctccaa gacgtggatc gggggcacaag cgggcctggg ctgctggtc 420
 aaggactact tcccccgaacc ggtgtacggtg tctgtggacta cagggcctc gaccaggcgc 480
 gtgcacacct tcccggtgt cctacagtcc tcaggactct actccctcag cagcgtggg 540
 accgtccctc ccaggcagtt gggcacccag acctacatctt gcaacgtgaa tcacaaggcc 600
 agcaacacca aggtggacaa gagagttag cccaaatctt gtgacaaaac tcacacatc 660
 ccaccgtgcc cagcacctga actcttgggg ggaccgtcag tttctctt ccccccaaaa 720
 cccaaggaca ccctcatgtat ctcccgacc cctgaggta catgcgtgtt ggtggacgtg 780
 agccacgaag accctggatg caagttaaac tggtaatcggtt acggcgtgga ggtgcataat 840
 gccaagacaa agccggggaa ggacgtgtt gggacgtt accgtgtgtt cagcgtcctc 900
 accgtccctc accaggactg gctaatggc aaggagttaca agtgcgtt gtcacacatc 960
 gcccctccag ccccccattca gaaaaccatc tccaaagccca aaggggcagcc cccgagaacca 1020
 caggtgtaca ccctggccccc atccggggatc gagatgtacca agaaccaggat cagcgtgacc 1080
 tgcctggatc aagggtttca tcccgatcgat atcggcgtgg aatggggagag caatggggcag 1140
 cccggagaaaca actacaagac caccgtccctt gttgtggactt cccggcgtt cttttctc 1200
 tacagcaagc tcaccgtggc caagagcagg tggcagcagg ggaacgtt ctcgtgtcc 1260
 gtgtatgtatc aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1320
 aaatga 1326

SEQ ID NO: 172 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: 172
 gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60
 tcctgtgcag tctctggaat cgacacctcg ggctactaca tgaactgggt ccgtcaggct 120
 ccagggaaagg ggctggagtg ggtcgaggatc attggattata atgggtgcac atatacgcg 180
 agctggcaga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
 caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgttag aggggacatc 300
 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
 gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60
 tcctgtgcag tctctggaat cgacacctcg 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 gaaggggtcg gagtggtcg 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

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organism = synthetic construct

SEQUENCE: 176
gtcattggta ttaatggtgc 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
cgattccaca tctccagaga caattccaag accacggtgt atcttcaa at gaacagcttg 60
agagctgagg acactgtgt 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 ggaccctcggt 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 ggtttcccc ctggcacccct cctccaagag cacctctggg 60
ggcacagccg ccttggctg cctggtcaag gactacttc ccgaaccgg gacgggtcg 120
tggaaacttag cggccctgac cagccgcgtg cacaccttc cggctgtctt acagtccctca 180
ggactctact ccctcagcag cgtggtgacc gtgccttcca gcagcttggg caccaggacc 240
tacatctgca acgttaatca caagccccc aacccaagg tggacaagg agttgaggccc 300
aaatcttggt cccaaaatca ccatgcccc cctgtccccc caccgtactt cctgggggg 360
ccgtcagtct ttcttctccc cccaaaaccc aaggacacc tcatgatctc ccggaccct 420
gagggtcacat gctgtgggtt ggacgtgago cacgaagacc ctgaggtaa gttcaactgg 480
taacgtggacc gctgtggagggt gcataatgcc aaacaaaaaccc cgcggggaggc gcacgtacgcc 540
agcacgtacc tggtggtcag cgttccacc gtcctgcacc aggactggg gaatggcaag 600
gagttacaatgtt gcaagggtctc caacaaagcc ctcccaaggcc cccatcgaaa aaccatctcc 660
aaagccaaatggcagcccccc agaaccacag gtgtacacc tggcccccacc cccggggagg 720
atggccaaatggcagccgttccacc cctgtccacc gtttctatcc cagccacatc 780
gcccgtggagggtt gggagagccaa tggccacccca acaagaccac gcctccctgg 840
ctggactccg acggccctt ctcccttac agcaagttca ccgtggacca gaggcagggtgg 900
cagcaggggaa acgttttctc atgtccgtt atgtcatgagg ctctgcacca ccactacac 960
cagaagggccatc ttcctctgtc tccgggtaaa 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
FIPPPSDEQL KSGTASVVCL LNNFYPREAK VQWVKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTTLSKAD 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

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SEQ ID NO: 183	moltype = AA length = 22
FEATURE	Location/Qualifiers
REGION	1..22
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	1..7
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 186	
DASTLAS	7
SEQ ID NO: 187	moltype = AA length = 32
FEATURE	Location/Qualifiers
REGION	1..32
source	note = Engineered antibody sequence
	1..32
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 187	
GVPSRFSGSG SGTDFTLTIS SLQPEDVATY YC	32
SEQ ID NO: 188	moltype = AA length = 13
FEATURE	Location/Qualifiers
REGION	1..13
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	1..11
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 189	
FGGGTKVEIK R	11
SEQ ID NO: 190	moltype = AA length = 106
FEATURE	Location/Qualifiers
REGION	1..106
source	note = Engineered antibody sequence
	1..106
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 190	
TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS	60

-continued

KDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	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 cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc	60
aattgccagg ccagtcagag tggttatcat aacacctacc tggcctggta tcagcagaaa	120
ccaggaaag ttccctaagca actgatctat gatgcaccca ctctggcatc tgggttccca	180
tetcgttca gtggcactgg atctggaca gatttcactc tcacatcag cagcgtcag	240
cctcgaatgtttca ttactgtctg ggcagttatg attgtactaa tggtgatgt	300
tttggggatcg cggcggaaac caagggtggaa atcaaacgtg cggcgttgc accatctgtc	360
ttcatcttcc cggccatctga tgacgacttg aaatctggaa ctgccttgt tggtgctg	420
ctgaataact tctatcccg agaggccaa gtacagtgaa aggtggataa cgccctccaa	480
tcggtaatcc cccaggagag tgtcacacag cagcacacca aggacacac ctacagcctc	540
agcagcaccctgacgttag caaaggcagac tacgagaaac acaaagtcta cgcctgcgaa	600
gtcaccatc accggccatc ctcggccgtc acaaaggtc 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 cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc	60
aattgccagg ccagtcagag tggttatcat aacacctacc tggcctggta tcagcagaaa	120
ccaggaaag ttccctaagca actgatctat gatgcaccca ctctggcatc tgggttccca	180
tetcgttca gtggcactgg atctggaca gatttcactc tcacatcag cagcgtcag	240
cctcgaatgtttca ttactgtctg ggcagttatg attgtactaa tggtgatgt	300
tttggggatcg cggcggaaac caagggtggaa atcaaacgtg cggcgttgc accatctgtc	339
SEQ ID NO: 193	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: 193	
caagtgtga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc	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 tcataacacc 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	
tggtatcagc agaaaaccagg gaaaattctt 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	
gatgcaccca ctctggcatc t	21
SEQ ID NO: 197	moltype = DNA length = 96

-continued

FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 197
 ggggtccat ctcgttcag tggcagtggaa tctgggacag atttcactt caccatcaggc 60
 agcctgcaggc 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
 ctggcaggat 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
 ttcccggagg gaaccaaggat ggaaaatcaaa 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
 acgggtggctg caccatctgt cttcatcttc ccgcacatcg atgagcaggta gaaatctgg 60
 actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
 aagggtggata acgcctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc 180
 aaggacacgca cctcagcct cagcagcacc ctgacgcgtga gcaaaggcaga ctacgagaaa 240
 cacaaggctc acgcctgcga ctacccat caggcgtga gtcgcggcgt cacaaggagc 300
 ttcaacacagg 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
 EVOLVESGGG LVQPGGSLRL SCAVSGIDLS GYYMNWVRQA PGKGLEWVGV IGINGATYYA 60
 SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
 PLAPSSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSVV 180
 TVPSSSLGTQ TYICCNVNHPK SNTKVNDARVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK 240
 PDKTLMISRT PEVTCVVVD SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVSVL 300
 TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
 CLVKGFYPSD IAVEWESNQG PENNYKTTPPP VLDSDGSSFL 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
 EVOLVESGGG LVQPGGSLRL SCAVSGIDLS GYYMNWVRQA PGKGLEWVGV 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

-continued

	organism = synthetic construct
SEQUENCE: 203	
EVQLVESGGG LVQPGGSLRL SCAVSGIDLS	30
SEQ ID NO: 204	moltype = AA length = 5
FEATURE	Location/Qualifiers
REGION	1..5
source	note = Engineered antibody sequence
	1..5
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 204	
GYMMN	5
SEQ ID NO: 205	moltype = AA length = 14
FEATURE	Location/Qualifiers
REGION	1..14
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	1..32
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 207	
RFTISRDNSK TTVYLMQNSL 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
source	note = Engineered antibody sequence
	1..11
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 209	
WGQGTLVTVS S	11
SEQ ID NO: 210	moltype = AA length = 330
FEATURE	Location/Qualifiers
REGION	1..330
source	note = Engineered antibody sequence
	1..330
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 210	
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYPPEPVTVWS WNSGALTSGV HTFPAVLQSS	60
GLYSLSSVVTPPSSSLGTQT YICCNVNHKPS NTKVDARVEP KSCDKTHTCP PCPAPELLGG	120
PSVFLFPKPKD TDTLMISRTPEVTCVVVDVSHEDPEVKPFW YVDGVDEVHNA KTKPREEQYA	180
STYRVSVS VLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTFIS KAKGQPREPQ VYTLPPSREE	240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGFSFFLY SKLTVDKSRW	300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	330
SEQ ID NO: 211	moltype = DNA length = 1326
FEATURE	Location/Qualifiers
misc_feature	1..1326
source	note = Engineered antibody sequence
	1..1326
	mol_type = other DNA

-continued

organism = synthetic construct

SEQUENCE: 211

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gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggc cctgagactc 60
tcttgtcag tctctggaat cgacctcagt ggctactaca tgaactgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggctggagtc attggattta atgggtccac atactacgct 180
agctggcgca aaggccgatt caccatctcc agagacaattt ccaagaccac ggtgtatctt 240
caaataatgaaaca gcctgagagc tgaggacact gctgtgtatt tctgtgttag aggggacatc 300
tggggcacaag ggaccctcgta caccgtctcg agcgccctcca ccaaggccc atcggtttc 360
ccctgtggac cctcttccaa gaggcacctc tggggcaacag egggccctggg ctgctgtgc 420
aaggactact tcccgaaacc ggtgacgggtg tcgtggaaact caggccgctt gaccaggcc 480
gtgcacacact tcccggtctgt cttacagtcc tcaggactctt actcttcctc cagcgtgtgc 540
accgtgeccctt ccacgtcgat gggccacccag acctacatctt gcaacgtgaa tcacaagccc 600
aquaacacca aagggtggacgc gagatgttagt cccaaatctt gtgacaaaac tcacacatgc 660
ccacgtgtcc caccgtcgatc actcttgggg ggaccgtcag ttttttttccccccaaaaa 720
cccaaggaca cccctcatgtat cttccggacc cttcgagggtca catcgctgtgtt ggtggacgtg 780
agccacgaag accctggaggt caagttaac tggtaatgtgg acggcggtt ggtgcataat 840
gccaagacaa accggccgggg ggacggatc gccagccgtt accgtgtgtt cagcgtctc 900
accgttcgtc accaggactg tctgtatggc aaggagtaca agtgcacgtt ctccaaacaaa 960
gccccccccc ccccatcgat gaaaaccatc tccaaagccca aaggggcaggcc cccggaaacca 1020
cagggtgtaca ccctggccccc atccggggag gagatgtaccat agaaccaggat cagcgtgacc 1080
tgcctgttca aagggttctca tcccgacgtatc atccgggtgg agtggggaggg caatgggcag 1140
ccggagaacaa actacaagac caccgttcccg tggctggactt cccggggctc cttttctc 1200
tacagcaacgc tccacgttgc acaaggcagg tggcaggcagg ggaacgttcc ctcgtgtcc 1260
gtgtatgtatc aggtctgtca 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

```

gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggc cctgagactc 60
tcttgtcag tctctggaat cgacctcagt ggctactaca tgaactgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggctggagtc attggattta atgggtccac atactacgct 180
agctggcgca aaggccgattt caccatctcc agagacaattt ccaagaccac ggtgtatctt 240
caaataatgaaaca gcctgagagc tgaggacact gctgtgtatt tctgtgttag aggggacatc 300
tggggcacaag ggaccctcgta caccgtctcg agcgccctcca ccaaggccc atcggtttc 333

```

SEQ ID NO: 213 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: 213

```

gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggc cctgagactc 60
tcttgtcag tctctggaat cgacctcagt 90

```

SEQ ID NO: 214 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: 214

```

ggctactaca tgaac                                              15

```

SEQ ID NO: 215 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: 215

```

tgggtccgtc aggctccagg gaaggggctg gatgtgggtcg ga                                              42

```

SEQ ID NO: 216 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

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SEQUENCE: 216
gtcattggta ttaatggtgc cacatactac gcgagctggg cgaaaggc 48

SEQ ID NO: 217 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: 217
cgattccacca tctccagaga caattccaag accacggtgt atcttcaa at gaacagcctg 60
agagctgagg acactgctgt gtatttctgt gctaga 96

SEQ ID NO: 218 moltype = length =
SEQUENCE: 218
000

SEQ ID NO: 219 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: 219
tggggccaag ggaccctcg caccgtctcg agc 33

SEQ ID NO: 220 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: 220
gcctccacca agggcccattt ggtttttccc ctggcacccctt cctccaagag cacctctggg 60
ggcacagcggg ccctgggtcg cctgttcaggacttcc cccgaaccggt gacgggtgtcg 120
tggaaacttag cgcgcctgac cagggcgtg cacaccccttc cggctgtctt acagtccctca 180
ggactctactt ccctcagcag cgtgtgtacc ttgtcccttca gtagcttggg caccaggacc 240
tacatctgtca acgtgaatca caagccccago aacaccaagg tggacggag agttgagccc 300
aaatcttgta acaaaatccatc cacaatccca ccgtggccatc caccatgtttt cctggggggga 360
ccgttcgtctt cccttccatc cccaaaaccacc aaggacaccctt tcatgtatctc ccggaccctt 420
gaggtaatccatc ggtgtgtgggt ggacgtgagc cacaagacc ctgaggtaaa gttcaactgg 480
tacgtggaccc ggtgtggaggt gcataatgcc aagacaaaggc cggggggggg gcaatgtaccc 540
agcacgttacc ggtgtgttcgg cgttccatcc gttctgtccaggactgtgtt gaaatggcaag 600
gagttacaatccatc gcaaggatccatc ccccaaggccccc ccatcgagaa aaccatctcc 660
aaaggccaaagg ggcaggcccccc agaaccacag gtgtacaccctt tgcccccattt ccgggggggg 720
atggccaaaggcc accaggatccatc cctgtaccatcc ctggtaaaatcc gtttctatcc cagcgacatc 780
ggccgtggatggggagccatc tggggagccgg gagaacaatccatc acaagaccac gcctccctgg 840
ctggacttcg acgggttccatc cttccatccatc agcaagatccatc ccgtggacaa gagcaggatgg 900
cagcaggggaa acgttccatc atgtccatccatc atgtccatccatc ccactacacg 960
cagaagagcc ttccttgc 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 DFTLTISLQ PEDVATYYCL GSYDCTNGDC FVFGGGTKVE IKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
SSTLTLASKAD 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 DFTLTISLQ PEDVATYYCL GSYDCTNGDC FVFGGGTKVE IKR 113

