Cara Therapeutics, Inc.

CARA : NASDAQ : US$14.48

BUY

Target: US$25.00

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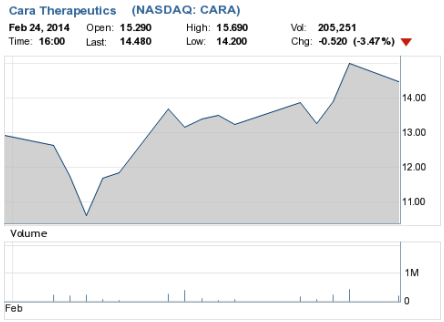
COMPANY STATISTICS:

Forecast Return:	73%
Shares Out (M):	21.8
Market Cap (M):	US$316.3
52-week Range:	US$10.40 - 15.69

EARNINGS SUMMARY:

FYE Dec		2013E	2014E	2015E
Revenue:		14.7	3.0	3.0
EPS:		0.09	(1.12)	(1.39)
Revenue:	Q1	3.7A	0.0	--
	Q2	3.7A	1.0	--
	Q3	3.7A	1.0	--
	Q4	3.7	1.0	--
Total		14.7	3.0	3.0
EPS:	Q1	0.04A	(0.18)	--
	Q2	0.04A	(0.22)	--
	Q3	0.04A	(0.31)	--
	Q4	(0.01)	(0.40)	--
Total		0.09	(1.12)	(1.39)

SHARE PRICE PERFORMANCE:



Source: Interactive Data Corporation

COMPANY DESCRIPTION:
CARA is a clinical-stage biotech company focused on developing novel kappa opioid receptor agonists for postoperative pain management. This novel class of pain drugs could also be formulated for oral delivery and could potentially treat chronic pain and various inflammatory conditions.

All amounts in US$ unless otherwise noted.

Life Sciences -- Biotechnology

HARNESSING THE BEST OF THE OPIATE RECEPTOR FOR POST-OP PAIN: INITIATING WITH BUY, $25 TARGET

Investment recommendation

Initiating coverage with BUY, $25 target on CR845's potential in adjunct post-operative pain relief. Cara's lead candidate is a peripherally restricted kappa subtype specific opiate receptor agonist. We think '845 could provide additional needed pain relief potentially superior to, but also complementary to, current post-op adjunct analgesics, without typical opiate side effects. We expect positive data from three upcoming post-op Ph3 studies in H2/15. We think '845 could gain significant market share and model potential US peak sales of $750M. Our $25.00 target is based on a pNPV analysis.

Investment highlights

- **CR845 is a novel peripherally restricted, highly kappa subtype selective opiate receptor agonist.** The kappa receptor, like the commonly targeted mu receptor, also mediates analgesia and reduces inflammation but does not cause (and may even antagonize) opiate-related nausea/ vomiting. Peripheral restriction prevents the hallucinogenic side effects seen with CNS kappa activation. We anticipate top-line data H2/15.
- **Excellent Phase 2 data gives us conviction in Ph3 success.** Phase 2 data in both FDA-required post-operative pain models showed excellent statistically significant pain reduction versus placebo, with some data sets showing statistically lower nausea/vomiting rates and no hallucinatory side effects. CARA's upcoming Ph3 trials are designed very similarly, giving them a very good chance of clinical success.
- **CR845 could allow potential cost-savings driven by an improved side effect profile, which could drive an additional market uptake and upside in the stock.** Post-op pain remains a problem despite the availability of multiple front-line and adjunct Tx options. Opiates have risks of side effects; non-opiates have only moderate analgesia. Further, opiate related nausea and vomiting side effects can result in long hospital stays and care costs. We think lower rates of side effects will drive CR845 adoption and model peak US sales estimates of $750M.

Figure 1: CARA upcoming catalysts

Expected date	Drug/Program	Item	Impact
Q1/14	CR845 in acute postoperative pain	renal impairment PK data	+
Q2/14	CR845 in acute postoperative pain	Human abuse liability trial data	++
Q4/14	Oral CR845	Ph1 single/multiple ascending dose data	++
Q4/14	CR845 in acute postoperative pain	Pivotal Ph3 trials initiation	+
Q2/15	CR845 in acute postoperative pain	Pivotal Ph3 trials data readout	+++

Source: Company reports and Canaccord Genuity estimates

Figure 2: CARA pipeline

Drug/ Program	Disease	Licensing/ Partnership	Preclinical	Phase 1	Phase 2	Phase 3	Post-Marketing
IV CR845	Acute pain	Maruishi (Japan) Chong Kun Dang (South Korean)					
Oral CR845	Acute and chronic pain	Maruishi (Japan) Chong Kun Dang (South Korean)					
CR701	Neuropathy and inflammatory pain	Wholly owned					

Source: Company reports

INVESTMENT THESIS

We think CR845 is a promising drug candidate for adjunct post-operative analgesia, which represents a significant unmet need. Cara's CR845 is a novel peripherally restricted selective kappa subtype opiate receptor agonist in pre-Phase 3 development for management of post-operative pain. Pain management is a critical part of post-operative care and patients who suffer from high post-procedural pain levels can have longer recovery times, higher morbidity and poorer outcomes. 75% of post-operative patients still suffer from moderate to severe pain despite being on PCA (patient-controlled analgesia) morphine. Clinicians do no give additional opiates to these patients out of concern for opiate side effects such as nausea and vomiting, respiratory depression and psychiatric side effects.

CR845 has a unique mechanism of action with strong scientific rationale. CR845 is a small tetrapeptide that cannot cross the blood brain barrier and has very high selectivity for the kappa subtype of opiate receptor. This subtype is thought to mediate pain relief very similar to the mu opiate receptor (the subtype activated by morphine, fentanyl and other typical opiates), but kappa activation is also thought to antagonize other mu subtype effects. These include nausea, vomiting, and addictive signaling. Further, kappa activation is thought to have potent anti-inflammatory effects that could mediate additional pain relief. Kappa receptor signaling in the CNS can lead to hallucinations and dysphoria however, so limiting activation to the periphery (proven by preclinical studies of CR845, but not a characteristic of earlier generation kappa agonists) is key for establishing a safe and effective drug profile for a pain relief therapy.

We think precedent IV CR845 Phase 2 data bodes well for Phase 3 success. Cara has conducted three previous Phase 2 studies of CR845 in post-operative pain models (two laparoscopic hysterectomy soft tissue trials and one bunionectomy hard tissue trial). All three trials showed clinically meaningful statistically significant pain reduction versus placebo. Two of the trials also showed statistically significant reduction in rates of nausea and vomiting, the holy grail of opiate analgesics with improved tolerability. Safety data from these trials also showed no evidence of respiratory depression. Interestingly, data from one of the soft tissue trials suggests CR845 could provide post-operative pain relief even when dose pre-operatively (although pain relief data did not reach statistical significance due to small patient numbers). Data also showed very good safety with the only side effect of note being facial tingling and aquaresis (which can be addressed with fluid replenishment with pure water, rather than saline).

Intelligent trial design also strongly supports a high chance of Phase 3 success, regulatory approval and pharmacoeconomic cost-savings arguments. Cara plans to initiate three Phase 3 trials of IV CR845 in the post-operative setting in H2/14 with proceeds from the recent IPO. Two of these trials (one in soft tissue, one in hard tissue) will be pivotal and support the CR845 NDA submission. Both of these trials closely resemble the successful Phase 2's, but are better powered due to larger patient numbers. As a result, we think these trials have a very good chance of success. The third trial in a soft-tissue model will investigate pre-operative dosing of CR845 and potentially generate additional data (e.g., opiate rescue medication sparing) that will be key for optimal marketing of CR845. We expect the design of this trial to generate pharmacoeconomic arguments for use of CR845

driven by lower opiate side effects which could result in lower cost of patient care and shorter length of stay.

We believe CR845 has significant commercial potential with $750M in peak US sales for IV and additional potential upside from an oral step-down formulation. We think CR845 could become a key treatment option for adjunct pain relief in the post-operative setting with the potential to both optimize pain relief while reducing potential opiate side effects, particularly nausea and vomiting. We think CR845 will be one of the most preferred adjunct therapies for post-operative pain management as we believe it will be a stronger pain reliever than current options like Ofirmev, Caldolor and IV ketorolac. We estimate peak potential penetration of ~20% for the inpatient and outpatient surgical market and 10% penetration of the inpatient and outpatient procedure market. This result in peak potential US sales of $750M.