SEQ ID NO: 223 moltype = AA length = 22

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FEATURE REGION	Location/Qualifiers 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 FEATURE REGION	moltype = AA length = 13 Location/Qualifiers 1..13 note = Engineered antibody sequence	
source	1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 224 QASQSVYHNT YLA		13
SEQ ID NO: 225 FEATURE REGION	moltype = AA length = 15 Location/Qualifiers 1..15 note = Engineered antibody sequence	
source	1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 225 WYQQKPGKVP KQLIY		15
SEQ ID NO: 226 FEATURE REGION	moltype = AA length = 7 Location/Qualifiers 1..7 note = Engineered antibody sequence	
source	1..7 mol_type = protein organism = synthetic construct	
SEQUENCE: 226 DASTLAS		7
SEQ ID NO: 227 FEATURE REGION	moltype = AA length = 32 Location/Qualifiers 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 FEATURE REGION	moltype = AA length = 13 Location/Qualifiers 1..13 note = Engineered antibody sequence	
source	1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 228 LGSYDCTNGD CFV		13
SEQ ID NO: 229 FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11 note = Engineered antibody sequence	
source	1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 229 FGGGTKVEIK R		11
SEQ ID NO: 230 FEATURE REGION	moltype = AA length = 106 Location/Qualifiers 1..106 note = Engineered antibody sequence	
source	1..106 mol_type = protein organism = synthetic construct	
SEQUENCE: 230 TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC		60 106

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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
 caaagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
 aattgcagg ccagtcaagag tgtttatcat aacacctacc tggcctggta tcagcagaaa 120
 ccagggaaag ttcctaagca actgatctat gatgcaccca ctctggcatc tgggttccca 180
 ttcgcgttca gtggcagtgg atctgggaca gatttcactc tcaccatcg cagcctgcag 240
 ctgcgaatgttca ttgcactcg tttactgtcg ggcatgtatc attgtactaa tggtgatgt 300
 ttgttttcg gggaggaaac caagggtggaa atcaaactgta cgggtggotgc accatctgtc 360
 ttcatcttcc cgccatctga tgacgatgttgg aaatctggaa ctgcctctgt tggtgctgt 420
 ctgaaataact tttatccccag agaggccaaa gtacagtggaa aggtggataa cgccttccaa 480
 tcgggttaact cccaggagatc tgtcacagag caggacagcagc accatcgatc 540
 agcagcaccc tcgcgttagt caaaggcagac tacggagaac acaaagtctc cgcctgcgaa 600
 gtcacccatc agggccttagt ctcggccgtc acaaagagct tcaacagggg agagtgttag 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
 caaagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
 aattgcagg ccagtcaagag tgtttatcat aacacctacc tggcctggta tcagcagaaa 120
 ccagggaaag ttcctaagca actgatctat gatgcaccca ctctggcatc tgggttccca 180
 ttcgcgttca gtggcagtgg atctgggaca gatttcactc tcaccatcg cagcctgcag 240
 ctgcgaatgttca ttgcactcg tttactgtcg ggcatgtatc attgtactaa tggtgatgt 300
 ttgttttcg gggaggaaac caagggtggaa atcaaactgta 339

SEQ ID NO: 233 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: 233
 caaagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
 aattgc 66

SEQ ID NO: 234 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: 234
 caggccagtc agagtgttta tcataacacc tacctggcc 39

SEQ ID NO: 235 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: 235
 tggtatcagc agaaaccagg gaaagtccct aagcaactga tctat 45

SEQ ID NO: 236 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: 236
 gatgcaccca ctctggcatc 21

SEQ ID NO: 237 moltype = DNA length = 96
 FEATURE Location/Qualifiers

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SEQUENCE: 243
QEQLKESGGR LVTPGTSLTL TCTVSGIDL
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
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
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
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
SEQUENCE: 247
RFTISRTSST TVDLKMTRLT TEDTATYFCA R
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
WGPGBTLVTVS S
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
GLYSLSVVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPPKP KDTLMISRTP EVTCVVDVDS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
STYRVVSVLT VLHQDWLNGE EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPSPREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESENQQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV 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

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SEQUENCE: 251
caggagcagc tgaaggagtc cgggggtcgc ctggtcacgc ctgggacatc cctgacactc 60
acacctgcacc tctctggaaat cgaccctcaat aaccactaca tgcataatgggt ccgcagggtt 120
ccaggaaagg ggctggatgt gatcgaggatc gtggatatttt atggtcgcac atatacagcg 180
agctgggcga aaggccgatt caccatctcc agaaacctcgta cgacoacgggt ggatctgaaa 240
atgaccaggc tgacaaccga ggacacggcc acctatcttctt gtgcacagggtt ggacatctgg 300
ggccggaggaa cccttggttcac ctgtcgagc gcctccacca agggccatc ggttcttcccc 360
ctggcacccctt ccttcggaaatg cacccttgggg ggcacagcggtt ccctgggtgtt ctgggtcaag 420
gactacttcc cogaacccgggt gacgggtgtcg ttggaaacttagtgc gegeoctgtac cagcggcgtg 480
cacaccccttc cggctgtctt acagtcttcga ggactctactt ccctcagcggc ctgggtgacc 540
gtggcccttca gcaactttggg caccacggacc tacatcttgc acgtgtaaatca caagccccggc 600
aaacaccaaaagg tggcaaaagg agttggggcc aaatcttgc acaaaaactca catatcgccca 660
cctgtggcccaag caccatgtactt cctgggggggatc ccgttcgttcc tccttccccccc 720
aaggacaccc tcatgtatctc cccggacccctt gagggtccatc gctgtgggttgg acgtgtggcc 780
cacaagacccatc ctgggttcaatc gttcaacttggg ttcgtgtggacg gctgtgggggttgc gataatggcc 840
agacaccaaaagg cccggggggggc gcaacttggggc agcaacttggc ttgtgtgttgc ctgggttcc 900
gtccctgcaccaggactggctt gaatggcaag gaggatcaatggc gcaagggttcc caacaaaggcc 960
ctcccaagccccc ccacatggaaa aaccatcttcc aaaggccaaatggc ggcaccccccggc agaacccacag 1020
gtgtacacccatc tggggccatcc cccggggggatc atggcaatggc accagggttcc cttgtaccc 1080
ctgggtcaatgg gttttatcttcc cttgtggatgtt gggggatggatc tggggggccggcc 1140
gagaacaactt acaagacccatc gcttccctgtt ctggacttcccg acgggttccctt cttecccttac 1200
agcaacttcaatc ccgtggacaaatc gagcagggttgc cttgtggatgttcccttacatc atgtccgtt 1260
atgcatggggatc ctctgcacaaatc ccactacacgc cagaagacccatc tttccctgttcccggtttaaa 1320
tga

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SEQUENCE: 252
caggcaggcgc tgaaggagtc cgggggtcgc ctggtcacgc ctgggacatc cctgacactc 60
acctgcacccg tctctggat cgcacctcg aaccactaa tgcaatgggt cccgcaggct 120
ccaggaggag ggctggagt gatcgaggc gttggatata atggtcgcac atactacgcg 180
agcttggccca aaggccgtt caccatctcg acaaaccctgt cgaccacccgtt ggatctgaaa 240
atgaccaggc tgacaaccggc ggacacggcc acatattttt gtgcacagggg ggacatctgg 300
ggcccaagca ccctgtgtcac cggtctcgac 330

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```
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
caggagcaga tggaggatgc cgggggtgcg ctggtcacgc ctgggacatc cctgacactc 60
acctgcaccg tctctggaaat ccacctcgat 90

SEQUENCE: 254
suggests no bases

```
SEQ ID NO: 255          moltype = DNA    length = 42
FEATURE
misc_feature           Location/Qualifiers
1..42
note = Engineered antibody sequence
source
1..42
mol_type = other DNA
```

SEQUENCE: 255 organism = synthetic construct
tgggtccaccc aqgctccaaqc qaaqqqqqctq qaqtggatcq qa 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

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gtcggtggta ttaatggtcg 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 ctcgtcgacc acgggtggatc tgaaaatgac caggctgaca 60
acccgaggaca cggccaccta tttctgtgcc 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
tggggccccag 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 agggcccatc ggtttcccc ctggcacccct cctccaagag caccctctggg 60
ggcacagccg ccctgggctg cctggtcaag gactacttc cccgaaacctg gacgggtgtcg 120
tggaaactcag gggcccttgac cagggcgtc cacaccccttc cggctgtctc acagtccctca 180
ggactctact ccctcagcag cgtggtgacc gtggcccttca gcagcttggg caccaggacc 240
tacatctgca acgttaatca caagcccaago aacccaagg tggacaagg agttgagccc 300
aaatcttgcg aaaaaactca cacatggcca ccgtgccccccg caccgtgaact cctgggggga 360
ccgtcgtact tccttcccccc cccaaaaacc aaggacacccc tcatgatctc ccggaccct 420
gaggtcacat gggtgggtt ggacgtggcgcg cagggacagg ctgaggtcaa gttcaactgg 480
taacgtggacg gggtggaggt gcataatgcc aagacaaacgc cgcggggaggc gcagtagcgc 540
agcacgtacc gtgtggtcag cgtccctcacc gtctgcacc accgtggct gaatggcaag 600
gajtacaagaat gcaaggctc caaacaaaggcc ctccccaggcc ccacatcgaaa aaccatctcc 660
aaaggccaaag ggccggcccg aaaaacccgacccatc tggtacaccc tcgttatcc ccggggaggag 720
atgaccaaga accaggctcag cctgacccctc ctgtcaaaag gttcttatcc cagcgacatc 780
gcccgtggagt gggagacaa tggcagccg gagaacaact acaagaccac gcctccctg 840
cttgactccg acggctccctt ctccctcacc agcaagctca ccgtggacaa gagcagggtgg 900
cagcaggggaa acgtttctc atgtccctgtg atgcatggg ctctgcacaa ccactacacg 960
cagaagaccc tccctctgtc tccggtaaa tga 993

SEQ ID NO: 261 moltype = AA length = 219
FEATURE Location/Qualifiers
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
SRFKGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSTGDC FVFGGGTEVV VKRTVAAPSV 120
FIRPPPSDQL KSGTASVVCL LNNFYPREAK VQWVKVDNALQ SGNSQESVTQE QDSKDSTYSL 180
STSTTLSKAD YEHKVYACE VTHQGLSSPV TKSFNRGEC 219

SEQ ID NO: 262 moltype = AA length = 113
FEATURE Location/Qualifiers
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
SRFKGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSTGDC FVFGGGTEVV VKR 113

SEQ ID NO: 263 moltype = AA length = 22
FEATURE Location/Qualifiers

-continued

REGION	1..22	
source	note = Engineered antibody sequence	
	1..22	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 263		
QVLTQTASPV SAAVGSTVTI NC		22
SEQ ID NO: 264	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
REGION	1..13	
source	note = Engineered antibody sequence	
	1..13	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 264		
QASQSVYNYN YLA		13
SEQ ID NO: 265	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
REGION	1..15	
source	note = Engineered antibody sequence	
	1..15	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 265		
WYQQKPGQPP KQLIY		15
SEQ ID NO: 266	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
REGION	1..7	
source	note = Engineered antibody sequence	
	1..7	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 266		
STSTLAS		7
SEQ ID NO: 267	moltype = AA length = 32	
FEATURE	Location/Qualifiers	
REGION	1..32	
source	note = Engineered antibody sequence	
	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	
source	note = Engineered antibody sequence	
	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	
source	note = Engineered antibody sequence	
	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	
source	note = Engineered antibody sequence	
	1..106	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 270		
TVAAPSVFIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC	60	106

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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
 aattgcagg ccagtcaagg tgtttaaat tacaactacc ttgcctggta tcagcagaaa 120
 ccagggcagc ctcccaagca actgatctat tctacatcca ctctggcatc tggggctc 180
 tcgcgattca aaggcagtgg atctgggaca cagttcactc tcaccatcag cgacgtgc 240
 tgtgacgtat ctgccactta ctactgtcta ggcagttatg actgttagtac tggtgattgt 300
 ttgttttcg cgccggggac cgagggtgtg gtcaaacgtg cgggtgtgc accatctgc 360
 ttcatcttc cggccatctgt tgacgatgg aatctggaa ctgccttgt tggtgctcg 420
 ctgaataact tctatcccag agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
 tcgggtaact cccaggagag tgccacagat cggacacgac ctacagctc 540
 agcagcaccc tgacgtcgaa acaaaggatc aacaaagtcta cgcctgcgaa 600
 gtcacccatc agggctgtg ctgcggcgtc acaaaggact tcaacagggg 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
 aattgcagg ccagtcaagg tgtttaaat tacaactacc ttgcctggta tcagcagaaa 120
 ccagggcagc ctcccaagca actgatctat tctacatcca ctctggcatc tggggctc 180
 tcgcgattca aaggcagtgg atctgggaca cagttcactc tcaccatcag cgacgtgc 240
 tgtgacgtat ctgccactta ctactgtcta ggcagttatg actgttagtac tggtgattgt 300
 ttgttttcg cgccggggac cgagggtgtg gtcaaacgtg 339

SEQ ID NO: 273 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: 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
 tggtatcaggc 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

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note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 277
 ggggtctcat cgcgattcaa aggcaagtggta tctgggacac agttcactct caccatcagc 60
 gagctgcagt gtgacgtgc 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
 cttaggcaggat 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
 ttccggcgag ggaccgaggt 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
 acgggtggctt caccatctgt cttagatcttc ccggccatctg atgaggcaggat gaaatctgg 60
 actggcctctg ttgtgtgc gctgaataac ttctatccca gagaggccaa agtacagtgg 120
 aaagggtggata acgcgcctcca atcgggttaac tcccaggaga gtgtcacaga gcaggacagc 180
 aaggacagca cctacagcct cagcagcacc ctgacgcgtga gcaaaggaga ctacgagaaa 240
 cacaaggatct acgcgcgtcga agtcacccat cagggcctgaa gctcgcggcgt 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
 PLAPSSSKSTS GGTAALGCLV KDYFPEPVTV WNSMGALTSG VHTFPAVLQS SGLYSLSSVV 180
 TVPSSSLTQ TYICCNVNHPK SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVPLFPKK 240
 PKDTLMISRT PEVTCCVVVD SHEDPEVKFN WYVDGVIEVHN AKTPREEQY ASTYRVSLSV 300
 TVLHQDWLNLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPSSRE EMTKNQVSLS 360
 CLVKGFYPSD IAVEWESNQG PENNYKTTPP VLSDSDGSFFL YSKLTVDKSR WQQGNVFSCS 420
 VMHEALHNHY TQKSLSLSPKG 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

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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	
NHMQ	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	
RFTISRDNSK TTVYLMQNSL 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	
WGQGTLVTVS 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 DYFPEPVTVS WNSGALTSGV HTFPAVLQSS	60
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG	120
PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA	180
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE	240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPPV 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	

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gagggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60
tcttgtcag tctctggaat cgacactcagt aaccactaca tgcaatgggt ccgtcaggt 120
ccagggaaagg ggctggagtg ggtcgagtc gtggatatac atggtcgac atactacgcg 180
agctggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggttatctt 240
caaatacaca gaactgagacg tgaggacact gctgttatt tctgtgttag aggggacatc 300
tggggccaag ggaccctcgta caccgttcg agcgcctcca ccaaggccc atcggtttc 360
ccccctggcac cctccctcaa gagcacctct gggggcacaag cggccctggg ctgctggc 420
aaggactact tccccgaacc ggtgacgggt tcgtgaaact caggcgcct gaccagcggc 480
gtgcacact tcccggtcc ctcaagtcg tcaggactct actccctcag cagcgtggg 540
accgtgcacc ctcccgactt gggccccc acctacatct gcaacgtgaa tcacaagccc 600
agcaacacca aggtggacaa gagagtttag cccaaatctt gtgacaaaac tcacatgc 660
ccacccgtgcc cagcacctga actectgggg ggaccgtca gtttctctt ccccccaaaa 720
cccaaggacca ccctcatgtat cttccggacc cctggggatc catgctgtgt ggtggacgtg 780
agccacacca accctgggtt caagtccaaat ttgtacgtgg acggcgtgaa ggtgcataat 840
gccaagacaa accccgggaa ggacgactt gccacgcgtt accgtgttgtt cagcgtctc 900
accgtcttc accaggactg gctgaatggc aaggagtaca aytgcaaggt ctccaacaaa 960
gcctcccccacccatcgaa gaaaaccatc tccaaaggca aaggccggcc cggagaacca 1020
cagggttaca ccttgcggcc atccggggatc gagatgacca agaaccaggat cagcgttacc 1080
tgccctggtaa aaggcttcta tccacgcaacttccgtt gatgggagatc caatggcag 1140
ccggagaaca actacaagac cactgctcc gttgtggactt cccacggcctt ctcttc 1200
tacagcaacg tcaccgtggc caagacggg tggcagcggg gaaacgttcc ctcatgtcc 1260
gtgtatgcatttggcatac acgcagaaga gctctccctt gtcctccgggt 1320
aatatgt 1326

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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
 tcttgtcag tctctggaat cgacactcagt aaccactaca tgcaatgggt ccgtcaggt 120
 ccagggaaagg ggctggagtg ggtcgagtc gtggatatac atggtcgac atactacgcg 180
 agctggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggttatctt 240
 caaatacaca gaactgagacg tgaggacact gctgttatt tctgtgttag aggggacatc 300
 tggggccaag ggaccctcgta caccgttcg agcgcctcca ccaaggccc atcggtttc 360
 333

SEQ ID NO: 293 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: 293
 gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60
 tcttgtcag tctctggaat cgacactcagt 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 gagtgggtc 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

US 12,384,836 B2

159

160

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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 accacgggt atcttcaa at gaacagcctg 60
 agagctgagg acactgctgt gtat tctgt 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
 tggggc caag ggaccctcg t 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 agggccccatc ggtcttcccc ctggcacccct cctccaagag cacctctggg 60
 ggacacagcgg ccctgggctg cctggtaa gactacttc cccgaacccgt gacgggtgtcg 120
 tggaaacttag cgcgcctgac cagcggcgtg cacaccttc cggctgtctt acagtcccta 180
 ggactctact ccctcagcag cgtgttgacc gtgcccctca gca gcttggg caccaggacc 240
 tacatctgca acgtgaatca caagcaggc aacacaagg tggacaagag agttgagccc 300
 aaatcttgc taaaactca cacatggca cctgtcccc caccctgaact cctgggggga 360
 ccgtcagtct tcttcttccc cccaaaaccc aaggacacc tcatacttc cccggaccct 420
 gaggtcaatcat ggtgtgggtt ggacatcgtgca cacaaggacc ctgggggtt gttcaactgg 480
 tacatggacg cgcgtggaggat gataatggc aagacaagg cgcggggga gca gtcacgcc 540
 agcactgtacc gtgtgttca gtccttcacc gtcctgacc aggactggtt gatggcaag 600
 gaggatcaatgt gcaaggcttc caacaaggcc ctcccaggccc ccatcgagaa aaccatctcc 660
 aaaggccaaagg ggcacccccc agaaccacccat tgcccccattt cccgggggg 720
 atgaccaaga accaggatcg cctgacatcg ctggtaaagg gttctatcc cagcgcacatc 780
 gcccgtggaggat gggagggacaa tggggaccc gagaacaactt acaagaccac gcctccctgt 840
 ctggactccg acggcttctt cttcctctac agcaagctca cctgtggacaa gaggcgggtt 900
 cagcaggggaa acgtcttctc atgctccgtt atgcatgagg ctctgcacaa ccactacacg 960
 cagaagagcc ttccctgtc tccgggtaaa 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
 QVLTQSPSSL SASVGDRVTI NCQASQSVYN YNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSTGDC FVFGGGTKVE IKRTVAAPSV 120
 FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALPQ SGNSQESVTE QDSKDSTYSL 180
 STSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 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
 QVLTQSPSSL SASVGDRVTI NCQASQSVYN YNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSTGDC FVFGGGTKVE IKR 113

SEQ ID NO: 303 moltype = AA length = 22
 FEATURE Location/Qualifiers
 REGION 1..22

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source	note = Engineered antibody sequence 1..22 mol_type = protein organism = synthetic construct	
SEQUENCE: 303		
	QVLTQSPSSL SASVGDRVTI NC	22
SEQ ID NO: 304	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
REGION	1..13	
source	note = Engineered antibody sequence 1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 304		
	QASQSVYNN YLA	13
SEQ ID NO: 305	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
REGION	1..15	
source	note = Engineered antibody sequence 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	
source	note = Engineered antibody sequence 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	
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	
source	note = Engineered antibody sequence 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	
source	note = Engineered antibody sequence 1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 309		
	FGGGTTKVEIK R	11
SEQ ID NO: 310	moltype = AA length = 106	
FEATURE	Location/Qualifiers	
REGION	1..106	
source	note = Engineered antibody sequence 1..106 mol_type = protein organism = synthetic construct	
SEQUENCE: 310		
	TVAAPSVIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC	60 106
SEQ ID NO: 311	moltype = DNA length = 660	

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FEATURE Location/Qualifiers
 misc_feature 1..660
 note = Engineered antibody sequence
 source 1..660
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 311
 caagtgtga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
 aattgcagg ccagtcacagtg tgtttacaat tacaactacc ttgcctggta tcagcagaaa 120
 ccagggaaag ttctctaagca actgtatcatat tctacatccat ctctggcata tgggtccca 180
 ttctcggttca gtggcagttgg atctgggaca gatttcacttc tcaaccatcg cagcctgcag 240
 cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgttagtac tggtgatgt 300
 ttgtgtttcg gcccatttcgaa caaggtggaa atcaaacgttca cggtggctgc accatctgtc 360
 ttcatcttcg ccgcatttcgaa tgacgttggaa aatctggataat ctgcctctgt tggtgatgt 420
 ctgaataact ttatcccaag agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
 tcgggttaact cccaggagag tgcacagtgatc caggacacgaa aggacagcac ctacagcctc 540
 agcagcacccttgcacgttggaa caaacgttca ttcggatggaa acaaagtcttca cgcctgcgaa 600
 gtcacccatc agggccttgc ttcggatggaa acaaaggttca tcaacagggg 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
 caagtgtga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
 aattgcagg ccagtcacagtg tgtttacaat tacaactacc ttgcctggta tcagcagaaa 120
 ccagggaaag ttctctaagca actgtatcatat tctacatccat ctctggcata tgggtccca 180
 ttctcggttca gtggcagttgg atctgggaca gatttcacttc tcaaccatcg cagcctgcag 240
 cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgttagtac tggtgatgt 300
 ttgtgtttcg gcccatttcgaa caaggtggaa atcaaacgttca 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
 organism = synthetic construct

SEQUENCE: 313
 caagtgtga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
 aattgc 66

SEQ ID NO: 314 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: 314
 caggccatc agagtgttta caattacaac taccttgcc 39

SEQ ID NO: 315 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: 315
 tggtatcggc agaaaaccagg gaaagttctt aagcaactgatc tctat 45

SEQ ID NO: 316 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: 316
 tctacatcca ctctggcata t 21

SEQ ID NO: 317 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence

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source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 317
 gggggtcccat ctcgtttcag tggcagtgg a tctgggacag atttcactct caccatcagc 60
 agectgcagc ctgaagatgt tgcaacttat tactgt 96

SEQ ID NO: 318 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: 318
 ctgggcagg t atgattttag tactggtgat tgttttgtt 39

SEQ ID NO: 319 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: 319
 ttcggcgagg g aaccaagg t ggaaatcaa a cgt 33

SEQ ID NO: 320 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: 320
 acgggtggcgtt caccatctgt cttcatcttc ccgcgcattgtt atgagcagg t gaaatctgg 60
 actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
 aagggtggata acggcccttcca atcgggttaa tcccaggaga gtgtcacaga gcaggacagc 180
 aaggacagca cttacagcc t cagcagcacc ctgacgcgtg a gcaaaaggcaga ctacgagaaa 240
 cacaaggatctt acggcttgcgtt a gtcacccat caggcctgtt g gtcgccccgtt cacaaggagc 300
 ttcaacagg g gaggtgtt a g 321

SEQ ID NO: 321 moltype = AA length = 439
 FEATURE Location/Qualifiers
 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 YFCTRGIWG PGTLVTVSSA STKGPSVFPL 120
 APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TPPAVLQSSG LYSLSSVTV 180
 PSSSLGTQTY ICNVNHHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP SVFLPPPKPK 240
 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAY TKPREEQYAS TYRVSVLTV 300
 LHQDWLNKE YKCKVSNKAL PAPIEKTISK AKQOPREPOV YTLPPSREEM TKNQVSLTCL 360
 VKGFYPDSIA VEWEWSNGQPE NNYKTTPPVVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCVM 420
 HEALHNHYTQ KSLSLSPGK 439

SEQ ID NO: 322 moltype = AA length = 109
 FEATURE Location/Qualifiers
 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 YFCTRGIWG PGTLVTVSS 109

SEQ ID NO: 323 moltype = AA length = 29
 FEATURE Location/Qualifiers
 REGION 1..29
 note = Engineered antibody sequence

source 1..29
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 323
 QSLEESGGRL VTPGTPLTLT CTVSGIGLSS 29

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SEQ ID NO: 324      moltype = AA length = 5
FEATURE
REGION
1..5
note = Engineered antibody sequence
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
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
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
1..31
mol_type = protein
organism = synthetic construct
SEQUENCE: 327
RFTISKTSST TVDLRMASLT TEDTATYFCT R
31

SEQ ID NO: 328      moltype = length =
SEQUENCE: 328
000

SEQ ID NO: 329      moltype = AA length = 11
FEATURE
REGION
1..11
note = Engineered antibody sequence
1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 329
WGPGTLTVVS S
11

SEQ ID NO: 330      moltype = AA length = 330
FEATURE
REGION
1..330
note = Engineered antibody sequence
1..330
mol_type = protein
organism = synthetic construct
SEQUENCE: 330
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYPPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKP KDTLMSRTP EVTCVVVDVS HEDPEVKPNW YVDGVEVHNA KTKPREEQVA 180
STYRVVSVLT VLHQDWLNKG EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 331      moltype = DNA length = 1320
FEATURE
misc_feature
1..1320
note = Engineered antibody sequence
1..1320
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 331
cagtcgtcgaggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60

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tgcacagtct	ctggaatcg	cctcagtag	tactacatgc	agtgggtccg	ccagtctcca	120
ggggggggc	tggaatggat	cggagtcatt	ggtagttagt	gtaagacata	ctacgcgacc	180
tgggcgaaag	gcccattcac	catctccaag	acctcgtcg	ccacgggtgg	tctgagaatg	240
gccagtcga	caaccgagga	cacggccacc	tatttctgt	ccagagggg	catctggggc	300
ccggggaccc	tcgtcaccgt	ctcagcgccc	tccaccaaa	gcccattcg	tctccccctg	360
gcacccctct	ccaagagcac	ctctggggg	acagcgcc	tgggctgc	ggtaaaggac	420
tacttccccc	aaccgggtac	ggtgtcg	aactcaggcg	ccctgaccag	cggcggtgcac	480
accttcccg	ctgtctaca	gtcctcagg	ctctactcc	tcagcagcgt	ggtgaccgt	540
ccctccagca	gtttgggcac	ccagactac	atctgcac	tgaatcaca	gcccagcaac	600
accaagggtg	acaagagact	tgagccccaa	tcttgtgac	aaactcac	atgcccaccg	660
tgcccgac	ctgaactct	ggggggaccc	tcagtc	tcttcccccc	aaaacccaa	720
gacaccctca	tgatetccc	gaccctgag	gtcacatgc	ttgtgtgg	cgtgagccac	780
gaagacccgt	aggteactt	caactggta	gtgacggcg	ttggagggt	taatgccaag	840
acaaggccg	gggaggagca	gtacggcag	actgtaccgt	ttgtcagcgt	cctcaccgtc	900
ctgcaccagg	actgggtgaa	tggcaaggag	tacaagtca	aggctccaa	caaaggccctc	960
ccagccccc	tcgagaaaaac	catctccaa	gccaaagggg	agccccgaga	accacagggt	1020
tacaccctgc	ccccatcccg	gggaggatg	accaagaacc	aggtaacgt	gacctgcctg	1080
gtcaaaggct	tctatccc	cgacatcg	gtggagtg	agagcaatgg	gcagccggag	1140
aacaactaca	agacaccg	tccctgtct	gactccgac	gtctcttctt	cctctacagc	1200
aagctcaccg	tggacaagag	caggtggcag	cagggaaac	tcttctcatg	ctccgtgt	1260
catgaggctc	tgcacaacca	ctacacgc	aagagcctct	ccctgtctcc	gggtaaatga	1320

SEQ ID NO: 332 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: 332
 cagtgcgtgg aggagtccgg ggggtccctg gtacgcctg ggacaccctt gacactcacc 60
 tgcacagtct ctggaatcg cctcagtag tactacatgc agtgggtccg ccagtctcca 120
 gggggggggc tggaatggat cggagtcatt ggtagttagt gtaagacata ctacgcgacc 180
 tgggcgaaag gcccattcac catctccaag acctcgtcg ccacgggtgg tctgagaatg 240
 gccagtcga caaccgagga cacggccacc tatttctgtt ccagagggg catctggggc 300
 cccggggacc tcgtcaccgt ctgcagc 327

SEQ ID NO: 333 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: 333
 cagtgcgtgg aggagtccgg ggggtccctg gtacgcctg ggacaccctt gacactcacc 60
 tgcacagtct ctggaatcg cctcagtag 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
 tgggtccccc 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 ggcacactggg cgaaaggc 48