INVESTMENT RISKS

Clinical risk – Cara's planned Phase 3 trials may not be successful. We note there is always risk in drug development trials, especially pain trials which can have unusually high unpredictable placebo signals which can confound trial statistics. Also, magnitude of benefit may be different in a less well controlled, real-world patient population. However, we think the planned pivotal Phase 3's so closely resemble the Phase 2's that chance of success is high.

Clinical risk – Additional trials may show CR845 to have an unacceptable safety and/or tolerability profile. Notable side effects seen in Phase 2 trials of IV CR845 included facial tingling and aquaresis (low electrolyte urine production) which can lead to hypovolemia. One instance of subclinical postural tachycardia was seen which was thought to be related to this hypovolemia. This event was not deemed clinically important. Should greater rates or severity of these side effects occur in Phase 3 trials, CR845's chance of regulatory and/or commercial success could be negatively impacted. We think this unlikely given strict protocols requiring pure water fluid replenishment. Further, other kappa agonists have shown problematic side effects including hallucination and dysphoria in clinical trials. This is thought to be related to CNS kappa signaling, which CR845, per preclinical data, should not be capable of.

Regulatory risk – CR845 may not be approved by the FDA and/or EMA despite Phase 3 success, or scheduling/REMS restriction may greatly impair the drug's chance of success. Should CR845's safety profile be more problematic than that seen in the Phase 2 trial, FDA and EMA could refuse to approve the therapy. Further, there is a chance that CR845 may be scheduled as a controlled substance by the US DEA (even if the planned Human Abuse Liability trial shows no abuse potential) just by its opiate subtype association. If the drug is scheduled, it could greatly complicate distribution and use of the therapy, limiting commercial potential.

Competitive risk – CR845 will be competing with other adjunct therapies that will have been established in the market for a number of years, some of which will be generic and therefor significantly cheaper than CR845. Ofirmev and Caldolor have been approved in the US since 2010 and 2009, respectively, and are widely included on current hospital formularies. They are already part of a number of physicians and surgeons post-operative

pain management habits. The clinicians could be resistant or slow to adopt a new adjunct pain reliever in the post-op setting.

Reimbursement risk – There is no guarantee that Cara, or its partners, will garner reimbursement for CR845. We also note CR845's initially pursued indication would dictate its use in the hospital setting, which will require prior approval from hospital P&T committees. P&T committees are notoriously cost-conscious and focused on the pharmacoeconomic savings afforded by new products and can represent formidable reimbursement hurdles. Failure to obtain such pharmacoeconomic arguments that would secure reimbursement could limit sales of the drug and have a negative impact on the company's share price.

VALUATION

We have built our valuation of CARA using a probability-weighted NPV model of peak sales.

Potential upside to valuation

We see the following as potential drivers of upside to our model:

- **Faster-than-expected development of oral CR845, a potential step-down pain therapy.** Oral CR845 could prove to be a potent analgesic with minimal addiction and side effect potential, based on scientific rationale. CARA is currently developing a new optimized formulation of oral CR845 which it hopes to take into Ph2 trials later in 2014. We note that the IV845 will provide significant proof of concept and significantly determine the ultimate value of the oral drug.
- **Better-than-expected Phase 3 efficacy or pharmacoeconomic data.** Should CR845 show strong pain relief, either by absolute SPID score or responder analysis, it could become the preferred post-op adjunct pain reliever. Further, if clinical data shows significant cost savings, hospitals may encourage its use in the post-op setting to generate overall operational savings, leading to additional peak sales above our current model.
- **Revenues generated in the EU and ROW markets.** Our valuation model is driven only by US peak sales as there is significantly more regulatory uncertainty around an EU approval. Further, Cara intends to partner CR845 in the EU and other territories. As such, there is potential, though hard to quantify opportunities, from potential sales in these territories.
- **Rapid development and positive data for CR-701**. Cara is developing a cannabinoid agonist with balanced signaling at the CB1 and CB2 receptors for chronic pain. This program is currently in preclinical development, but rapid advanced development could result in additional upside to Cara shares.

Potential downside to valuation

As with all companies in commercial and clinical development, there always exists the risk of failed or inconclusive clinical trials, slower-than-expected commercial launches, or lower-than-expected peak sales, which could lead to downward pressure on the stock. For more detailed risks, see our "Investment Risks" section.

Figure 3: CARA valuation

Product Development

Drug name	Indication	Status	Launch	Years to Launch	Years to Launch plus 6	Success	Sales (US$m)	Probability weighted Peak Sales (US$m)	Royalty	Profitability	Probability weighted Peak Profit (US$m)	Discount Factor	NPV (US$)
CR845	Post-op pain	Phase 3	2017	3	9	60%	747.9	448.8	90%	80%	323.10	6.21	25.33
										Total			**25.33**

Source: Company reports and Canaccord Genuity estimates

REVENUE MODEL AND FINANCIALS

Our forecast financial model is built on the assumption that IV CR845 will launch in the US in H2/17 for use in postoperative acute mild to severe pain. Our CR845 market model in postoperative pain assumes peak CR845 market share of 20% in US inpatient/outpatient surgeries and 10% in US inpatient/outpatient non-surgical setting. We assume peak sales will be reached in 2023, six years from launch.

We assume that CARA will price one course of IV CR845 around $120 in the US. However, we think this is a very conservative estimate and we expect further market research to support an even higher pricing based superior phamacoeconomics and safety profile. Overall, we forecast peak sales for IV CR845 in 2023 of ~$750M. We have not modeled potential revenue streams from EU or ROW, which could increase the peak sales figure significantly.

CARA reported current asset of $17.7M on September 30, 2013 and received $55.9M net proceeds from recent initial public offering. We think CARA has sufficient cash to operate until Phase 3 CR845 data readout in Q2/15. CARA has stated it has enough cash to operate through mid-2015 when the Phase 3 CR845 data is due, at which point we think the company will likely have 2-3 quarters of operating cash remaining. This amount will not be able to take the company through a full scale commercial launch in the US. We think CARA may consider an equity issue either after Phase 3 CR845 data or approval to secure operating expenses as well as funds for the commercial launch of CR845 for postoperative acute mild to severe pain management.

Figure 4: CR845 revenue projections

		2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
CR845 (post-op pain) market model														
US population	1.0%	321.2	324.4	327.6	330.9	334.2	337.6	340.9	344.3	347.8	351.3	354.8	358.3	361.9
Hospital inpatient setting		14,890,702	15,190,005	15,495,324	15,806,780	16,124,497	16,448,599	16,779,216	17,116,478	17,460,519	17,811,476	18,169,486	18,534,693	18,907,240
Incidence	1.0%	*0.046364*	*0.046827*	*0.047295*	*0.047768*	*0.048246*	*0.048729*	*0.049216*	*0.049708*	*0.050205*	*0.050707*	*0.051214*	*0.051726*	*0.052244*
Surgical		11,168,027	11,392,504	11,621,493	11,855,085	12,093,372	12,336,449	12,584,412	12,837,359	13,095,390	13,358,607	13,627,115	13,901,020	14,180,430
% of hospital inpatient	0.0%	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
Non-surgical		2,792,007	2,848,126	2,905,373	2,963,771	3,023,343	3,084,112	3,146,103	3,209,340	3,273,847	3,339,652	3,406,779	3,475,255	3,545,108
% of hospital inpatient	0.0%	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*
Hospital outpatient setting		18,161,870	18,893,794	19,655,214	20,447,319	21,271,346	22,128,581	23,020,363	23,948,083	24,913,191	25,917,193	26,961,655	28,048,210	29,178,553
Incidence	3.0%	*0.056549*	*0.058245*	*0.059992*	*0.061792*	*0.063646*	*0.065555*	*0.067522*	*0.069548*	*0.071634*	*0.073783*	*0.075997*	*0.078277*	*0.080625*
Surgical		13,621,403	14,170,345	14,741,410	15,335,489	15,953,509	16,596,436	17,265,272	17,961,062	18,684,893	19,437,894	20,221,242	21,036,158	21,883,915
% of hospital outpatient	0.0%	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
Non-surgical		3,405,351	3,542,586	3,685,353	3,833,872	3,988,377	4,149,109	4,316,318	4,490,266	4,671,223	4,859,474	5,055,310	5,259,039	5,470,979
% of hospital outpatient	0.0%	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*	*25%*
Total addressable patients		30,986,787	31,953,561	32,953,629	33,988,218	35,058,602	36,166,106	37,312,105	38,498,026	39,725,353	40,995,627	42,310,446	43,671,472	45,080,431
CR845														
Inpatient segment														
% of inpatient - surgical					*1.0%*	*5.0%*	*10.0%*	*15.0%*	*17.5%*	*19.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*
Number of pts on Tx					118,551	604,669	1,233,645	1,887,662	2,246,538	2,488,124	2,671,721	2,725,423	2,780,204	2,836,086
% of inpatient - non-surgical					*1.0%*	*2.0%*	*4.0%*	*6.0%*	*8.0%*	*9.0%*	*10.0%*	*10.0%*	*10.0%*	*10.0%*
Number of pts on Tx					29,638	60,467	123,364	188,766	256,747	294,646	333,965	340,678	347,525	354,511
Outpatient segment														
% of outpatient - surgical					*2.0%*	*4.0%*	*8.0%*	*14.0%*	*16.0%*	*18.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*
Number of pts on Tx					306,710	638,140	1,327,715	2,417,138	2,873,770	3,363,281	3,887,579	4,044,248	4,207,232	4,376,783
% of outpatient - non-surgical					*1.0%*	*2.0%*	*4.0%*	*6.0%*	*8.0%*	*9.0%*	*10.0%*	*10.0%*	*10.0%*	*10.0%*
Number of pts on Tx					38,339	79,768	165,964	258,979	359,221	420,410	485,947	505,531	525,904	547,098
Number of pts on CR845					493,237	1,383,043	2,850,689	4,752,545	5,736,276	6,566,461	7,379,213	7,615,880	7,860,865	8,114,478
Gross price	2.0%				120.00	122.40	124.85	127.34	129.89	132.49	135.14	137.84	140.60	143.41
Net revenue					90.00	91.80	93.64	95.51	97.42	99.37	101.35	103.38	105.45	107.56
CR845 Revenue					44.39	126.96	266.93	453.91	558.82	652.49	747.92	787.34	828.92	872.78

Source: Company reports and Canaccord Genuity estimates

RECOMMENDATION

We think CR845 could become a very important treatment option for adjunct pain relief in the post-operative setting. Strong Phase 2 data (statistically significant analgesia versus placebo in both of the FDA-required post-op pain models) suggests to us the drug provides statistically significant, clinically meaningful pain relief over placebo.

We think CR845's therapeutic profile will provide preferable risk/benefit proposition in terms of strength of analgesia versus current adjunct post-op analgesia options including IV acetaminophen, IV ibuprophen (both thought to have moderate analgesia) and other opiate post-op rescue medications. CR845 likely has superior pain relief compared to moderate analgesics like IV acetaminophen (Ofirmev) and better safety compared to rescue opiate drugs (due to lower levels of nausea and vomiting). Further, some researchers believe the CR845 kappa receptor mechanism could antagonize (and partially offset) nausea and vomiting from first-line standard of care mu opiate receptors. We think CR845's most notable side effect of facial tingling and subclinical aquaresis/related hypovolemia are easily managed and unlikely to result in clinical issues.

We expect the all 3 planned Phase 3 trials of CR845 to yield positive statistically significant pain relief data versus placebo as well as positive safety data with low rates of nausea and vomiting, and no hallucination signals. Further, we believe the 3nd of these Phase 3 trials, the one designed to be supportive rather than required for FDA approval, will yield key pharmaco-economic cost savings data on use of CR845. We think this trial will show strong evidence of less nausea/vomiting leading to shorter hospital stays and cost-savings to hospitals. Together, we think this data will support full FDA approval as well as a potential deal for EU and ROW commercial rights.

We believe evidence of cost-savings to the hospital will drive uptake in the hospital in-patient setting. In the U.S., we expected CR845 to reach peak market share of 20% of in the inpatient setting and around 10% in the outpatient setting. This could lead to $750M in peak market share driven sales in the U.S. in 2023 assuming a 2017 U.S. approval.

COMPANY OVERVIEW

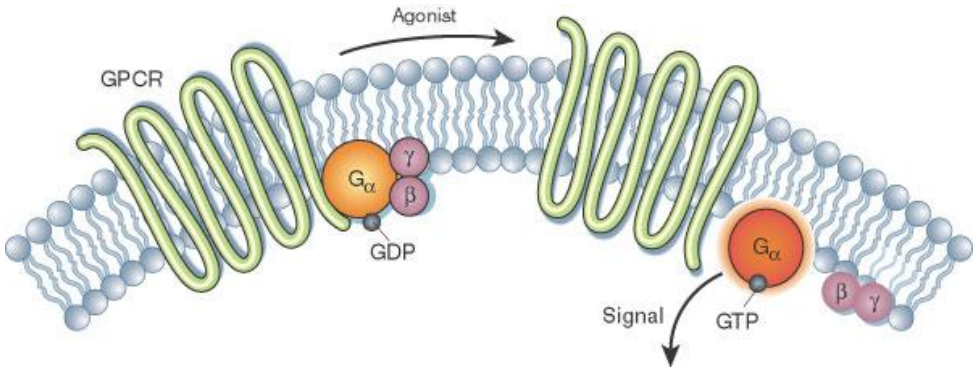
Novel opioid analgesics – peripheral kappa receptors agonists

CARA is a clinical stage biotechnology company focused on the development and commercialization of new chemical entities that can ease pain by selectively activating the kappa opioid receptors. The novel kappa opioid agonists target only the body's peripheral nervous system and have shown efficacy in alleviating moderate-to-severe pain. More importantly, these novel kappa opioid receptors achieve pain reduction without side effects seen in conventional mu opioid receptor agonists that include nausea, vomiting, respiratory depression, and euphoria. CARA's Phase 3 ready pipeline candidate, I.V. CR845, a tetrapeptide-based kappa agonist, has demonstrated unprecedented levels of peripheral selectivity in three Phase 2 trials with patients suffering from postoperative pain. With its expertise in kappa agonist and knowledge of the structure and function of opioid receptors, CARA plans to develop a pipeline of potent analgesics that specifically target the kappa opioid receptors. We think these new chemical entities can be useful in the management of acute pain from surgical operations and chronic pain from a wide range of inflammatory diseases such as arthritis, irritable bowel syndrome, and pruritus.

BIOLOGY OF KAPPA-OPIOID RECEPTOR (KOR)

Opioid receptors are a part of the large family of seven transmembrane-spanning (7TM) G protein-coupled receptors (GPCRs). As a class, GPCRs govern the fundamental physiological function of mediating neurotransmitters and hormones. There are two principal signal transduction cascades involving the GPCRs: the cyclic adenosine monophosphate (cAMP) pathway and the phosphatidylinositol pathway. GPCRs undergo a conformational change as ligands bind to the receptors. The GPCR, in its new conformation, then acts as a guanine nucleotide factor by activating an associated G-protein by releasing a bound guanosine diphosphate (GDP) to allow the binding of a guanosine triphosphate (GTP). The alpha-subunit of the G-protein with the bound GTP will then dissociate from the beta and gamma subunits to relay the intracellular signal further.

Figure 5: GPCR structure



Source: Li, 2002

Pharmacology – receptor subtypes and opioid ligands

Opioid receptors are activated by endogenously produced opioid peptides and by exogenously administered opioid compounds such as morphine. To date, there are multiple subtypes of opioid receptor classified by their unique responses to the repertoire of opioid ligands: MOR (mu for morphine), KOR (kappa for ketocyclazocine), DOR (delta for deferens) and NOR (for nociceptin/orphanin FQ).

The endogenous opioid peptides are derived largely from four precursors: pro-opiomelanocortin, proenkephalin, prodynorphin, and pronociceptin/orphanin FQ. With the exception of nociceptin/orphanin FQ, all peptides derived from the other precursors contain a pentapeptide sequence YGGFM/L (TyrGlyGlyPheMet/Leu). Nociceptin/orphanin FQ, on the other hand, contains a phenylalanine (F) instead of the N-terminal tyrosine, which is a necessary residue for high-affinity binding to the classic opioid receptors.