SEQ ID NO: 337 moltype = DNA length = 93

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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
 accgaggaca 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
 tggggccccgg 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 agggccccc ggttcttccc ctggcacccct cctccaagag caccctctggg 60
 ggcacagccg ccctggctg cctgttcaag gactacttcc cccgaacgggt gacgggtgtcg 120
 ttggactctgac ggcgcctgac cagggcgtg cacacccctc cggctgtctt acagtccctca 180
 ggactctact ccctcagcagc cgtgttgacc gtgccctcca gcagcttggg caccaggacc 240
 tacatctgc aacgtgaatca caagcccago aacaccaagg tggacaagag agttgagccc 300
 aaatcttgcg aaaaaactca cacaatccca ccgtgccccag caccctgaact cctggggggga 360
 ccgtcagtct tccttctccc cccaaaaccc aaggacaccc tcatgatctc ccggaccct 420
 gaggtcacat gggtgtgggt ggacgtgagc cacaagacc ctgaggtaaa gttcaactgg 480
 tacgtggacg ggcgtggaggt gcataatgcc aagacaaagg cgcggggagga gcagtacgcc 540
 agcacgtacc gggtgtgtcg cgtgttccacc gtctgtcacc aggactgtcg gaatggcaag 600
 gactacaatg gcaaggatctc caacaaggcc cccatcgagaa aaccatctcc 660
 aaaggccaaag ggcagccccg agaaccacag gtgtacacc tgccccccatc ccgggaggag 720
 atgaccaaga accaggtcag cctgacccctc ctggtaaaag gttctatcc cagcgacatc 780
 gccgtggagt gggagagcaa tggggcaggg gagaacaact acaagaccac gcctccctg 840
 ctggactctg acggcttctc ctcccttac agcaagctca ccgtggacaa gagcaggatgg 900
 cagcaggggaa acgttcttc atgtccgtg atgtcatgg ctctgcacaa ccactacacg 960
 cagaagagcc ttcctctgtc tccggtaaa tga 993

SEQ ID NO: 341 moltype = AA length = 219
 FEATURE Location/Qualifiers
 REGION 1..219
 note = Engineered antibody sequence
 source 1..219
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 341
 QVLQTQTPSPV SAAVGSTVTI NCQASQNLYNNYLAWYQQK PGQPPKQLIYSTSTLASGVS 60
 SRFRGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSRGDC FVFGGGTEVV VKRTVAAPSV 120
 FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQSGNSQESVTE QDSKDSTYSL 180
 SSTLTLASKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 219

SEQ ID NO: 342 moltype = AA length = 113
 FEATURE Location/Qualifiers
 REGION 1..113
 note = Engineered antibody sequence
 source 1..113
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 342
 QVLQTQTPSPV SAAVGSTVTI NCQASQNLYNNYLAWYQQK PGQPPKQLIYSTSTLASGVS 60
 SRFRGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSRGDC FVFGGGTEVV VKR 113

SEQ ID NO: 343 moltype = AA length = 22
 FEATURE Location/Qualifiers
 REGION 1..22
 note = Engineered antibody sequence
 source 1..22

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SEQUENCE: 343	mol_type = protein organism = synthetic construct	
QVLTQTPSPV SAAVGSTVTI NC		22
SEQ ID NO: 344	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
REGION	1..13	
source	note = Engineered antibody sequence	
SEQUENCE: 344	1..13	
QASQNVYNNN YLA	mol_type = protein organism = synthetic construct	
SEQ ID NO: 345		13
FEATURE	moltype = AA length = 15	
REGION	Location/Qualifiers	
source	1..15	
SEQUENCE: 345	note = Engineered antibody sequence	
WYQQKPGQPP KQLIY	1..15	
SEQ ID NO: 346	mol_type = protein organism = synthetic construct	
FEATURE		15
REGION	moltype = AA length = 7	
source	Location/Qualifiers	
SEQUENCE: 346	1..7	
STSTLAS	note = Engineered antibody sequence	
SEQ ID NO: 347	1..7	
FEATURE	mol_type = protein organism = synthetic construct	
REGION		7
source	moltype = AA length = 32	
SEQUENCE: 347	Location/Qualifiers	
GVSSRFRGSG SGTQFTLTIS DVQCDDAATY YC	1..32	
SEQ ID NO: 347	note = Engineered antibody sequence	
FEATURE	1..32	32
REGION	mol_type = protein organism = synthetic construct	
source		
SEQUENCE: 348		
LGSYDCSRGD CFV	moltype = AA length = 13	
SEQ ID NO: 348	Location/Qualifiers	
FEATURE	1..13	
REGION	note = Engineered antibody sequence	
source	1..13	
SEQUENCE: 348	mol_type = protein organism = synthetic construct	
LGGSYDCSRGD CFV		13
SEQ ID NO: 349		
FEATURE	moltype = AA length = 11	
REGION	Location/Qualifiers	
source	1..11	
SEQUENCE: 349	note = Engineered antibody sequence	
FGGGTEVVVK R	1..11	
SEQ ID NO: 349	mol_type = protein organism = synthetic construct	
FEATURE		11
REGION		
source		
SEQUENCE: 350		
TVAAPSVIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS	moltype = AA length = 106	
KDSTSYLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC	Location/Qualifiers	
	1..106	60
SEQ ID NO: 351	note = Engineered antibody sequence	
FEATURE	1..106	
misc_feature	mol_type = protein organism = synthetic construct	
SEQUENCE: 350		
TVAAPSVIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS		
KDSTSYLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC		60
SEQ ID NO: 351		
FEATURE	moltype = DNA length = 660	
misc_feature	Location/Qualifiers	
	1..660	

-continued

source note = Engineered antibody sequence
 1..660
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 351
 caagtgtga cccagactcc atccccctgt tctgcagctg tgggaagcac agtcaccatc 60
 aattgcagg ccagtcaaaaa tgtttataat aacaactacc tagcctggta tcagcagaaa 120
 ccagggcagc ctcccaagca actgatctat tctacgtcca ctctggatc tgggtctca 180
 tcgcgattca gaggcagttg atctgggaca cagttcactc tcaccatcag cgacgtgcag 240
 tggacgtatc ctgcactta ctactgtcta ggcaagtttgc attgttagtgc tggtgatgt 300
 ttgttttcg gggggggac cgagggttgt gcacaaacgtt cgggtggotgc accatctgtc 360
 ttcatcttcc cgccatctga tgacgatgg aaatctggaa ctgcctctgt tggtgctcg 420
 ctgaataact ttatcccaag agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
 tcgggtaacttcccaag gggggggac ttgtacagatc caggacagcac ctacagctc 540
 agcagcaccc tgacgctgatc caaaacgttca cgcctcgaa 600
 gtcacccatc agggcctgatc ctcggccgtc acaaagatc tcaacagggg agagtgttag 660

SEQ ID NO: 352 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: 352
 caagtgtga cccagactcc atccccctgt tctgcagctg tgggaagcac agtcaccatc 60
 aattgcagg ccagtcaaaaa tgtttataat aacaactacc tagcctggta tcagcagaaa 120
 ccagggcagc ctcccaagca actgatctat tctacgtcca ctctggatc tgggtctca 180
 tcgcgattca gaggcagttg atctgggaca cagttcactc tcaccatcag cgacgtgcag 240
 tggacgtatc ctgcactta ctactgtcta ggcaagtttgc attgttagtgc tggtgatgt 300
 ttgttttcg gggggggac cgagggttgt gcacaaacgtt 339

SEQ ID NO: 353 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: 353
 caagtgtga cccagactcc atccccctgt tctgcagctg tgggaagcac agtcaccatc 60
 aattgc 66

SEQ ID NO: 354 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: 354
 caggccagtc agaatgttta taataacaac tacctagcc 39

SEQ ID NO: 355 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: 355
 tggtatcagg agaaaccagg gcaggctccc aagcaactga tctat 45

SEQ ID NO: 356 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: 356
 tctacgtcca ctctggatc t 21

SEQ ID NO: 357 moltype = DNA length = 96
FEATURE Location/Qualifiers
misc_feature 1..96
 note = Engineered antibody sequence
source 1..96
 mol_type = other DNA

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organism = synthetic construct

SEQUENCE: 357
ggggtctcat cgcgattcag aggaggatgga tctggggacac agttcactt caccatcagc 60
gacgtgcagt gtgacgtgc tgccacttac tactgt 96

SEQ ID NO: 358 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: 358
ctaggcaggat atgattttag tcgtggttag tgttttgtt 39

SEQ ID NO: 359 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: 359
ttcggcgag ggaccggagg ggtggtcaaa cgt 33

SEQ ID NO: 360 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: 360
acgggtggctg caccatctgt ctatcttc ccggccatctg atgaggcaggtaa 60
actgcctctg ttgtgtgcct gctaataac ttctatccca gagaggccaa agtacagtgg 120
aagggtggata acggccatcca atcggtaaac tcccaggaga gtgtcacaga gcaggacagc 180
aaggacagca cctacagcct cagcagcacc ctgacgcgtg gcaaaggcaga ctacgagaaa 240
cacaaggctt acggccatcca agtacccat cagggccctgta gctcgccctg cacaaggcgc 300
ttcaacagggg gagatgttta g 321

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
EVQLVESGGG LVQPGGSLRL SCAVSGIGLS SYYMQWVRQA PGKGLEWVGIV IGSDGKTYYA 60
TWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCTRGRDI WGQGTLVTVS SASTKGPSVF 120
PLAPSSKSTS GGTAALGCLV KDYPPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
TPVSSSLGTQ TYICCNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVPLFPPK 240
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVVSVL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSR EMTKNQVSLT 360
CLVKGFYPSD IAVEWESNGQ PENNYKTTPPP VLDSDGSSFL YSKLTVDKSR WQQGNVFSCS 420
VMHEALHHY 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 SYYMQWVRQA PGKGLEWVGIV IGSDGKTYYA 60
TWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCTRGRDI 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

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FEATURE REGION	Location/Qualifiers 1..5 note = Engineered antibody sequence	
source	1..5 mol_type = protein organism = synthetic construct	
SEQUENCE: 364 SYYMQ		5
SEQ ID NO: 365	moltype = AA length = 14	
FEATURE REGION	Location/Qualifiers 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 REGION	Location/Qualifiers 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 REGION	Location/Qualifiers 1..32 note = Engineered antibody sequence	
source	1..32 mol_type = protein organism = synthetic construct	
SEQUENCE: 367 RFTISRDNSK TTVYIQLMNSL RAEDTAVYFC TR		32
SEQ ID NO: 368	moltype = length =	
SEQUENCE: 368 000		
SEQ ID NO: 369	moltype = AA length = 11	
FEATURE REGION	Location/Qualifiers 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 REGION	Location/Qualifiers 1..330 note = Engineered antibody sequence	
source	1..330 mol_type = protein organism = synthetic construct	
SEQUENCE: 370 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYPPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSVSVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPKPK KDTLMISRTP EVTCVVVDVS HEDPEVKFNM VYDGVEVHNA KTKPREEQYA STYRWSVLT VLHQDWLNKG EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESENQGP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	60 120 180 240 300 330	
SEQ ID NO: 371	moltype = DNA length = 1326	
FEATURE misc_feature	Location/Qualifiers 1..1326 note = Engineered antibody sequence	
source	1..1326 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 371 gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc tcctgtgcag tctctggaat cgccctcagt agtactaca tgcaatgggt ccgtcaggct ccagggaagg ggctggagtg ggtcgaggta attggtagtg atggtaagac atactacgcg	60 120 180	

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acctggcgca aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
caaatgaaca ccctgagagc tgaggacact gctgtgtatt tctgtaccag aggggacatc 300
tggggccaag ggacctctcg caccgtctcg agcgcctcca ccaaggccc atcggtcttc 360
ccccctggcac cctcctccaa gagcacctct gggggcacag cggccctggg ctgcctggc 420
aaggactact tcccccgaacc ggtgacgggt tcgttggaaact caggcgcctt gaccagccg 480
gtgcacacct tcccggtgt ctacagtcc tcaggactct actccctcag cagcgtggg 540
accgtgcctt ccagcagctt gggcaccag acctacatct gcaacgtgaa tcacaagccc 600
agcaacacca aggtggacaa gagagtttag cccaaatctt gtgacaaaac tcacacatgc 660
ccaccgtgcc caccgttcc actctgggg ggaccgtcaq tcttcttccc ccccccaaaa 720
cccaaggaca ccctcatgtat ctcgggacc cctgagggtca catgcgtgtt ggtggacgtg 780
agccacaaag accctggaggt caagtcaac tggtaatgtt acggcgtgaa ggtgcataat 840
gccaagacaa agccgcggga ggagcgtac gccagcactt accgtgtgtt cagcgtctc 900
accgtgcctc accaggactgt gtcataatggc aaggagtatac agtgtcaatggt ctccaacaaa 960
gcccccccgcccccataccatca gaaaacatc tccaaaggcca aaggccggcc cccggaaacca 1020
cagggttaca ccctggggcc atccccggag gatgttccca agaaccaggat cagcgttacc 1080
tgctgttca aagggttcta tcccgccgac atcgccgtgg agtggggagag caatggggcag 1140
ccggagaaaca actacaagac caegcctccc gtgttggact ccgacggctc ctcttcctc 1200
tacagcaagc tcaccgttgc caagcgggg tggcagcagg ggaacgttcc tcatgttcc 1260
gtgtatcgat aggcttgcac caaccatcc accgcagaaga gcttccttgcgttccgggt 1320
aaatga                                         1326

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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
gaggtgcagc ttgtggagtc tgggggagggc ttgttccagc ctggggggtc cctgagactc 60
tccctgtgcag tctctggaaat cggccctcgtt agtactaca tgcaatgggt ccgtcaggct 120
ccagggaaagg ggctggaggt ggtgggggtt attggtaggtt atggtaagac atactacgg 180
acctggcgca aaggccgatt caccatctcc agagacaattt ccaagaccac ggtgtatctt 240
caaatgaaca ccctgagagc tgaggacact gctgtgtatt tctgtaccag aggggacatc 300
tggggccaag ggacctctcg caccgtctcg 333

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SEQ ID NO: 373      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: 373
gaggtgcagc ttgtggagtc tgggggagggc ttgttccagc ctggggggtc cctgagactc 60
tccctgtgcag tctctggaaat cggccctcgtt 90

```

```

SEQ ID NO: 374      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: 374
agtactaca tgcaa                                         15

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SEQ ID NO: 375      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: 375
tgggtccgtc aggctccagg gaagggggctg gatgtgggtcg ga 42

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SEQ ID NO: 376      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: 376
gtcattggta gtgtatggtaa gacatactac ggcacgtggg cgaaaggc 48

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SEQ ID NO: 377      moltype = DNA length = 96
FEATURE             Location/Qualifiers

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misc_feature      1..96
                  note = Engineered antibody sequence
source           1..96
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 377
cgatttacca tctccagaga caattccaag accacgggt atcttcaa at gaacagcctg 60
agagctgagg acactgctgt 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 ggaccctcg 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 agggcccatc ggtttcccc ctggcacccct cctccaagag cacctctggg 60
ggcacagcggg ccctgggctg cctggtcaag gactacttc cccgaaacctg gacgggtgtcg 120
tggaaacttcg gaccccttgac cagggcgtg cacaccccttc cggctgtctt acagtccctca 180
ggactctact ccctcagcag cgtgtgacc gtggccctca gcagcttggg caccaggacc 240
tacatctgca acgttaatca caagcccggg aacaccaagg tggacaagg agtgtgagccc 300
aaatcttggc aaaaaactca cacatggcca ccgtggccagg caccctaact cctggggggga 360
ccgtcgttctt ccctttccccc cccaaaaccc aaggacaccc ttatgtatcc ccggaccct 420
gagggtcacat gctgtgggtt ggacgtggcggc cacaaaggacc ctggatggccaa gttcaactgg 480
tacgtggacg ggtgtggaggc gtataatggc aagacaaaacg cgccgggggg gcaagtacgcc 540
agcacgttacc gtgtgggtcc cgtccctcacc gtccctgcacc aggactggct gaatggcaag 600
gagtacaatgtt gcaagggttcc caaacaaaggg cttcccgccccc ccattcgagaa aaccatctcc 660
aaaggccaaag ggccggccgg agaaccacag gtgtacacc cccggggccatc ccgggggggg 720
atgaccaaga accagggttcc cctggccatcc ctgtgttccaa gcttctatcc cagcgacatc 780
ggccgtggagg gggagggccaa tggccggccgg gagaacaact acaagaccac gcctccctgg 840
ctggactccg acgggttccctt cttcccttac agdaagctca ccgtggacaa gagcagggtgg 900
cagcaggggaa acgttcccttc atgtccgtt atgcgttggg ctgtgcacaa ccactacacg 960
cagaagagggc ttccttgc tccgggtaaa tga 993