Figure 6: Selective opioid receptor ligands

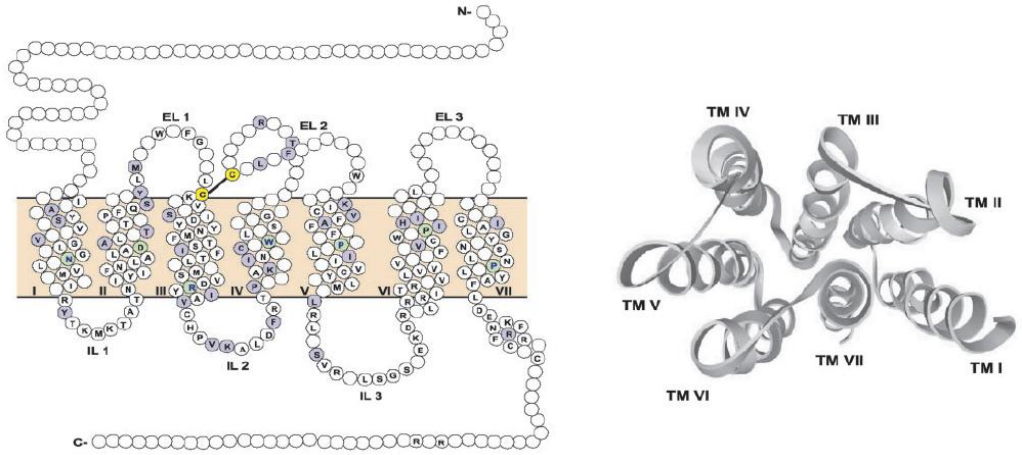
Receptor	Endogenous peptides	Peptide agonists	Peptide antagonists	Agonists	Antagonists
MOP-R	Endomorphin-1 Endomorphin-2 β-endorphin β-neoendorphin Dermorphin	DAMGO PL 017	CTOP Octreotide (SMS201,995)	Fentanyl Morphine Sufentanyl	β-FNA (affinity label) Naloxonazine (irreversible)
DOP-R	Leu^5-Enkephalin Met^5-Enkephalin Met^5-Enkephalin-Arg^6-Phe^7 Met^5-Enkephalin-$Arg^6Gly^7Leu^8$ Deltorphin Deltorphin I Deltorphin II	DADLE DPDPE DSLET	ICI 174,864 (inverse agonist) TIPP TIPP[ψ]	BW373U86 SIOM SNC 80 TAN-67	Benzylidenenaltrexone (BNTX) Naltriben (NTB) Naltrindole (NTI) NTI 5′ isothiocyanate (NTII)
KOP-R	Dynorphin A Dynorphin B	Dynorphin 1a		Bremazocine Ethylketocyclazocine (EKC) Ketocyclazocine CI-977 U-50,488 Spiradoline (U-62,066) U-69,593 ICI 199,441 ICI 197,067 BRL 52,537 BRL 52,656 6′-GNTI	DIPPA Nor-binaltorphimine (nor BNI) 5′-Guanidinonaltrindole (5′-GNTI)
NOP-R[a]	Nociceptin/orphanin FQ	$[Arg^{14}, Lys^{15}]$nociceptin [(pX)Phe^4]nociceptin (1-13) amide analogues $NC(1-13)NH_2$ Cyclo[Cys^{10}, Cys^{14}]$NC(1-14)NH_2$ ZP120	[N-Phe^1]$NC(1-13)NH_2$ UFP-101	Ro 64-6198	Benzimidazolinone (J-113397) JTC-801 TRK-820

Source: Whistler, 2004

Opioid receptors – structure

Opioid receptors is a member of the class A rhodopsin family of GPCRs with an extracellular N-terminal domain, 7TM helical domains connected by three extracellular and three intracellular domains, and an intracellular C-terminal tail that forms a fourth intracellular loop with its putative palmitoylation sites. According to the 2.8 angstrom resolution 3-D rhodopsin structure Palczewski et al elucidated in *Science* in 2000, it is widely accepted that the seven transmembrane helices of opioid receptors are arranged in a counter clockwise sequence that forms a tight helical bundle. The transmembrane helices and the extracellular domains of the receptor help dynamic binding of various opioid ligands. All four receptors have two cysteine residues that are conserved in the first and second extracellular loops that form a disulfide bridge and have multiple Asn-linked glycosyl modifications in the N-terminal domain.

Figure 7: Structure of opioid receptors



Source: Palczewski, 2000

Opioid receptors – ligand binding

All opioid receptors share a common binding pocket that situates in the inner interhelical conserved region amongst transmembrane helicies 3 through 7. And this cavity is partly covered by the extracellular loops. The highly diversified extracellular loops, along with residues from the extracellular ends of the transmembrane segments, significantly affect ligand selectivity.

Large ligands such as norbinaltorphimine fill almost all of the free space in the binding pocket and interface with both conserved and variable residues. On the other hand, small alkaloid agonists, namely morphine, interact predominantly with residues at the bottom of the pocket that are often conserved.

Ligand binding and selectivity are conferred through the recognition of two distinct structures inherent to the ligand. During binding, message tyramine moiety of the cyclic peptides lies at the bottom of the binding pocket and interacts with residues common to all types of opioid receptors. The ligands are oriented toward the extracellular surface of the transmembrane domain in the extracellular loop. These extracellular loops allow for the passage of certain ligands while excluding others.

In addition to distinct transmembrane residues, agonist ligand selectivity for KORs has been attributed to the second extracellular loop. Key residues in KORs determine peptide versus synthetic ligand binding and the process involves the negatively charged second extracellular loop. The loop in turn forms an amphiphilic helix that interacts with six positively charged residues in the endogenous peptide agonist ligand dynorphin A. On the other hand, binding of KOR selective agonists of the acylacetamide class utilizes residues Asp 138 in TM3 and Ile294, Leu295, and Ala298 as anchors for receptor binding.

G-protein-effector activation

Opioid receptors are predominantly coupled to G-proteins, and upon receptor activation, both subunits (alpha and beta-gamma) interact with multiple cellular effector cascades. The cascades then go on to inhibit adenylyl cyclases and volgate-gated calcium channels

and stimulate G-protein-activated inwardly rectifying potassium channels and phospholipase C beta.

Activation of GPCRs/7TM receptors involves ligand-induced transmembrane motions that result in exposure of the intracellular loops that makes them more readily accessible to G-proteins. Intracellular loop 3 is the key determinant of coupling specificity among the different G-protein alpha subunits, whereas intracellular loop 2 is linked to the efficiency of G-protein activation.

An opioid agonist normally binds to one of the hydrophobic clusters in extracellular loop 3 or in N-terminal regions, which destabilizes the interactions between TM6 and TM7 on extracellular side of the receptor. The ligand then enters the binding pocket and disrupts hydrophobic and hydrophilic interactions within TM helices 3, 6, and 7. Movements of these helices ultimately result in a break of cytoplasmic ionic locks and the exposure of intracellular receptor domains to G proteins and other effector proteins.

Opioid receptors – function

Opioid receptor activation by endogenous and exogenous ligands results in a multitude of effects, which include analgesia, respiratory depression, euphoria, hormone release, inhibition of gastrointestinal transit, and effects on anxiety. In general, morphine remains the analgesics of choice for the treatment of chronic pain. However the major limitation to their long-term use is the development of physiological tolerance. In addition to tolerance, physiological dependence can ensue in certain patients.

Animal models of opioid receptor function

Tolerance to opioids is measured as a change in analgesic responses. The two most common behavioral assays in animals are the hot plate and the tail flick tests, where a heat source is applied to either the tail or hind paw of an animal. Dependence is measured in morphine-tolerant animals by either withdrawing the opioid agonist or administrating an opioid antagonist. The typical behaviors reflecting withdrawal/dependence symptoms in animals are elevated level locomotion, jumping, and weight loss. In addition, opioids induced addiction is hypothesized to result from modulation of neural brain circuits associated with stress and anxiety, positive reinforcement, as well as learning and memory. In animals, positive reinforcement is measured by a method that monitors an animal's ability to develop a preference for a certain environment when paired with a drug. Anxiety is induced by exposing animals to a stressful situation, namely a forced swim test.

KOR-deficient animals do not show increased basal nociceptive sensitivity to heat or mechanical pain. However, their sensitivity to peritoneal injections of acetic acid is elevated. Based on this finding, Gebhard et al thought KOR agonists may be good analgesics for visceral pain. In contrast to their wild-type littermates, KOR-deficient mice do not show conditioned place aversion or dysphoria to KOR-selective agonists. Moreover, after chronic morphine treatment, naloxone-precipitated withdrawal behavior is attenuated in these animals. Though KOR-deficient mice do not show any change in stress-induced analgesia after forced swim test, their stress-induced emotional responses seem to be moderated by KORs. Specifically, stress-induced analgesia and immobility are reduced in mice with a defective prodynorphin gene. This has also been observed in wild-type animals upon administration of the KOR antagonist.

Morphine and opioid receptor trafficking

Morphine-activated MORs are unique because they do not require G-protein coupled receptor kinase phosphorylation nor do they efficiently recruit beta-arrestin. In addition, morphine fails to promote endocytosis of the wild-type MOR in cultured cells and native neurons, whereas endogenous peptide ligands, such as endorphins, encephalin, and several other opioid drugs readily promote receptor endocytosis. As such morphine-activated MORs generally elude an important, highly conserved regulatory mechanism designed to rapidly modulate receptor-mediated signaling.