SEQ ID NO: 381      moltype = AA length = 219
FEATURE
REGION            1..219
                  note = Engineered antibody sequence
source            1..219
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 381
QVLTQSPSSL SASVGDRVTI NCQASQNLYNNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
SRFGSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSRGDC FVFGGGTKVE IKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWVKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRRGEC 219

SEQ ID NO: 382      moltype = AA length = 113
FEATURE
REGION            1..113
                  note = Engineered antibody sequence
source            1..113
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 382
QVLTQSPSSL SASVGDRVTI NCQASQNLYNNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
SRFGSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSRGDC FVFGGGTKVE IKR 113

SEQ ID NO: 383      moltype = AA length = 22
FEATURE
REGION            1..22
                  note = Engineered antibody sequence
source            1..22
                  mol_type = protein

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	organism = synthetic construct	
SEQUENCE: 383		
QVLTQSPSSL SASVGDRVTI NC		22
SEQ ID NO: 384	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
REGION	1..13	
source	note = Engineered antibody sequence	
	1..13	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 384		
QASQNVYNNN YLA		13
SEQ ID NO: 385	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
REGION	1..15	
source	note = Engineered antibody sequence	
	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	
source	note = Engineered antibody sequence	
	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	
source	note = Engineered antibody sequence	
	1..32	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 387		
GVPSRFSGSG SGTDFTLTIS 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		
TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS	60	
KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC	106	
SEQ ID NO: 391	moltype = DNA length = 660	
FEATURE	Location/Qualifiers	
misc_feature	1..660	
	note = Engineered antibody sequence	

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source          1..660
               mol_type = other DNA
               organism = synthetic construct

SEQUENCE: 391
caagtgtga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccagg ccagtcaagaa tgtttacaat aacaactacc tagcctggta tcagcagaaaa 120
ccaggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tgggttccca 180
tetcgttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240
cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgttagtcg tggtgatgt 300
tttgtttcg gcgaggaaac caaggtggaa atcaaacgtcg cgggtgc accatctgtc 360
ttcatcttcc cgccatctga tgacgttg aaaaatctggaa ctgcctctgt tggtgctgt 420
ctgaataact tctatcccag agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcgggtactt cccaggagag tgcacacgg cggacacgac ctacagctc 540
agcagcaccc tgcgtcgaa caaaggcagac tacggaaaac acaaagtcta cgcctgcgaa 600
gtcaccatc atgggcctgag ctgcctgcg acaaagagct tcaacagggg agagtgttag 660

SEQ ID NO: 392      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: 392
caagtgtga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccagg ccagtcaagaa tgtttacaat aacaactacc tagcctggta tcagcagaaaa 120
ccaggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tgggttccca 180
tetcgttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240
cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgttagtcg tggtgatgt 300
tttgtttcg gcgaggaaac caaggtggaa atcaaacgtcg 339

SEQ ID NO: 393      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: 393
caagtgtga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
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 agaatgttta caataacaac tacctagcc                                     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
tggttatcaggc agaaaccagg gaaagttctt 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

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SEQUENCE: 397
 ggggtcccat ctcgtttag tggcagtgg a 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
 ctgggcagg atgattttag tcgtggtag tttttttt 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
 ttcgccggag gaaccaaggt ggaaatcaaa 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 cttcatcttc ccgcacatctg atgaggcaggtaaaatcttgg 60
 actggcctctg ttgtgtccgt gctgaataac ttctatccca gagaggccaa agtacatgtgg 120
 aagggtggata acggccctcca atcggttaac tccccaggaga gtgtcacaga gcaggacagc 180
 aaggacacgca cctacagccct cagcagcacc ctgacgcgtga gcaaaggcaga ctacgagaaa 240
 cacaaggct acgcctgcga agtcacccat cagggcgtga gtcgcggcgt cacaaggagc 300
 ttcaacaggg gagagtgtta g 321

SEQ ID NO: 401 moltype = AA length = 439
 FEATURE Location/Qualifiers
 REGION 1..439
 note = Engineered antibody sequence
 source 1..439
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 401
 QSLEESGGLR VTPGGSLTLT CTVSGIDVTN YYMQWVRQAP GKGLEWIGVI GVNGKRYYAS 60
 WAKGRFTISK TSSTTVDLKM TSLTTEDTAT YFCARGDIWG PGTLVTVSSA STKGPSVFPL 120
 APSSKSTGG TAALGCLVKD YFPEPVTWSW NSGALTSGVH TFPAVLQSSG LYSLSSVTV 180
 PSSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCPV CPAPELLGGP SVFLPPPKPK 240
 DTMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAAK TKPREEQYAS TYRVVSVLTV 300
 LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL 360
 VKGFYPSDIA VEWESNGQPE NNYKTPPPVLDSDGSFFLYS KLTVDKSRWQ QGNVPSCVM 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
 QSLEESGGLR VTPGGSLTLT CTVSGIDVTN YYMQWVRQAP GKGLEWIGVI GVNGKRYYAS 60
 WAKGRFTISK TSSTTVDLKM TSLTTEDTAT 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
 QSLEESGGLR VTPGGSLTLT CTVSGIDVT 29

SEQ ID NO: 404 moltype = AA length = 5
 FEATURE Location/Qualifiers

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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	
source	note = Engineered antibody sequence	
1..14	mol_type = protein	
SEQUENCE: 405	organism = synthetic construct	
WVRQAPGKGL EWIG		14
SEQ ID NO: 406	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
REGION	1..16	
source	note = Engineered antibody sequence	
1..16	mol_type = protein	
SEQUENCE: 406	organism = synthetic construct	
VIGVNGKRYY ASWAKG		16
SEQ ID NO: 407	moltype = AA length = 31	
FEATURE	Location/Qualifiers	
REGION	1..31	
source	note = Engineered antibody sequence	
1..31	mol_type = protein	
SEQUENCE: 407	organism = synthetic construct	
RFTISKTSST TVDLKMTSLT TEDTATYFCA R		31
SEQ ID NO: 408	moltype = length =	
SEQUENCE: 408		
000		
SEQ ID NO: 409	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
source	note = Engineered antibody sequence	
1..11	mol_type = protein	
SEQUENCE: 409	organism = synthetic construct	
WGPGTTLTVS S		11
SEQ ID NO: 410	moltype = AA length = 330	
FEATURE	Location/Qualifiers	
REGION	1..330	
source	note = Engineered antibody sequence	
1..330	mol_type = protein	
SEQUENCE: 410	organism = synthetic construct	
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60 GLYSLSSVVT VPSSSLGTQT YICVNHNKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120 PSVFLFPPKPK DDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180 STYRVRVSVPLT VLHQDWLNGE EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLEPSREE 240 MTKNQVSLTC LVKGFYPSDI AVEWESENQQP ENNYKTTPPV LDSDGFFLY SKLTVDKSRW 300 QQGNVFCSV MHEALHNHYT QKSLSLSPGK 330		
SEQ ID NO: 411	moltype = DNA length = 1320	
FEATURE	Location/Qualifiers	
misc_feature	1..1320	
source	note = Engineered antibody sequence	
1..1320	mol_type = other DNA	
SEQUENCE: 411	organism = synthetic construct	
cagtcgtgg aggagtccgg gggtcgcctg gtcacgcctg gaggatccct gacactcacc 60 tgcacagtct ctggaatcga cgtcaactaac tactatatgc aatgggtccg ccaggctcca 120 ggaaaggggc tggaaatggat cggagtcatt ggtgtgaatg gtaagagata ctacgcgagc 180 tgggcgaaag gccgattcac catctccaaa acctcgtcgaa ccacggtgaa tctgaaaatg 240		

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accagtctga caaccgagga cacggccacc tatttctgtg ccagaggcga catctgggc 300
 cccggggacc tcgtcaccgt ctgcagcgcc tccaccaagg gccatcggt cttccctg 360
 gcaccctct ccaagagcac ctctggggcc acagcggccc tgggctgct ggtcaaggac 420
 tacttccccg aaccggtgac ggtgtcggtg aactcaggcg ccctgaccag cggcggtcac 480
 accttccccg ctgtcctaca gtccctcgga ctctactccc tcagcagcgt ggtgaccgtg 540
 ccctccagca gttgggcac ccagaccta atctgcaacg tgaatcacaa gcccagcaac 600
 accaagggtgg acaagagagt tgagccaaa tcttgtgaca aaactcacac atgcccaccc 660
 tgcccagcac ctgaactctt ggggggaccc tcagtcttcc tcttcccccaaaaacccaag 720
 gagaccctca tgatctcccg gaceccctgag gtcacatcgcc tgggtgggtga cgtgagccac 780
 gaagacctgt aggtcaaggta caactggtaat gttggacggcg tggagggtgca taatgccaag 840
 acaaaggccg gggaggagca gtacggccacg acgttacccgt tggtcagcgt cctcaccgtc 900
 ctgcaccagg actggctgaa tggeaaggag tacaagtgca aggtctccaa caaaggccctc 960
 ccagccccca tggaaaaaa catctccca gccaaggaaaggcc accacagggtg 1020
 tacaccctgc ccccatcccg ggaggagatg accaagaaccc aggtcagct gacgtgcctg 1080
 gtcaaaggct tctatcccg cgacatcgcc gtggagttgg agagcaatgg gcagccggag 1140
 aacaactaca agaccacgac tccctgtctg gactccgacg gtcctttt cctctacacg 1200
 aagctcaccg tggacaagag cagggtggcag caggggaacg tcttctcatg ctccgtgtatg 1260
 catgagggtc tgcacaacca ctacacgcac aagagcctctt ccctgtctcc gggtaatga 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
 cagtcgtgg aggagtccgg gggtcgcctg gtcacgcctg gaggatccct gacactcacc 60
 tgcacagtct ctggaatcga cgtcaactaa tactatatgc aatgggtccg ccaggctcca 120
 gggaaaggggc tggaaatggat cggagtccat ggtgtgaaatg gtaagagata ctacgcgagc 180
 tgggcgaaag gccgattcac catctccaaa acctcgatcgca ccacgggtgaa tctgaaaatg 240
 accagtctga caaccgagga cacggccacc tatttctgtg ccagaggcga catctgggc 300
 cccggggacc tcgtcaccgt ctgcagcgcc 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
organism = synthetic construct

SEQUENCE: 413
 cagtcgtgg aggagtccgg gggtcgcctg gtcacgcctg gaggatccct gacactcacc 60
 tgcacagtct ctggaatcga cgtcaactaa 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
 tgggtccgcc aggctccagg gaaggggctg 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 gagatactac gcgagctggg cgaaaggc 48

SEQ ID NO: 417 moltype = DNA length = 93
FEATURE Location/Qualifiers
misc_feature 1..93
note = Engineered antibody sequence

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```

source          1..93
               mol_type = other DNA
               organism = synthetic construct

SEQUENCE: 417
cgattcacca tctccaaaac ctcgtcgacc acgggtggatc tgaaaatgac 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
tggggccccc ggaccctcgta 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 ggtttccccct ctggcacccct cctccaagag cacctctggg 60
ggcacacggg ccctgggtg cctgtcaag gactactcc ccgaaccgggt gacgggtgcg 120
tggaaacttag cggccctgac cagcgccgtg cacaccttc cggctgtctt acagtctca 180
ggactctact coctcagtag cgtgttgacc gtgccttcca gcagcttggg cacccagacc 240
tacatctgca acgtgtca caagccccc aacccaagg tggacaagag agttgagccc 300
aaatcttgcg aaaaaactca cacaatggccca ccgtgcccccc caccctgaaact cctgggggg 360
ccgtcgtctt tcctttccc cccaaaaccc aaggacaccc tcataatcttc ccggaccct 420
gagggtcataat gctgttggtt ggacgtgago cacgaagacc ctgagggtcaa gttcaactgg 480
taactgtggacg gctgtggaggt gcataatggc aagacaaaagg cgccggggaga gcagtacgccc 540
agcacgttacc ttgtgggttag cgttccacc cgttccacc aggactggctt gaatggcaag 600
gagttacaatgtt gcaagggtctc caaaaaaggcc ctcccaagcc ccatacgaaaa aaccatctcc 660
aaaggccaaagg ggcagccccg agaaccacag gtgtacacc tgccccatc ccggggaggag 720
atggccaaaggc accagggttacc cctgtggatc ctgtcaatgg gcttctatcc cagcgacatc 780
ggcgtggagg tgggagagccaa gagaacaaact acaagaccac gcctccctgt 840
cttgacttcg acgggtccctt ctcccttac agcaaggtca ccgtggacaa gagcagggtt 900
cagcaggggaa acgttttctc atgtccgtt atgtcatggg ctctgcacaa ccactacacg 960
cagaagggcc tctccctgtc tccgggtaaa 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
FIFPPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTTLSKAD YEKKHVKYACE 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

```

-continued

QVLTQTASPV SPAVGSTVTI NC	22
SEQ ID NO: 424	moltype = AA length = 13
FEATURE	Location/Qualifiers
REGION	1..13
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	1..32
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 427	
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
	organism = synthetic construct
SEQUENCE: 428	
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
	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
	organism = synthetic construct
SEQUENCE: 430	
TVAAPSVIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC	60 106
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

-continued

organism = synthetic construct

SEQUENCE: 431

```
caggtgctga cccagactgc atccccgtg tctccagctg tgggaagcac agtcaccatc 60
aattgccggg ccagtcagag tgtttattat aacaactacc tagcctggta tcagcagaaa 120
ccagggcagc ctcccaagca actgtatctat tctacatcca ctctggcatc tgggtctca 180
tcgcggttca aaggcagtgg atctgggaca cagttcactc tcaccatcag cgacgtgcag 240
tgtgacgatg ctgcccactt ctactgtcta ggcagttatg attgttagaa tggtgatgt 300
tttggtttcg gcgaggggac cgagggtggtgcgtaa acatctgtc 360
tcatcttcc cccatctgtg tgagcgttg aaatctgttgc ctgcctctgt tggtgctg 420
ctgataact tctatcccg agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcggtaact cccaggagag tgtcacagag cagacagcac ctacagcctc 540
agcagcaccc tgacgtgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600
gtcaccatc agggcttagtgcgttca acacagggg agagtgttagt 660
```

SEQ ID NO: 432 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: 432

```
caggtgctga cccagactgc atccccgtg tctccagctg tgggaagcac agtcaccatc 60
aattgccggg ccagtcagag tgtttattat aacaactacc tagcctggta tcagcagaaa 120
ccagggcagc ctcccaagca actgtatctat tctacatcca ctctggcatc tgggtctca 180
tcgcggttca aaggcagtgg atctgggaca cagttcactc tcaccatcag cgacgtgcag 240
tgtgacgatg ctgcccactt ctactgtcta ggcagttatg attgttagaa tggtgatgt 300
tttggtttcg gcgaggggac cgagggtggtgcgtaa acatctgtc 339
```

SEQ ID NO: 433 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: 433

```
caggtgctga cccagactgc atccccgtg tctccagctg tgggaagcac agtcaccatc 60
aattgc 66
```

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 agagtgtttata ttataacaac tacctagcc 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 ctctggcatc 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

```
gggttctcat cgcggttcaa aggcaactggaa tctggacac agttcactt caccatcagc 60
```

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gacgtgcagt 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	
ctaggcaggat 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	
ttcggcgagg ggaccggaggt 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 ctcatcttc ccgcctatctg atgagcaggta gaaatctgga 60	
actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggocaa agtacagtgg 120	
aagggtggata accgcctcca atcgggtaac tcccaggaga gtgtcagaca gcaggacagc 180	
aaggacagca cttacagcct cagcacccacc ctgacgctga gcaaagcaga ctacgagaaa 240	
cacaaggatc acgcctgca agtacccat caggcctga gctcggccctg cacaaggagc 300	
ttcaacacagg gagagtgtta g 321	
SEQ ID NO: 441 moltype = AA length = 441	
FEATURE Location/Qualifiers	
REGION 1..441	
note = Engineered antibody sequence	
source 1..441	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 441	
EVQLVESGGG LVQPGGSLRL SCAVSGIDVT NYYMOWVRQA PGKGLEWVGIVGVNGKRYYA 60	
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLTVVS SASTKGPSVF 120	
PLAPSSKSTS CGTAALGCLV KDYPPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSVV 180	
TPVSSLGLTQ TYICCNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK 240	
PKDTLMSRT PEVTCVVVD SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVVSVL 300	
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360	
CLVKGFYPSD IAVEWESNGQ PENNYKTTPPP VLDSDGFFL YSKLTVDKSR WQQGNVFSCS 420	
VMHEALHNHY TQKSLSLSPG K 441	
SEQ ID NO: 442 moltype = AA length = 111	
FEATURE Location/Qualifiers	
REGION 1..111	
note = Engineered antibody sequence	
source 1..111	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 442	
EVQLVESGGG LVQPGGSLRL SCAVSGIDVT NYYMOWVRQA PGKGLEWVGIVGVNGKRYYA 60	
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLTVVS S 111	
SEQ ID NO: 443 moltype = AA length = 30	
FEATURE Location/Qualifiers	
REGION 1..30	
note = Engineered antibody sequence	
source 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	
note = Engineered antibody sequence	

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source	1..5 mol_type = protein organism = synthetic construct	
SEQUENCE: 444		
NYYMQ		5
SEQ ID NO: 445	moltype = AA length = 14	
FEATURE	Location/Qualifiers	
REGION	1..14	
	note = Engineered antibody sequence	
source	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	
	note = Engineered antibody sequence	
source	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	
	note = Engineered antibody sequence	
source	1..32 mol_type = protein organism = synthetic construct	
SEQUENCE: 447		
RTFTISRDN SK TTVYLQMNSL RAEDTAVYFC AR		32
SEQ ID NO: 448	moltype = length =	
SEQUENCE: 448		
000		
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	
PSVFLFPPKP KDLMISRTTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA	180	
STYRVSLSVT VLHQDWLNGK EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPPSREE	240	
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV 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		
gagggtcagc ttgtggagtc tggggggagc ttgggtccagc ctggggggtc cctggagactc	60	
tcttgtcgac tctctggaaat cgacgtcaact aactactaca tgcaatgggt ccgtcaggct	120	
ccagggaaagg ggctggagtg ggtcgagtc attgggtgta atggtaagag atactacgcg	180	
agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt	240	
caaataatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgccag aggggacatc	300	
tggggccaag ggaccctcg taccgtctcg agcgcctcca ccaaggccc atcggcttc	360	

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cccttggcac cttcttccaa gggcacctct gggggcacag cggccctggg ctgcctgtc 420
aaggactact tccccgaacc ggtgacggtg tcgtgaaact caggcgcct gaccaggcg 480
gtgcacacct tcccgctgt cctacagtc tcaggactct actccctca gaggctgtc 540
acccgtgcctt ccaggcgtt gggcccccag acctacatctt gcaacgtgaa tcacaagccc 600
agaacaccca aggtggacaa gagagtgttgg cccaaatctt gtgacaaaac tcacacatgc 660
ccaccgtgcc caggcactga actccctggg ggacccgtca g tttccctt ccccccaaaa 720
cccaaggaca cctcatgtat cttccggacc cctgagggtca catgcgttgtt ggtggacgtg 780
agccacacaa accctgaggta caagtcaac ttgtacgtgg acggcgtgga ggtgcataat 840
gccaagacaa accccgggaa ggacggactt gggccgggaa gggccgggaa gggccgggaa 900
accgttcgtc accaggactt gctgtatggg aaggagtata agtgcacagg ctccaaacaaa 960
ggccctcccg cccccatcgaa gaaaaccatcgaa aaggcggcc cccggaaacca 1020
cagggttaca cctgtcccccc atccccgggag gagatgacca agaaccagg cagccgtacc 1080
tgcctgttca aagggttcta tcccgccgtc atccgggtgg agtggggaggg caatggcgg 1140
ccggagaacaa actacaagac caccgtcccgatccgtggccgtc ctccgtcc 1200
tacagcaacg cttccgtggaa caagggcggg tggcggcggg ggaacgttcc tccatgtcc 1260
gtgtatgcgtt aggtctgtca caaccactac acgcagaaga gctctccctt gtctccgggt 1320
aatgaa 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 tggggggggc ttgttccagc ctgggggggtc cctgagactc 60
 tccctgtcag tctctggaaat cgacgtcaact aactactaca tgcaatgggt ccgtcaggct 120
 ccagggtggaa ggctgggggtg ggtgggggtc attgggtgtta atggtaaggg atactacggc 180
 agtggggcga aaggccgatt caccatctca agagaaatctt ccaagacccac ggtgtatctt 240
 caaatgaaca gcctgagggc tggggggggc ggtgtgtt tctgtggccag agggggacatc 300
 tggggccaaat ggaccctcgat caccgtctcg 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

SEQUENCE: 453
 gaggtgcagc ttgtggagtc tggggggggc ttgttccagc ctgggggggtc cctgagactc 60
 tccctgtcag tctctggaaat 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 gagtggttcg 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 gagataactac 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

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```

mol_type = other DNA
organism = synthetic construct

SEQUENCE: 457
cgattcacca tctccagaga caattccaag accacggtgt atcttcaa at gaacagcctg 60
agagctgagg acactgctgt gtatctgt 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 t 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 a gggcccatc ggtttcccc ctggcaccc t cctccaagag cacctctgg 60
ggcacagcgg ccttggctg cctgttcaag gactacttc cccaaacggg gacgggttgc 120
ttggactctag ggcgcctgac cagcggctg tccacaccc tcccggtctt acagtcc 180
ggactctact ccctcagcag cgtgttgc accgttccca gcagcttggg caccaggacc 240
tacatctgca acgtgaatca caagcccagc aacccaagg tggacaagag agttgagccc 300
aatatctgtg tacatctgca acatgccc cccgttccca cccatgttgc acttggggg 360
ccgtcagtct tccttctcc cccaaaaccc aaggacaccc tcatgtatcc cccggaccc 420
gagggttcat ggtgttgggt ggacgttgc cccaaaccc cccatgttgc acttggggg 480
tacgttggacg cccgttgggtt gtcataatgc aagacaaagg cccgggggg gtcacttgc 540
agcacgttcc ggtgttgggtt cccatgttgc accgttgc accgttgc gatggcaag 600
gagtttacat gcaagggttcc caacaaaggcc cccatgttgc acttggggg 660
aaaggccaaag ggcaggcccg agaaccacag gtgttgc accgttgc acttggggg 720
atgaccaaga accagggttcc cccatgttgc ctggtaaa gtttctatcc cccatgttgc 780
gccttgggggtt gggaggaccc tggggaggcc gagaacaatc acaaggaccac gccttgggggtt 840
ctggacttccg acgggttccctt ctggacttccg acgggttccctt ctggacttccg 900
caacggggggg acgttccctt atgttgc accgttgc acttggggg 960
cagaagggcc ttccttgc tccgggtaaa 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 DFTLTISSLQ PEDVATYYCL GSYDCSNGDC FVFGGGTKVE IKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTLTLKAD 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 DFTLTISSLQ 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

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SEQ ID NO: 464	moltype = AA length = 13
FEATURE	Location/Qualifiers
REGION	1..13
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	1..32
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 467	
GVPSRFSGSG SGTDFTLTIS SLQPEDVATY YC	32
SEQ ID NO: 468	moltype = AA length = 13
FEATURE	Location/Qualifiers
REGION	1..13
source	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	Location/Qualifiers
REGION	1..11
source	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	Location/Qualifiers
REGION	1..106
source	note = Engineered antibody sequence
	1..106
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 470	
TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS	60
KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC	106
SEQ ID NO: 471	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

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SEQUENCE: 471

```
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccggg ccagtcagag tgttactat aacaactacc tagcctggta tcagcagaaa 120
ccagggaaag ttccctaagca actgatctat tctacatcca ctctggatc tgggttccca 180
tctcggttca gtggcagtgg atctgggaca gatttcactc tcaccatcg cagctgcag 240
cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgttagaa tggtgtatgt 300
tttgtttcg goggaggaac caagggtggaa atcaaacgtg cgggtggc accatctgtc 360
ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgggtgtctg 420
ctgaataact tctatccag agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcgggttaact cccaggagtg tgcacagag caggacagac aggacagc acatgcctc 540
agcagcaccc tgacgtcgag caaaagcagac tacgagaaac acaaagtcta cgcctcgaa 600
gtcaccatc agggcctgag ctcggccgtc acaaagagct tcaacaggaa agagtgttag 660
```

SEQ ID NO: 472 moltype = DNA length = 339
FEATURE
misc_feature 1..339
source note = Engineered antibody sequence
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 472

```
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccggg ccagtcagag tgttactat aacaactacc tagcctggta tcagcagaaa 120
ccagggaaag ttccctaagca actgatctat tctacatcca ctctggatc tgggttccca 180
tctcggttca gtggcagtgg atctgggaca gatttcactc tcaccatcg cagctgcag 240
cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgttagaa tggtgtatgt 300
tttgtttcg goggaggaac caagggtggaa atcaaacgtg 339
```

SEQ ID NO: 473 moltype = DNA length = 66
FEATURE
misc_feature 1..66
source note = Engineered antibody sequence
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
FEATURE
misc_feature 1..39
source note = Engineered antibody sequence
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 474

```
cggccagtc agagtgttta ctataacaac tacctagcc 39
```

SEQ ID NO: 475 moltype = DNA length = 45
FEATURE
misc_feature 1..45
source note = Engineered antibody sequence
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 475

```
tggtatcagg agaaaccagg gaaagttct aagcaactga tctat 45
```

SEQ ID NO: 476 moltype = DNA length = 21
FEATURE
misc_feature 1..21
source note = Engineered antibody sequence
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 476

```
tctacatcca ctctggatc t 21
```

SEQ ID NO: 477 moltype = DNA length = 96
FEATURE
misc_feature 1..96
source note = Engineered antibody sequence
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 477