Tolerance

Though opioids like morphine are the analgesic of choice for many settings, their long-term use is often linked to the development of physiological tolerance. The development of opioid tolerance in humans varies depending on the route of administration and on the disease state for which the opioids are prescribed. Tolerance is usually not a concern for patients on short-term postoperative epidural or intrathecal opioids. Rather, tolerance often manifests after chronic exposure to epidural or intrathecal opioid use. On the other hand, patients with terminal malignancies experience an escalation in pain as their disease progresses, and this makes it difficult to distinguish between the development of opioid tolerance and an increase in opioids consumption for their pain. The development of tolerance involves multiple molecular and cellular mechanisms: receptor downregulation, receptor desensitization, and uncoupling from cAMP pathway.

Dependence and withdrawal

In addition to the side effects of tolerance, respiratory depression, constipation, long-term use of opioids also lead to physiological dependence in some patients, who rely on continued administration of escalating opioid doses to prevent withdrawal. The physiological drug-dependent state often emerges after the analgesic is stopped.

Tolerance and dependence are complex physiological phenomena, but they may share a common mechanism as the severity of withdrawal signs and the extent of the development of tolerance are correlated in vivo and in vitro. For example, cAMP uncoupling has been suggested to play an important role in the development of tolerance and dependence.

One region of the brain that has been studied extensively as a model for opioid dependence and withdrawal is the locus coeruleus (LC). Following the chronic administration of morphine, the LC neurons show tolerance to morphine as well as cellular correlates of dependence and withdrawal. Some of the cellular changes include increases in the levels of G-protein subunits and adenylyl cyclases. Interestingly, upregulation of the cAMP pathway has been consistently observed in the LC, nucleus accumbens, amygdala, doral raphe nucleus, and ventral tegmental area. These considerations suggest that the pathway may be a cellular hallmark of the development of not only tolerance, but also dependence.

Opioid receptors – pain pathway

Opioid receptors are abundantly expressed on nerves principally responsible for pain transmission and modulation in the brain, spinal cord, and the periphery. Opioid receptors are present on C-fibers of primary sensory afferent and they inhibit the release of pain transmitters by blocking the activation and sensitization of these fibers. Moreover, opioid receptors in dorsal root ganglia are transported to the peripheral sensory nerve endings during the inflammatory process, while endogenous opioid peptides accumulate within

immune cells in the inflamed tissue. Upon release, the opioid peptides interact with the neuronal opioid receptors to achieve local analgesia.

KORs are present on immune cells and they exert an immunemodulatory function that controls the release of the cytokines. Peripheral KORs produce anti-inflammatory responses and antinociception through multiple neuroimmune mechanisms. For instance, through the inhibition of tumor necrosis factor-alpha release, KOR agonists induce local analgesic effects in rheumatoid arthritis models.

KOR agonists are potent analgesics after systemic administration in visceral pain models. The antinociceptive effects of KOR agonists seem to be reproducible irrespective of species, targeted visceral organ, noxious stimuli, or measured endpoints. The consciousness and inflammatory state also do not seem to impact the antinociceptive effects. However, the analgesic potency of KOR agonists are enhanced as inflammation decreases pain threshold.

Friese et al found KOR agonists to block peritoneal irritation-induced pain and it often leads to a normalized intestinal transit. We think the ability of KOR agonists to reverse peritoneal irritation-induced ileus suggests increasing antinociceptive potency. Taken together, we believe k-agonists have significant promise in treating postoperative pain. In addition, KOR agonists have been shown to directly inhibit the visceral sensory input in the periphery by eliminating the firing of decentralized pelvic afferents triggered by colorectal distension.

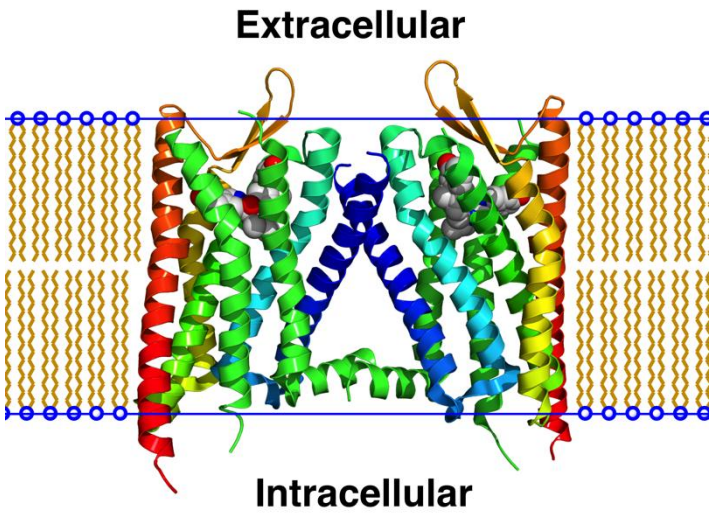
We think the analgesic activity of KOR agonists are mediated by KORs in the periphery and through several nonopioid mechanisms through sodium channels on peripheral nerve endings of primary sensory afferents. The analgesic effect of KOR agonists is enhanced when inflammation is ongoing. We think KOR agonists act on multiple neuroimmune sites and effect pain reduction.

Kappa opioid receptors agonists

KOR agonists, like MOR and DOR agonists, demonstrated potent analgesics in various experimental pain models with no euphoria, addiction, respiratory depression, or GI transit inhibition, which are common side effects seen in patients on MOR agonists. As such, the KOR agonists were considered to be a promising alternative for designing efficacious and safe analgesics. However, first generation KOR agonists turn out to penetrate the blood-brain barrier and induce side effects such as sedation and dysphoria. As a result, the development of KOR agonists was discontinued.

KORs are functionally different from MOR and DOR, and two heterogeneous binding sites (kappa-1 and kappa-2) exist in brain membrane penetration. KOR1 is the human clone of the kappa-1 receptor previously characterized and has virtually identical pharmacology to wide-type. KOR1 is a 7TM receptor coupled to G-proteins and negatively coupled to adenylate cyclase. We note that none of the other putative KOR subtypes has been successfully cloned and no ligand selective enough for these KORs is available. Therefore, it is difficult to assess the functionality of differentiated KOR subtypes. Most of the selective KOR agonists available are optimized at the kappa-1 binding site or KOR1. Therefore, these agents are highly sensitive to kappa-1 with potency between 0.1 to 10 nanomolar.

Figure 8: Crystallographic structure of human KOR1



Source: Wacker, 2012.

The role of KORs in dopamine release, stress signaling, and abuse

The endogenous kappa opioid receptor circuit is directly linked to physiological processes such as analgesia, pruritus, and diuresis. KORs are also involved in the modulation of dopaminergic signaling. Activated KORs lead to the downregulation of dopamine because of the distribution of KORS in the neostriatum. KORs are located on the presynaptic terminals of mesolimbic dopaminergic neurons synapsing in the nucleus and they assist in dynorphin hyperpolarization, which subsequently inhibit dopamine release. KORs are also associated with certain behavioral stress signals such as depression-like behavior and stress-induced analgesia.

KOR agonists generally lack reinforcing effects and they have been reported to reduce tolerance to morphine in a variety of antinociceptive studies. Since KOR agonists can modulate mesolimbic dopamine levels, they have been considered as potential treatments of drug abuse, such as cocaine. Cocaine blocks dopamine reuptake and increases extracellular dopamine. There is a considerable body of evidence that indicates cocaine's reinforcing effects are mediated by these increases in extracellular dopamine. Since KOR agonists have been shown to decrease dopamine levels, they may act as functional antagonists of cocaine. Studies by Mello et al have demonstrated that KOR agonists decrease cocaine self-administration and suppress the rewarding effects of cocaine in a variety of animal models.

Recent studies have, however, shown that repeated KOR agonist exposure can, counterintuitively, increase extracellular dopamine levels and enhance dopamine signaling, which leads to higher likelihood of cocaine-seeking behavior. In behavioral studies by McLaughlin et al, repeated infusion of a KOR-selective agonist led to a dose-dependent leftward shift in the cocaine choice dose-effect curve in monkeys self-administering cocaine. Although the mechanism through which this time-mediated paradoxical phenomenon works is unclear, chronic activation of KOR may play a role in the reinforcing efficacy of cocaine. And this is consistent with the effects of stress on drug-seeking

behavior. In any event, we still believe KOR agonists are well positioned to be the therapeutic of choice for acute pain, while their long term treatment effects are being investigated.

Mechanisms for opioid-induced nausea and vomiting

Opioid-induced nausea and vomiting are may be due to three major opioid effects: enhanced vestibular sensitivity, direct effects on the chemoreceptor trigger zone (CTZ), and delayed gastric emptying.

Opioids can directly stimulate the vestibular apparatus and increase vestibular sensitivity. The vestibular apparatus provides direct input into the vomiting center by way of histamine H1 and cholinergic (AchM) pathway. Endogenous opioids are involved in opioid-induced vomiting via stimulating MORs and DORs in the CTZ of the vomiting center. Due to its incomplete blood-brain barrier, the CTZ, which is in the floor of the fourth ventricle, is considered peripheral. Therefore, the neurons in the CTZ are exposed to the effects of various metabolites and ligands.

Opioid-induced nausea has been postulated to act predominantly through MOR. In a study by Seidner et al, opioid receptor antagonists such as naloxone have been demonstrated to effectively treat opioid-induced nausea. Even though naloxone is a broad spectrum antagonist at all three opioid receptors, it has the highest affinity to MOR.

Long-term, repeated opioid use may lead to chronic activation of MOR in the myenteric and submucosal plexi that often lead to uncoordinated bowel dysfunction. Opioids have been shown to reduce peristalsis by decreasing GI secretions and relaxing longitudinal muscle in the colon while simultaneously increasing circular muscles contractions. In the absence of this propulsion, stool may dry, leading to bowel distention and cramping. All of these phenomena are associated with nausea and vomiting.

MORs have been identified as the principal actor on most of the mechanisms related to opioid-induced nausea and vomiting, while the emetic effects of some opioids seem most likely to occur secondary to activation of the DOR. In clinical settings, multiple receptors may play a role in contributing to nausea and vomiting and it is still unclear, from their limited reference to AEs, how big a role KORs have in opioid-induced nausea and vomiting.

PAIN: A COMPLEX SENSORY EXPERIENCE

Pain is a complex sensory experience and is modulated significantly by the central nervous system. In fact, pain is the most common reason for medical appointments. Every year there are 40M pain-related visit to US hospitals and clinicians. The associated cost of care is estimated to be close the tune of $100M. There are two major classes of pain analgesics: opioids, such as codeine, fentanyl, and morphine, and non-opioid inhibitors of cyclooxygenase (COX), namely aspirin and ibuprofen. Both opioid and non-opioid analgesics are efficacious and widely used. Sales from these pain management products in the US exceeded $18B in 2012.

Opioid analgesics used in clinical settings like morphine act primarily through the MOR and have been considered the gold standard for the treatment of severe pain. However,

AEs associated with opioid receptor agonists like tolerance, respiratory depression, and constipation reduce their usefulness.

Physiology of pain

Acute pain and chronic pain are initiated by activation of a nociceptor, the sensory receptors in the periphery that respond to noxious stimuli that give rise to pain. Nociceptors are ubiquitous throughout the human body and they are the end organs that transduce noxious stimulus energy into electrical signals that are passed on to a second order neuron via axon in the spinal cord. Peripheral terminal of nociceptors are typically without a defining structure as nociceptors are often described as free nerve endings with no encapsulated end organ.

Pain is mediated by nociceptors that respond directly to some stimuli and other via the release of chemical signals from surrounding tissues such as histamine or acetylcholine. Based on the type of stimulus that evokes a response, nociceptors are classified into three distinct types: mechanical, thermal, and polymodal.

Mechanoreceptors respond to painful tactile stimuli and they are myelinated fast-conducting A-delta afferents that relay sharp pain sensations. Thermal receptors, on the other hand, can respond to noxious heat or a lack thereof. Thermal nociception is mediated by both vanillioid type 1 receptors and vanillioid receptor-like protein-1. Type 1 vanillioid receptors response to noxious heat that exceeds 45 centigrade and they are sensitive to capsaicin. Au contraire, vanillioid receptor-like protein-1 is insensitive to capsaicin and response to a heat threshold in excess of 52 centigrade. The majority of nociceptors are polymodal nociceptors, and they respond to a wide range of mechanical, thermal and chemical stimuli.

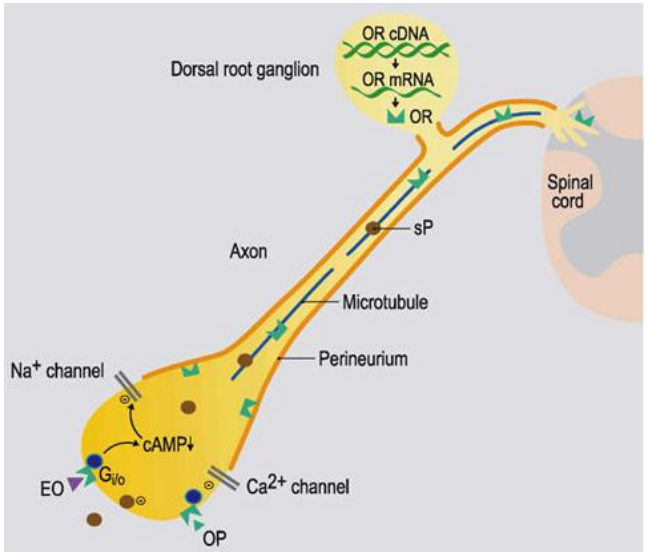
KORs are located both in the CNS and in the periphery. Centrally located KORs are involved in spinal-mediated thermal nociception, whereas peripherally located KORs are principally responsible for antinociceptive effects. In rodent visceral pain model, upregulation of endogenous KOR peptide dynorphin occurs following pain and mice lacking preprodynorphin experience increased tail flick and hot place responses while KOR deficient mice show elevated writhing response after peritoneal acetic acid injection.

Nociception pathways

Fast A-delta fibers and unmyelinated C fibers are involved in nociceptive transmission. Fast A-delta generates a sharp, well-defined pain sensation, while the unmyelinated C fibers relay slow burning sensation in damaged tissue and inflamed skin. It is important to note that all nociceptive afferents terminate in the dorsal horn of the spinal cord and the termination of various afferent fibers in distinct laminae shows rigid functional and anatomical control.

KORs are predominantly expressed on the cell linings of small nociceptive afferents in the dorsal root ganglion and spinal cord. In fact, high KOR expression is observed in the dorsal horn and substantia gelatinosa while lower expression is found in zona intermedia and ventral horn.

Figure 9: Opioid receptor transport and signaling in primary afferent neurons



Source: Nature, 2003

High levels of KORs are found in brain regions responsible for transmitting nociceptive signals such as the nucleus of the solitary tract and hypothalamic nuclei. KORs are also found in pain circuitries through the body. Anatomical distribution of KORs alongside MORs suggests close physiological interaction in nuclei-relaying nociceptive stimuli. The KOR positive neurons are located in the trigeminal and dorsal root ganglia, while peripheral KORs and peptides are found in nerve terminals of sensory neuron in the skin, muscles, and joints.

Preclinical behavioral models of pain

There is a plethora of established pre-clinical models for pain study and characteristic behaviors measured following external stimuli. Multiple behavioral models are necessary to evaluate and interpret the complexity of pain.

Thermal stimuli – This model of pain relies on ramped thermal stimuli to activate thermoreceptors. However the subject tends to quickly remove itself from the stimulus before nociceptor stimulation. The tail flick test is a common thermal model for pain and has been used to study the analgesic effects of opioids. However, KOR agonists tend to be less effective in thermal antinociceptive assays compared with other modes of stimuli.

Inflammatory model and hyperalgesia – This model is developed by injecting inflammatory agents into the paws of mice and involves longer stimuli duration. The animal model of inflammatory hyperalgesia closely resembles the clinical conditions for pain in human. There are two phases of this pain model. The inflammatory pain takes place after 0.5% to 1.5% of formalin is injected into the rodent paw, and the neuropathic pain sets in after the potency of the stimuli wears off with time. Pain effects are limited to the injected limbs in this model and the endpoints are often measured by paw withdrawal latency, flinching, or the duration of licking the affected paw. KOR agonists have shown to attenuate antinociceptive behaviors and decrease stimuli-induced edema by Obara et al. Injection of carrageenan, phorbol ester, or yeast elicit similar effects.

Neuropathic pain

Nerve ligation often results in thermal hyperalgesia, which is commonly measured by lower paw withdrawal latency in response to heat stimulus or focused light beam. In this model, cold and mechanical stimuli cause spontaneous pain and allodynia. KOR agonists produced a prolonged, reversible antinociceptive effect in a rodent model of peripheral mononeuropathy conducted by Keita el al. The pain was produced by moderate constriction of the sciatic nerve and the investigators measured vocalization thresholds to paw pressure as a nociceptive test.