```
ggggtcccat ctcggttcag tggcagtgg a tctgggacag atttcactct caccatcagc 60
agcctgcagc ctgaagatgt tgcaacttat tactgt 96
```

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SEQ ID NO: 478      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: 478
ctgggcagtt atgattttagt taatggtgat tgttttgtt                                39

SEQ ID NO: 479      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: 479
ttcggcgagg gAACCAAGGT ggAAATCAAA CGT                                         33

SEQ ID NO: 480      moltype = DNA length = 321
FEATURE          Location/Qualifiers
misc_feature     1..321
source           note = Engineered antibody sequence
                 1..321
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 480
acggtgttgc caccatctgt ctccatcttc ccggccatctg atgagcagtt gaaatctgga  60
actgcctctg ttgtgtgcct gctgataaac ttctatccca gagaggccaa agtacagtgg 120
aagggtggata acggccctcca atcggtaac tcccaggaga gtgtcacaga gcaggacgc 180
aaggacacgca cttacagcct cagcagcacc ctgacgcgtg gcaaaggcaga ctacgagaaa 240
cacaaggatct acggcctgcga agtcacccat cagggcctga gctcgccctg cacaaggagc 300
ttcaacaggg gagagtgtta g                                              321

SEQ ID NO: 481      moltype = AA length = 441
FEATURE          Location/Qualifiers
REGION           1..441
source           note = Engineered antibody sequence
                 1..441
mol_type = protein
organism = synthetic construct

SEQUENCE: 481
QSVEESGGGL VQPEGSLTLT CTASGFDFSS NAMWWVRQAP GKGLEWIGCI YNGDGSTYYA 60
SWVNNGRFSIS KTSSTTVTLQ LNSLTVADETA TYYCARDLNL WGPGLTVTVS SASTKGPSVF 120
PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
TVPSSSLGTQ TYICCNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVPLFPPK 240
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVVSVL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSR EMTKNQVSLT 360
CLVKGFYPSD IAVEWESNGQ PENNYKTTTP VLSDGGSFFL YSKLTVDKSR WQQGNVFSCS 420
VMHEALHNHY TQKSLSLSPG K                                              441

SEQ ID NO: 482      moltype = AA length = 111
FEATURE          Location/Qualifiers
REGION           1..111
source           note = Engineered antibody sequence
                 1..111
mol_type = protein
organism = synthetic construct

SEQUENCE: 482
QSVEESGGGL VQPEGSLTLT CTASGFDFSS NAMWWVRQAP GKGLEWIGCI YNGDGSTYYA 60
SWVNNGRFSIS KTSSTTVTLQ LNSLTVADETA TYYCARDLNL WGPGLTVTVS S                                              111

SEQ ID NO: 483      moltype = AA length = 29
FEATURE          Location/Qualifiers
REGION           1..29
source           note = Engineered antibody sequence
                 1..29
mol_type = protein
organism = synthetic construct

SEQUENCE: 483
QSVEESGGGL VQPEGSLTLT CTASGFDFSS                                         29

SEQ ID NO: 484      moltype = AA length = 5
FEATURE          Location/Qualifiers
REGION           1..5
source           note = Engineered antibody sequence
                 1..5

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mol_type = protein
organism = synthetic construct

SEQUENCE: 484
SNAMEW                                         5

SEQ ID NO: 485      moltype = AA length = 14
FEATURE
REGION
1..14
note = Engineered antibody sequence
1..14
mol_type = protein
organism = synthetic construct

SEQUENCE: 485
WVRQAPGKGL EWIG                               14

SEQ ID NO: 486      moltype = AA length = 17
FEATURE
REGION
1..17
note = Engineered antibody sequence
1..17
mol_type = protein
organism = synthetic construct

SEQUENCE: 486
CIYNGDGSTY YASWVNG                           17

SEQ ID NO: 487      moltype = AA length = 31
FEATURE
REGION
1..31
note = Engineered antibody sequence
1..31
mol_type = protein
organism = synthetic construct

SEQUENCE: 487
RFSISKTTSST TVTLQLNSLT VADTATYYCA R          31

SEQ ID NO: 488      moltype = AA length = 4
FEATURE
REGION
1..4
note = Engineered antibody sequence
1..4
mol_type = protein
organism = synthetic construct

SEQUENCE: 488
DLDL                                           4

SEQ ID NO: 489      moltype = AA length = 11
FEATURE
REGION
1..11
note = Engineered antibody sequence
1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 489
WGPGTLLTVVS S                                11

SEQ ID NO: 490      moltype = AA length = 330
FEATURE
REGION
1..330
note = Engineered antibody sequence
1..330
mol_type = protein
organism = synthetic construct

SEQUENCE: 490
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYPPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKPK KDTLMSRTP EVTCVVVDVS HEDPEVKPNW YVDGVEVHNA KTKPREEQVA 180
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSSFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK                330

SEQ ID NO: 491      moltype = DNA length = 1326
FEATURE
misc_feature
1..1326
note = Engineered antibody sequence
1..1326
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 491
cagtcgggtgg aggagtccgg gggaggccctg gtccagcctg agggatccct gacactcacc 60

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tgcacagcct ctggattcga cttcagtago aatgcaatgt ggtgggtccg ccaggctcca 120
 gggaaaggccc tggagtggat cgatgcatt tacaatggtg atggcagcac atactacgcg 180
 agctgggtga atggccgatt ctccatctcc aaaacctcgat cgaccacggt gactctgcaa 240
 ctgaatagtc tgacagtcgc ggacacggcc acgtattatt gtgcgagaga tcttgacttg 300
 tggggccccg gcacccctcgat caccgtctcg aggcgcctcca ccaaggccc atcggtcttc 360
 cccctggcac cctctccaa gagcacctctt gggggcacag cggccctggg ctgcctggtc 420
 aaggactact tcccgaaacc ggtgacggtg tcgtggaaact caggcgccct gaccagggc 480
 gtgcacacct tcccggtgt cctacagtcc tcaggactct actccctcag cagcgtgg 540
 accgtgcctc ccacgcgtt gggacccccc acctacatct gcaacgtgaa tcacaaggcc 600
 agcaacacca aggtggacaa gagatggatgg cccaaatctt gtgacaaaac tcacacatgc 660
 ccaccgtgcc cagcacctga actcttgggg ggaccgtca gtcgtggat cccccc 720
 cccaaggaca ccctcatgtat ctcccgacc cctgaggatca catgcgtggt ggtggacgtg 780
 agccacacca accctggatgg caaqtcaad tggatcgatgg acggcgatgg ggtgcataat 840
 gccaagacaa accccgggaa ggacacgtac gcaacgtgaa accgtgtggt cagcgtctc 900
 accgtctgc accaggactg gctaatggc aaggagtaca atgtcaatgg ctccaacaaa 960
 gcctcccaag ccccccatacgaa gaaaaccatc tccaaagccca aaggggcagcc ccgagaacca 1020
 caggtgtaca ccctggccccc atccggggaa gagatggacca agaaccatgg cagctgacc 1080
 tgcctggatca aaggcttcta tcccgacatcgcgtgg aatggggagag caatgggac 1140
 cccggagaaaca actacaagac caegcctcc qgtctggact cccacggctc cttcttc 1200
 tacagcaagc taccatggaa caagacggg tggcagcagg ggaacgtttt ctcatgtcc 1260
 gtgtatgcatg aggctctgca caaccatc acgcagaaga gcctctccct gtctccgggt 1320
 aaatga 1326

SEQ ID NO: 492 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: 492
 cagtccgtgg aggagtccgg gggaggccctg gtccagcctg agggatccct gacactcacc 60
 tgcacagcct ctggattcga cttcagtago aatgcaatgt ggtgggtccg ccaggctcca 120
 gggaaaggccc tggagtggat cgatgcatt tacaatggtg atggcagcac atactacgcg 180
 agctgggtga atggccgatt ctccatctcc aaaacctcgat cgaccacggt gactctgcaa 240
 ctgaatagtc tgacagtcgc ggacacggcc acgtattatt gtgcgagaga tcttgacttg 300
 tggggccccg gcacccctcgat caccgtctcg 333

SEQ ID NO: 493 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: 493
 cagtccgtgg aggagtccgg gggaggccctg gtccagcctg agggatccct gacactcacc 60
 tgcacagcct ctggattcga cttcagtago 87

SEQ ID NO: 494 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: 494
 agcaatgcaatgtgg 15

SEQ ID NO: 495 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: 495
 tgggtccggcagg gaaggggctg gagatggatcg ga 42

SEQ ID NO: 496 moltype = DNA length = 51
 FEATURE Location/Qualifiers
 misc_feature 1..51
 note = Engineered antibody sequence
 source 1..51
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 496
 tgcatttaca atgggtatgg cagcacatac tacgcgagct gggtaatgg c 51

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SEQ ID NO: 497
FEATURE
misc_feature
source
SEQUENCE: 497
cgattctcca tctccaaaac ctcgtcgacc acggtaactc tgcaactgaa tagtctgaca 60
gtcgccgaca cggccacgta ttattgtgcg aga 93

SEQ ID NO: 498
FEATURE
misc_feature
source
SEQUENCE: 498
gatcttgact tg 12

SEQ ID NO: 499
FEATURE
misc_feature
source
SEQUENCE: 499
tggggcccg gcaccctcg 33

SEQ ID NO: 500
FEATURE
misc_feature
source
SEQUENCE: 500
gcctccacca agggcccatc ggtttcccc ctggcacccct cctccaaagag cacctctggg 60
ggcacagcgg ccctgggtg ctctgtcaag gactactcc cggacacggt gacgggtgtcg 120
tggaaactcag ggcgcctgac cagccggctg cacacccctt cggctgtctt acagtctca 180
ggactctact ccctcagcag cgtgtgtgacc gtgccttcca gcagcttggg caccaggacc 240
tacatctgc 300
acgtgaatca caagccca 360
aaatcttgcg acaaataactca catatccc 420
ccgtcagtc 480
tccttctcc cccaaaaacc 540
gggtcagat 600
gcgtgtgtt 660
ggacgtgago 720
cacaagagacc 780
ctgaggtaa 840
ctgtcaatgg 900
gcataatgcc 960
aagacaaagg 993

SEQ ID NO: 501
FEATURE
REGION
source
SEQUENCE: 501
AIVMTQTPSS KSVPVGDTVT INCQASESLY NNNNALAWFQQ KPGQPPKRLI YDASKLASGV 60
PSRFSGGGG TQFTLTISGV QCDDAATYYC GGYRSDSVDG VAFAGGTTEVV VKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
SSTLTLASKAD YEKHKVYACE VTHQGLSSPV TKSFNRRGEC 219

SEQ ID NO: 502
FEATURE
REGION
source
SEQUENCE: 502
AIVMTQTPSS KSVPVGDTVT INCQASESLY NNNNALAWFQQ KPGQPPKRLI YDASKLASGV 60

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PSRFSGGGSG TQFTLTISGV QCDDAATYYC GGYRSDSVDG VAFAGGTEVV VKR	113
SEQ ID NO: 503 moltype = AA length = 23	
FEATURE Location/Qualifiers	
REGION 1..23	
source note = Engineered antibody sequence	
1..23	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 503 AIVMTQTPSS KSVPVGDTVT INC	23
SEQ ID NO: 504 moltype = AA length = 13	
FEATURE Location/Qualifiers	
REGION 1..13	
source note = Engineered antibody sequence	
1..13	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 504 QASESLYNNN ALA	13
SEQ ID NO: 505 moltype = AA length = 15	
FEATURE Location/Qualifiers	
REGION 1..15	
source note = Engineered antibody sequence	
1..15	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 505 WFQQKPGQPP KRLIY	15
SEQ ID NO: 506 moltype = AA length = 7	
FEATURE Location/Qualifiers	
REGION 1..7	
source note = Engineered antibody sequence	
1..7	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 506 DASKLAS	7
SEQ ID NO: 507 moltype = AA length = 32	
FEATURE Location/Qualifiers	
REGION 1..32	
source note = Engineered antibody sequence	
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	
source note = Engineered antibody sequence	
1..12	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 508 GGYRSDSVDG VA	12
SEQ ID NO: 509 moltype = AA length = 11	
FEATURE Location/Qualifiers	
REGION 1..11	
source note = Engineered antibody sequence	
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	
source note = Engineered antibody sequence	
1..106	
mol_type = protein	
organism = synthetic construct	

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SEQUENCE: 510
 TVAAPSVIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
 KDSTYSLST LTLSKADYEK HKVYACEVTH 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
 gccatcgta tgacccagac tccatcttcc aagtctgtcc ctgtgggaga cacagtacc 60
 atcaattgcc aggccagtga gagtttttat aataacaacg cttggcctg gttcagcag 120
 aaaccagggc agccccc aa ggcctgatc tatgtatcat ccaaactggc atctgggtc 180
 ccatcgcggt tcagtgccgg tgggtctggg acacagtta ctctcaccat cagtgccgt 240
 cagtgtgacg atgctgccc ttactactgt ggaggctaca gaagtgtatag tggatgg 300
 gttgcttcg cggaggac cgaggatggc gtcaaacatc cggtgccgtc accatctgtc 360
 ttcatcttcc cggccatctga tgacgatgtt aatctggaa ctgccttgt tggatgtc 420
 ctgaataact tctatccag agaggccaaa gtacagtggg aggtggataa cgcctccaa 480
 tcggtaact cccaggagag tggcacagag caggacacca accagcac ctacagctc 540
 agcagcaccc tgacgcttag caaaggac tacgagaaac acaaagtcta cgcctgcgaa 600
 gtcacccatc agggccttag ctgcggcgtc acaaaggact 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
 gccatcgta tgacccagac tccatcttcc aagtctgtcc ctgtgggaga cacagtacc 60
 atcaattgcc aggccagtga gagtttttat aataacaacg cttggcctg gttcagcag 120
 aaaccagggc agccccc aa ggcctgatc tatgtatcat ccaaactggc atctgggtc 180
 ccatcgcggt tcagtgccgg tgggtctggg acacagtta ctctcaccat cagtgccgt 240
 cagtgtgacg atgctgccc ttactactgt ggaggctaca gaagtgtatag tggatgg 300
 gttgcttcg cggaggac cgaggatggc gtcaaacatc 339

SEQ ID NO: 513 moltype = DNA length = 69
 FEATURE Location/Qualifiers
 misc_feature 1..69
 note = Engineered antibody sequence
 source 1..69
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 513
 gccatcgta tgacccagac tccatcttcc aagtctgtcc ctgtgggaga cacagtacc 60
 atcaattg 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
 caggccagtg agagtcttta taataacaac gccttggcc 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 gcagcctccc aagcgcctga 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
 gatgcattca aactggcattc 21

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SEQ ID NO: 517      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: 517
gggggtcccat cgccgttcag tggcggtggg tctgggacac agttcactct caccatcagt 60
ggcgtgcagt gtgacgtgc tgccacttac tactgt                         96

SEQ ID NO: 518      moltype = DNA length = 36
FEATURE          Location/Qualifiers
misc_feature     1..36
source           note = Engineered antibody sequence
                 1..36
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 518
ggagggtatac gaagtgtatag tggatgtatgt gttgct                         36

SEQ ID NO: 519      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: 519
ttcgcggag ggaccgaggt ggttgtcaaa cgt                                33

SEQ ID NO: 520      moltype = DNA length = 321
FEATURE          Location/Qualifiers
misc_feature     1..321
source           note = Engineered antibody sequence
                 1..321
                 mol_type = other DNA
                 organism = synthetic construct
SEQUENCE: 520
acgggtggctg caccatctgt ctgcatttc ccgcctatcg atgaggcaggtaa gaaatctgg 60
actgcctctc ttgtgtgcct gctgaaataac ttttatccca gagaggccaa agtacagtgg 120
aagggtggata acggccctcca atcggttaac tccaggaga gtgtcacaga gcaggacagc 180
aaggacacgca cttcagccct cagcagcacc ctgacgtcgta gcaaaacgaga ctacgagaaa 240
cacaaggatct acgcctgcga agtcacccat caggccctga gtcgcggctg cacaaggagc 300
ttcaacaggg gagagtgtta g                                         321

SEQ ID NO: 521      moltype = AA length = 441
FEATURE          Location/Qualifiers
REGION          1..441
source           note = Engineered antibody sequence
                 1..441
                 mol_type = protein
                 organism = synthetic construct
SEQUENCE: 521
EVOLVESGGG LVQPGGSLRL SCAVSGIGLS SYYMQWVRQA PGKGLEWVGV IGSDGKTYYA 60
TWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCTRGRDI WGQGTLVTVS SASTKGPSVF 120
PLAPSSSKTS CGTAALGCLV KDYFPPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
TVPSSSLGTQ TYICNVNHPK SNTKVDARVE PKSCDKTHTC PPCPAPELIG GPSVFLFPPK 240
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVVSL 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
source           note = Engineered antibody sequence
                 1..111
                 mol_type = protein
                 organism = synthetic construct
SEQUENCE: 522
EVQLVESGGG LVQPGGSLRL SCAVSGIGLS SYYMQWVRQA PGKGLEWVGV IGSDGKTYYA 60
TWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCTRGRDI WGQGTLVTVS S             111

SEQ ID NO: 523      moltype = AA length = 30
FEATURE          Location/Qualifiers
REGION          1..30
source           note = Engineered antibody sequence

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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		
VIGSDGKTYY ATWAKG		16
SEQ ID NO: 527	moltype = AA length = 32	
FEATURE	Location/Qualifiers	
REGION	1..32	
	note = Engineered antibody sequence	
source	1..32	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 527		
RFTISRDN SK TTVYIQLQMNSL 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		
WGQGTLVTVS 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 DYPPEPVTVS WNSGALTSGV HTFPAVLQSS	60	