It is widely accepted that the endogenous KORs are activated by nerve ligation as many studies found Prodynorphin derived opioids are released into the blood stream post-ligation to increase KOP receptor activation and produce antinociceptive effects.

Models for visceral pain

Distension and stretching of visceral muscle often trigger the activation of sensory innervations in the viscera. All visceral nociceptive fibers are relayed in both sympathetic and parasympathetic circuitries. As a result, pain signals transmitted through these C fibers have no spatial localization. Peripheral primary afferent neurons are principally responsible for nociception activation, transduction of sensory input. Recent studies by Gebhart et al suggest their expanded role in integrating nociceptive inputs and modulating peripheral sensitization.

Visceral nociceptor afferents are colocalized with sommatocutaneous afferents in the dorsal root ganglion and in the dorsal horn, and this is thought to contribute to somatic referred pain that often comes with visceral nociception. KOR agonists have been demonstrated to be antinociceptive in both cutaneous and mechanical visceral nociceptive models and their efficacy are directly proportional to KOR density in the periphery.

KOR agonists as analgesics

There has been significant interest in developing a new class of analgesics based on KOR agonists that would not have the AE profile of morphine and other MOR agonists. Even though many pan-opioid receptor analgesics used in clinical settings have KOR agonist activity, the use of KOR-specific agonists is hindered by dose-limiting neuropsychiatric effects such as sedation and dysphoria. These side effects are unique to KORs and are attributed to the activation of centrally located KORs behind the blood-brain barrier that blocks dopamine release. As a result, research efforts have been focused on identifying peripherally restricted KORs.

Asimadoline is an early drug candidate with purported peripheral KOR activity. It has high potency due to its arylacetamide structure and it has low permeability across the blood-brain barrier. Anatomically, it has a relatively low distribution in the CNS. Unfortunately, asimadoline was not able to show clinical benefits without triggering severe central side effects. However, asimadoline did show potent effects on visceral sensation and moderate improvement in patients with dyspepsia and irritable bowel syndrome.

ADL-10-0101, a novel analog based on ICI 199,441, was another KOR-specific ligand from the acylacetamide class that reported peripheral selectivity and showed reduction in pain scores in patients with chronic pancreatitis. The polar reef structure of '0101 was designed to decrease its lipophilic properties and the bulky compound was thought to prevent entry into the blood-brain barrier. However, in early Phase 2 trial, patients on '0101 suffered

from severe hallucination after 48 hours and this AE profile was clearly unsuitable for further development.

JNJ-38488502 is a tetrapeptide KOR agonist that is chemically distinct from the arylacetamide class and has no known interaction with other opioid receptors. A recent clinical study assessed the effect of '8502 on colonic distention showed no reduction in non-nociceptive sensations with '8502 compared to placebo.

FE 200665 and FE 200666 are two other tetrapeptides that have been pharmacologically characterized as peripherally restricted KOR-specific agonists and they have shown analgesic and anti-inflammatory properties in a study done by Vanderah et al. Additional studies revealed that the antinociceptive doses of FE 200665 and FE 200666 lack CNS KOR-mediated dysphoric effects, and their therapeutic window is 109-fold and 357-fold wider than asimadoline and endaoline, respectively.

Neoclerodane diterpenes are the latest chemotype of KOR ligands and is structurally related to Salvinorin A, which has been linked to increased antinociception in mice. However, the benefits of salvinorin A are short-lived. MOM-Sal B, a semi-synthetic derivative of salvinorin A, was found to produce antinociception in vivo that lasts longer than salvinorin A.

Figure 10: Summary of KOR agonists and antagonists in different animal models of pain

Pain Model	KOPr agonist/ antagonist	Findings	Reference
Models of visceral pain	Agonist		
Colorectal distension	C1977 U69,593 U50, 488H EMD61,7F3	Antinociceptive. dose-dependent attenuation of pressor and visceromotor responses. Order of potency as listed.	Burton and Gebhart 1998
Colonic inflammation induced by trinitrobenzene sulfonic acid	ICI204,488 EMD61,753 ICI204,488	Antinociceptive. dose-dependent inhibition of pelvic nerve afferent fibers with significantly greater potency in the inflamed colon.	Su et al. 1997; Sengupta et al. 1999
Thermal stimuli			
Heat-induced nociception	Ethlyketazocine Pentazocine	Inactive at doses producing sedation effects Inactive tail immersion, antinociceptive hot plate, also produced motor incoordination	Tyers 1980
Hot plate and tail immersion 50°C and 55°C	Nalorphine Mr2034	Inactive Inactive; tail immersion, antinociceptive in hot plate tests.	
	Mr1353	Antinociceptive in hot plate and tail immersion.	
Inflammatory models of pain and hyperalgesia	agonist		
Writhing and paw pressure tests. Acetic acid	SK-9709	Antinociceptive	Hiramatsu et al. 2001
Formalin test and writhing test	EMD60400	Antinociceptive in non-inflammatory and inflammatory pain	Barber et al. 1994
	ICI 197067	Antinociceptive in non-inflammatory and inflammatory pain	Machelska et al. 1999
Formalin	ICI 204448	Antinociceptive in non-inflammatory and inflammatory pain	
Complete Freund's adjuvant (CFA)	U50,488H	Antinociceptive	
	Dynorphin	Antinociceptive	Obara et al. 2009
	CI-977	Antinociceptive, decreased flinching response	Zhou et al. 1998
Mycobacterium butyricum (ankle joint)	U50,488H	Anti-inflammatory, antinociceptive	Bileviciute-Ljungar et al. 2006;
	Antagonist		
Formalin test	Dynorphin anti-sera nor-binaltorphimine (nor-BNI)	Increased flinching Increased flinching	Ossipov et al. 1996 Ossipov et al. 1996
CFA	Nor-BNI	Inflamed paw had increased response to mechanical and thermal sensitivity. Mechanical sensitivity in non-inflamed paw	Schepers et al. 2008
Neuropathic pain	Agonist		
Chronic nerve constriction of sciatic nerve	Asimadoline	Antinociceptive	Walker et al. 1999
	EMD60400	Antinociceptive	
	ICI 197067	Antinociceptive	
	ICI 204448	Antinociceptive	Keïta et al. 1995;
	U69593	Antinociceptive	Andreev et al. 1994
	Dynorphin	Pronociceptive and antinociceptive	Xu et al. 2004
	ICI 199441	Antinociceptive	Obara et al. 2009
Sham spinal surgery	U50,488H	Increased hypersensitivity	Herrero and Headley 1991
Spinalization	U50,488H	Antinociceptive	
	antagonist		
Spinal nerve ligation (SNL)	Dynorphin anti-sera	Reversed neuropathic pain following day 10 of SNL	Wang et al. 2001

Source: Prisinzano, 2010

KOR agonists have demonstrated antinociceptive activity in a number of pain models and their effects occur both centrally and peripherally. The pharmacological profile of KOR agonists in visceral pain models suggests that peripherally acting KOR agonists have tremendous clinical benefits for a variety of peripheral pain states. Further clinical investigation of peripherally restricted KOR agonists will no doubt elucidate the conditions in which KOR agonists will be most useful.

Pain management - the market opportunity

Pain is categorized as either acute or chronic, and is graded by severity as mild, moderate or severe. Acute pain is usually caused by an injury resulting in nerve, tissue or bone damage. It is expected to decrease in severity with tissue healing. Postoperative pain is an acute injury that constitutes a specific part of acute pain market. Chronic pain last significantly longer (from weeks to years), and can result from either an acute injury or an ongoing disease, such as diabetes and related diabetic neuropathic pain.

A 2011 Institute of Medicine report estimates ~100 million U.S. adults have chronic pain. Millions of others at any given time have acute pain from events like surgery, childbirth, injury and acute/episodic illness. Decision Resources estimated the total pain therapies sales in the seven major pharmaceutical markets (US, France, Germany, Italy, Spain, UK and Japan) were north of $37 billion in 2011.

Pain severity is critical determining the appropriate therapy for pain relief. Mild or mild-to-moderate pain can be treated with OTC products, like oral aspirin, acetaminophen and ibuprofen. Moderate-to-severe pain is usually treated with traditional mu opioids analgesics. Mu opioids are considered quite effective, but they have a poor side effect/ abuse profile, which greatly limits their use. However, opioid analgesics may be the only effective method of treating moderate to severe pain. As a consequence, opioids are among the largest US prescription drug classes. Opioid analgesics represented 71% of the 341 million prescriptions written in 2012 with over $8.3 billion in sales.