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDARVEP KSCDKTHTCP PCPAPELLGG	120	
PSVFLFPKPK KDTLMISRTP EVTCVVVDVS HEDPEVKPNW YVDGVDEVHNA KTKPREEQVA	180	
STYRVVSVLT VLHQDWLNKG EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE	240	
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGFFLY 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	

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source 1..1326
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 531
 gaggtgcagc ttgtggagtc tgggggaggo ttgggtccagc ctggggggtc cctgagactc 60
 tcctgtgcag tctctggaat cggcctcagt agtactaca tgcaatgggt ccgtcagget 120
 ccagggaaagg ggctggagtg ggtcgagtc attggtagtg atggtaagac atactacgct 180
 acctgggoga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
 caaatgaaca gcgtggagac tgaggacact gctgtgtatt tctgttaccag aggggacate 300
 tggggccaag ggaccctcgat caccgttcag agcgcctcca ccaaggggccc atcggttetc 360
 ccacctggac cctcttccaa gagacctctt gggggcacagc eggccttggg ctgcttggc 420
 aaggactact tccccgaacc ggtgacgggtg tcgtggaaact caggcgcctt gaccagcggc 480
 gtgcacaccc tcccggtctg ctcatcgact tcaggactct actccctcag cagcgtgtg 540
 accgtgcctc accagcagtt gggcaccacg actacatctt gcaacgtgaa tcacaagccc 600
 agcaacacca aggtggacgc gagagtttag cccaaatctt gtgacaaaac tcacacatgc 660
 ccaccgtgcc cagcacctga actctgggg ggaccgtcaq tcttcctt ccccccaaaa 720
 cccaaggaca cccctcatgtat ctcggggacc cctgagggtca catgcgtgtt ggtggacgtg 780
 agccacgaag accctggatg caagttaac tggtagctgg acggcgtgaa ggtgcataat 840
 gccaqaagcaa accggcgggaa ggacgactac gccacgactt accgtgtgtt cagcgtctc 900
 accgtcttc accaggactg gctgaatggc aaggagtaca agtgcacagg tctcaacaaa 960
 gccccttcccg ccccccattcgaa gaaaaccatc tccaaaggcca aaggcggacc cccgagaacca 1020
 cagggtgtaca ccttggggatc atccggggatc gagatgacca agaaccaggat cagcctgacc 1080
 tgccctggta aaggcttcta tcccgacatc atccgggtt gttggagagag caatgggcag 1140
 ccggagaaca actacaagac cacgcctccg gtgtgttactt ccggacggcctt cttttcttc 1200
 tacagcaacg tcaccgtgga caagacggg tggcagcgg ggaacgttctt ctcatgtcc 1260
 gtgtatgcattt aggctctgca caacoactac acgcagaaga gctctccctt gtctccgggt 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 ttgggtccagc ctggggggtc cctgagactc 60
 tcctgtgcag tctctggaat cggcctcagt agtactaca tgcaatgggt ccgtcagget 120
 ccagggaaagg ggctggagtg ggtcgagtc attggtagtg atggtaagac atactacgct 180
 acctgggoga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
 caaatgaaca gcgtggagac tgaggacact gctgtgtatt tctgttaccag aggggacate 300
 tggggccaag ggaccctcgat caccgttcag 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 tgggggaggo ttgggtccagc ctggggggtc cctgagactc 60
 tcctgtgcag tctctggaat cggcctcagt 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
 agtactaca 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
 tgggtccgtc aggctccagg gaaggggctg gagtggttcg ga 42

SEQ ID NO: 536 moltype = DNA length = 48
 FEATURE Location/Qualifiers
 misc_feature 1..48
 note = Engineered antibody sequence
 source 1..48

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mol_type = other DNA
organism = synthetic construct

SEQUENCE: 536
gtcattggta gtgatggtaa gacatactac gcgacctggg cgaaaggc 48

SEQ ID NO: 537      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: 537
cgattcacca tctccagaga caattccaag accacgggt atcttcaa at gaacagcctg 60
agagctgagg acactgctgt gtatttcgt accaga 96

SEQ ID NO: 538      moltype = length =
SEQUENCE: 538
000

SEQ ID NO: 539      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: 539
tggggccaag ggaccctcg taccgtctcg agc 33

SEQ ID NO: 540      moltype = DNA length = 993
FEATURE
misc_feature        Location/Qualifiers
1..993
note = Engineered antibody sequence
source              1..993
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 540
gcctccacca aggggccatc ggtttcccc ctggcaccc cctccaagag cacctctggg 60
ggcacagccg ccctggctg cctggtaag gactacttc cccgacccgt gacgggtgtcg 120
tggaaacttag cgcgcctgac cagcggcggtg cacaccttc cggctgtct acagtctca 180
ggactctact ccctcagtag cgtgttgacc gtggccctca gcagcttggg caccaggacc 240
tacatctgca acgtgaatca caagggccagc aacaccaagg tggacgcgag agttgagccc 300
aaatcttgtc acaaaaactca cacatggca cccgtggccag caccctgact cctgggggg 360
ccgtcgtct tccttctccc cccaaaaccc aaggacacc tcatgtatc cccggccct 420
gaggtaacat ggtgtgggtt ggacgtgacg caccggacgg ctgggggttcaaa gttcaactgg 480
tacgtggacg cgtgtgggtt gataatggc aagacaaaggc cgggggggg gcatgtacgccc 540
agcacgtacc gtgtgtttag cgtcttacc gtcctgcacc aggactgggt gaatggcaag 600
gagtaacatg gcaaggatcc caacaaaggcc ctcccaaggccc ccatcgagaa aaccatctcc 660
aaaggccaaag ggccggcccg agaaggccacg gtgtacacc tgccccatc cccgggggg 720
atgaccaaga accaggtagt cctggatccctt ctggtaaaatc gttttatcc cagcgacatc 780
ggccgtggagt gggagagcaa tggggcagcc gagaacaact acaagaccac gcctccctgt 840
ctggactccg acggcttctt cttctctac agaagctca ccgtggacaa gaggcgggtgg 900
cagcagggggaa acgttcttc atgtccgtg atgcatggg ctctgcacaa ccactacacg 960
cagaagaccc tctccctgtc tccgggtaaa tga 993

SEQ ID NO: 541      moltype = AA length = 219
FEATURE
REGION             Location/Qualifiers
1..219
note = Engineered antibody sequence
source              1..219
mol_type = protein
organism = synthetic construct

SEQUENCE: 541
QVLTQSPSSL SASVGDRVTI NCQASQNLYNNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
SRFSGSGSGT DFTLTISLQ PEDVATYYCL GSYDCSRGDC FVFGGGTKVE IKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNYFPREAK VQWVKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 219

SEQ ID NO: 542      moltype = AA length = 113
FEATURE
REGION             Location/Qualifiers
1..113
note = Engineered antibody sequence
source              1..113
mol_type = protein
organism = synthetic construct

SEQUENCE: 542
QVLTQSPSSL SASVGDRVTI NCQASQNLYNNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
SRFSGSGSGT DFTLTISLQ PEDVATYYCL GSYDCSRGDC FVFGGGTKVE IKR 113

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SEQ ID NO: 543	moltype = AA length = 22
FEATURE	Location/Qualifiers
REGION	1..22
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	1..13
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 544	
QASQNQVYNNN YLA	13
SEQ ID NO: 545	moltype = AA length = 15
FEATURE	Location/Qualifiers
REGION	1..15
source	note = Engineered antibody sequence
	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
source	note = Engineered antibody sequence
	1..7
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 546	
STSTLAS	7
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	
FGGGTKVEIK 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	

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

SEQ ID NO: 551 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: 551
caagtgtga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccagg ccagtcaagaa tgtttacaat aacaactacc tagcctggta tcagcagaaa 120
ccaggaaatg ttccctaagca actgtatcatcttacatcca ctctggcata tgggtccca 180
tctcggttca gtggcagttgg atctgggaca gatttcacttc acatccatcg cagcctgcag 240
cctgaagatg ttgcaactta ttactgtctg ggcagttatg atttgtatcg tggtgatgt 300
tttgtttcg gcccggaaac caagggtggaa atcaaactggaa cgggtggcgc accatctgtc 360
ttcatcttcc cgccatctga tgacgttgg aaatctggaa ctgcctctgt tggtgctg 420
ctgaataact ttatcccg agggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcgggttaact cccaggagag tgcacagag caggacagca aggacagcac ctacagcctc 540
agcagcaccc tgacgttgg caaaggcagac tacgagaaac acaaagtcta cgcctgcga 600
gtcaccatc agggccttag ctcggccatc acaaaggttgc tcaacaggagg 660

SEQ ID NO: 552 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: 552
caagtgtga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccagg ccagtcaagaa tgtttacaat aacaactacc tagcctggta tcagcagaaa 120
ccaggaaatg ttccctaagca actgtatcatcttacatcca ctctggcata tgggtccca 180
tctcggttca gtggcagttgg atctgggaca gatttcacttc acatccatcg cagcctgcag 240
cctgaagatg ttgcaactta ttactgtctg ggcagttatg atttgtatcg tggtgatgt 300
tttgtttcg gcccggaaac caagggtggaa atcaaactggat 339

SEQ ID NO: 553 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: 553
caagtgtga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgc 66

SEQ ID NO: 554 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: 554
caggccagtc agaatgttta caataacaac tacctagcc 39

SEQ ID NO: 555 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: 555
tggttatcagc agaaaccagg gaaagttcct aagcaactga tctat 45

SEQ ID NO: 556 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: 556
tctacatcca ctctggcata t 21

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SEQ ID NO: 557 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: 557
 ggggtcccat ctcgtttcag tggcaagtgg a tttca ctctt caccatc agc 60
 agcctgcagc ctgaagatgt tgcaacttat tactgt 96

SEQ ID NO: 558 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: 558
 ctgggcagg t atgattgttag tcgtggt gat tgttttg tttt 39

SEQ ID NO: 559 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: 559
 ttccggcgag gaaccaagg t ggaaatcaaa cgt 33

SEQ ID NO: 560 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: 560
 acgtgtggctg caccatctgt cttcatcttc ccgc catctg atgaggcagg t gaaatctt gaa 60
 actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
 aagggtggata acggccctccaa atccggtaac tcccaggaga gtgtcacaga gcaggacagc 180
 aaggacagca cttacagcc t cagc accc cttc acgtcgta gcaaa gcaaa ctacgaaaa 240
 cacaaggatct acggctgcga agtacccat caggccctga gtcgc cccgt cacaaggagc 300
 ttcaacagg g gatgttta 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 GMVKS N FVPT NVGSKAF 37

SEQ ID NO: 563 moltype = AA length = 106
 FEATURE Location/Qualifiers
 source 1..106
 mol_type = protein
 organism = Homo sapiens

SEQUENCE: 563
 TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
 KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC 106

SEQ ID NO: 564 moltype = AA length = 330
 FEATURE Location/Qualifiers
 REGION 1..330
 note = Engineered antibody sequence

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source 1..330
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 564
 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVWS WNSGALTSGV HTFPAVLQSS 60
 GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
 PSVFLFPKPK KDTLMISRTP EVTCVVVDVS HEDPEVKFNV YVDGVENVHNA KTKPREEQYA 180
 STYRVSVLTL VHLDWLNKG EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPPSREE 240
 MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV 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 DYFPEPVTVWS WNSGALTSGV HTFPAVLQSS 60
 GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
 PSVFLFPKPK KDTLMISRTP EVTCVVVDVS HEDPEVKFNV YVDGVENVHNA KTKPREEQYA 180
 STYRVSVLTL VHLDWLNKG EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPPSREE 240
 MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW 300
 QQGNVFSCSV MHEALHNHYT QKSLSLSPG 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
 EVQLVESGGG LVQPGGSLRL SCAVGIDLS GYYMNWVRQA PGKGLEWVGIGINGATYYA 60
 SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
 PLAPSSKSTS CGTAALGCLVK KDYFPEPVTV SWNSGALTSGVHTFPAVLQSGLYSLSSVV 180
 TVPVSSSLGTQ TYICCNVNHKPS SNTKVDARVE PKSCDKTHTCP PPCPAPELLG GPSVFLFPK 240
 PKDTLMISRT PEVTCVVVDV SHEDPEVKFNV YWDGVENVHNA KTKPREEQY ASTYRVSVL 300
 TVLHQDWLNKG KEYKCKVSNKA ALPAPIEKTI SKAKGQPREPQ VYTLPPSRE EMTKNQVSLT 360
 CLVKGFYPSDI IAVEWESNGQ PENNYKTTTPV VLDSDGSSFL YSKLTVDKSR WQQGNVFSCS 420
 VMHEALHNHY TQKSLSLSPG 440

SEQ ID NO: 567 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: 567
 gaggtgcagc ttgtggagtc tgggggaggc ttgttccagc ctggggggtc cctgagactc 60
 tcttgtcagc tctcttgaat cgacctcagt ggctactaca tgaactgggt ccgtcaggct 120
 ccagggaaagg ggctggagtg ggtcgaggc attggattata atgggtccac atactacgcg 180
 agctggggaa aaggcgatt caccatctca agagacaat ccaagaccac ggttatctt 240
 caaatgagaac gccttagagc tgaggactact gctgtgtat tetgtgtctg agggggacatc 300
 tggggccaag ggaccttcgt caccgtctcg agccgcctca ccaaggcccc atcggtttc 360
 cccctggcac cttcttccaa gagcacctct gggggcacag cggccctggg ctggcgttgc 420
 aaggactact tccccgaacc ggtgacgggt tcgttggact caggcgccct gaccagccgc 480
 gtgcacactt tcccggtctgt cctcagactt tcaggactt actccctcag cagcgtgttg 540
 accgtgcaccc ctccgtgtt gggcccccac acctacatctt gcaacgtgaa tcacaaggcc 600
 agcaacaccaa aggtggacgc gagagtttag cccaaatctt gtgacaaaac tcacacatgc 660
 ccaccgtgcc cagcacctga actcttgggg ggaccgtcag tttttttt cccccccaaa 720
 cccaaaggaca ccctcatgtat cttccggacc cctgagggtca catgcgttgt ggtggacgtg 780
 agccacaaagg accctggaggt caagtcaac tggtaactgg acggcggtga ggtgcataat 840
 gccaagacaa agcccgggga ggacgtac gccacgtact accgtgttgt cagcgtcctc 900
 accgtccctgc accaggactg gctgaatggc aaggagttaca agtgcgttgtt ctccaaacaaa 960
 gcccctcccg ccccccattca gaaaaaccatc tccaaagcca aaggccggcc ccgagaacca 1020
 cagggttaca ccctggggcc atccccggag gagatgacca agaaccaggc cagcgttgc 1080
 tgcctggtca aaggcttcta tccccggccatc atccgggtgg agtggggagag caatgggcag 1140
 cccggagaaca actacaagac cacccctccg gtgctggact cccacggctc cttttcttc 1200
 tacacgaaacg tcaccgttca caagcggcagg ggaacgttcc ctcacatgc 1260
 gtgtatgcatc aggcttgcac caaccactac acgcagaaga gctctccctt gtctccgggt 1323
 tga

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What is claimed is:

1. A method of treating migraine in a patient, comprising intravenously administering to the patient an effective amount of an anti-calcitonin gene related peptide (CGRP) antibody comprising: (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, wherein said administration starts after the onset of a migraine attack while the patient is exhibiting at least one symptom of the migraine attack.

2. The method of claim **1**, wherein said at least one symptom comprises one or more of headache, nausea, photophobia, and phonophobia.

3. The method of claim **2**, wherein said administration begins within 1-6 hours of the onset of at least one symptom of said migraine attack.

4. The method of claim **1**, wherein said administering begins between about 1-6 hours from the onset of said migraine attack.

5. The method of claim **1**, wherein said administering is by intravenous infusion.

6. The method of claim **1**, wherein said administering is by intravenous infusion over a period of approximately 30 minutes to 60 minutes.

7. The method of claim **1**, wherein said administering is by intravenous infusion over a period of approximately 30 minutes.

8. 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.

9. The method of claim **1**, wherein said anti-CGRP antibody is administered in a 0.9% sodium chloride solution, optionally 100 ml of a 0.9% sodium chloride solution.

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10. The method of claim **1**, wherein said administering is by intravenous infusion of a solution comprising about 100 mg to about 300 mg of said anti-CGRP antibody.

11. The method of claim **1**, wherein said administering is by intravenous infusion of a 0.9% sodium chloride solution comprising about 100 mg to about 300 mg of said anti-CGRP antibody.

12. The method of claim **1**, wherein said administering is by intravenous infusion of 100 ml of a 0.9% sodium chloride solution comprising about 100 mg to about 300 mg of said anti-CGRP antibody over a period of approximately 30 minutes.

13. 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.

14. The method of claim **1**, wherein said anti-CGRP antibody is an IgG molecule.

15. 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.

16. The method of claim **15**, wherein said anti-CGRP antibody consists of said light and heavy chain polypeptides.

17. 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.

18. The method of claim **1**, wherein the patient has episodic migraine.

19. The method of claim **1**, wherein the patient has chronic migraine.

20. The method of claim **1**, wherein said anti-CGRP antibody is an IgG1 molecule.

21. The method of claim **12**, wherein said anti-CGRP antibody is an IgG1 molecule.

* * * * *