Postoperative pain market

Postoperative pain is a substantial part of the overall acute pain market. Over 46M inpatient and 53M outpatient surgeries are performed every year in the US. In the in-patient setting, moderate-to-severe pain is treated with injectable analgesics. The US IV analgesics market consists primarily of mu opioid agonists. These include fentanyl, morphine hydromorphone and non-opioid analgesics like Toradol or IV ketorolac generics, Caldolor (IV ibuprofen), and Ofirmev (IV acetaminophen). The postoperative pain market reached $5.9 billionin 2010, roughly one-fifth of the total pain therapeutics market).

The standard of care for treating acute postoperative pain is multimodal analgesia. Multimodal treatment paradigm is based on the administration of two or more drugs that act through different mechanisms for providing analgesia in a way that minimizes AEs. When patients are ready to be discharged, a transition is made to a prescription oral pain medication thereby allowing patients to administer relatively strong analgesics on their own. The transition from a potent IV painkiller to an oral analgesic is often described as IV-to-oral “step-down” therapy.

Strong mu opioid analgesics are the mainstay pain treatment during the immediate postoperative period. However, they come with a wide array of serious side effects, including postoperative opioid-induced respiratory depression, postoperative opioid related nausea and vomiting, and opioid-induced bowel dysfunction, which contributes to the severity of postoperative ileus. Opioid-induced respiratory depression can occur unexpectedly in 3 out of 10 patients and this has a clear negative impact on the length of stay and total treatment costs. On the other hand, post-op opioid related nausea and vomiting occurs in one-third of all surgical patients, and it is one of the most important factors in determining length of stay after surgery. The resulting annual cost to the US

healthcare system has been projected to be around $1 billion. It is evident that mu opioid-related AEs not only drastically increase the cost of care, but lead to sub-optimal recovery.

Nonopioid analgesics formulated for injection or infusion, such as IV acetaminophen and NSAIDs, namely IV ibuprofen, are viable alternatives to mu opioids in helping patients relieve acute pain. However, their use is limited in a postoperative care setting due to their moderate efficacy. Like opioids, IV acetaminophen and NSAIDs have dose-dependent AEs that limit their use at higher doses. Acetaminophen has liver toxicity that can be fatal, and NSAIDs are associated with bleeding risks, serious GI AEs, kidney damage, and serious CV thrombotic events such as stroke and heart attack.

POST-OP PAIN DRUGS: A CLEAR UNMET NEED

Even with the large size of the pain market, there has been little to no recent innovation in new analgesics. Almost all recent new approvals are reformulations of existing drugs with alternate delivery methods. Mu opioids are still the most prescribed drugs for pain management despite inherent safety drawbacks. Clinicians are acutely aware of the drawbacks of mu opioid agonist and trend to prescribe suboptimal doses that result in suboptimal pain relief. As a result, we think there remains large unmet need in post-operative pain management for patients with moderate to severe pain. Clinicians we have spoken to would like better options to balance pain management with risks of causing severe AEs. Healthcare organizations and hospitals bear the costs and consequences of undertreated pain and AEs.

According to the Centers for Disease Control and Prevention, 46 million inpatient surgical procedures were performed in 2010 and almost all patients experience postoperative acute pain of varying intensity and duration that depend on the type, length, and tissue damaged in surgery. Unsurprisingly, pain is the most severe in the first days immediately following the operation. Many epidemiological studies estimate that ~50% of patients self-report inadequate pain relief with current treatments. Currently postoperative pain management is based on a multimodal approach:

Continuous wound infiltration – Prior to suturing up the incision site, a local anesthetic, usually sodium channel blockers such as ropivacaine, bupivacaine, or other ‘caines, is injected directly into and around the incision site. This treatment option provides immediate, robust postoperative base for pain relief while allowing additional pain treatments to be layered on top as needed. Importantly, this is a non-systemic method of action and limits potential side effects while allowing combinatorial therapeutic approach. ‘Caines, in particular bupivacaine, are universally used by surgeons and anesthesiologists because of their familiarity and a robust, decade-long safety and tolerability database. However, these sodium channel blockers have short half-life and short duration of analgesia, which is the greatest limitation of this approach. Case in point: bupivacaine, the longest acting ‘caines, only lasts up to 3.5 hours in adults. It is not feasible to repeat injection into the wound site for a recovering patient after surgery. Therefore, the majority of patients are put on additional systemic treatment of longer duration pain management agents such as opioids and non-steroidal anti-inflammatories (NSAIDs). Approximately 23M continuous wound infiltrations are performed in the US every year.

Figure 11: Agents used in continuous wound infiltration procedures

Local anesthetic	Usage (number of procedures)
Ropivacaine	0.6M
Bupivacaine	7M
Lidocaine	15M

Drug	Half-life (hours)	Usage
Bupivacaine	3.5	Infiltration, nerve block, and epidural administration
Prilocaine	2.5	IV local anesthesia; combined with lidocaine for dermal
Ropivacaine	2	Infiltration, nerve block, epidural, intrathecal administration
Lidocaine	1.5 – 2	Minor surgery, dental procedures; topical outpatient use

Source: CDC reports and Canaccord Genuity research

We note the conventional immediate-release formulation of bupivacaine was approved by the FDA many years ago under the name Marcaine. The drug has since then been genericized and is commercially available through a number of manufacturers in the U.S: Hospira (NYSE:HSP) distributes both the branded and generic versions and APP Pharma (now a subsidiary of Fresenius SE) distributes the branded generic Sensorcaine.

Opioids – Commonly used opioids for postoperative pain include morphine, hydromorphone, oxycodone, and fentanyl and they are considered the standard of care for acute pain management. 300M IV units of opioids are consumed in the US every year, and over 650M IV units are consumed annually worldwide. The potency and multiple modes of administration for opioids make them a popular choice among hospitalists as they offer consistent efficacy.

We note that since morphine is cleared through the kidneys, potential accumulation of the drug poses additional toxicity risks for renal impaired patients. For instance, the morphine metabolite morphine-6-glucuronide (M6G) is a stronger analgesic than morphine itself and it crosses the blood-brain-barrier much more slowly. As such, it is possible that in patients with impaired renal functions, CNS effects such as sedation and dizziness will not only be more severe than in patients with normal renal functions, but can also be persist after morphine dosing has been completed.

As discussed in previous sections, excessive sedation, constipation, nausea, vomiting, and respiratory depression, are all common AEs associated with opioid use. Further, for certain patients subgroups such as the elderly, obsess, renal, or liver impaired patients, use of opioid would be ill-advised. The opioid related AEs (ORAEs) have clear negative implications for patient recovery, complication risk, concomitant medications, length of stay in high acuity hospital beds, and the overall cost of care. Therefore, opioid sparing is practically a universal objective.

Non-steroidal anti-inflammatories (NSAIDs) – These agents are less potent opioid alternative, but they are not with complications. NSAIDs inhibit cyclooxygenase-1 and 2 and play a key role in inflammation through COX's involvement in the formation of prostaglandins. Ketorolac, diclofenac, ofirmev, and ibuprofen inhibit both COX-1 and 2 and they do not have the same risk of constipation or respiratory depression. However, besides being less potent analgesics, NSAIDs cause diarrhea, ulceration, and renal dysfunction.

NSAIDs are useful in postoperative pain management as they are antipyretic activity, but they can cause fluid retention in renal impaired patients and exacerbate hypertension.

Ketorolac is the most commonly used NSAIDs in the post-operative setting and it can be administered via IV, which means it can be used in wound infiltration and in patients who are unable to hold down oral solids. This class of drug is considered to be safer than opioids, and has played a role in reducing opioid consumptions.

Figure 12: Drug classes used for postoperative pain management

	Sodium channel blockers	Opioids	NSAIDs	Acetaminophen
Description	Binds to and blocks sodium channels on nerve cells to prevent depolarization	Binds to opioid receptors that mediate pain; most used in acute post-op pain	Reduces inflammation by inhibiting pro-inflammatory COX	Universal antipyretic and centrally acting analgesic
Common names	Bupivacaine Lidocaine Ropivacaine	Fentanyl Morphine Oxycodone	Ketorolac Ibuprofen Aspirin	Ofirmev Mapap Panadol
Usage	Administered directly to the wound; nerve block and epidural	Administered through IV PCA; management of break through pain	Often combined with opioids; maintain baseline control	In combination with NASIDs and opioids; maintain baseline control
Advantages	Limited systemic exposure	Most efficacious agent for post-op pain	No risk of respiratory depression	Orally administered; antipyretic
Shortcomings	<3.5hrs of efficacy	Numerous SAEs	GI/bleeding risk	Least potent

Source: CDC reports, company filings, and Canaccord Genuity research

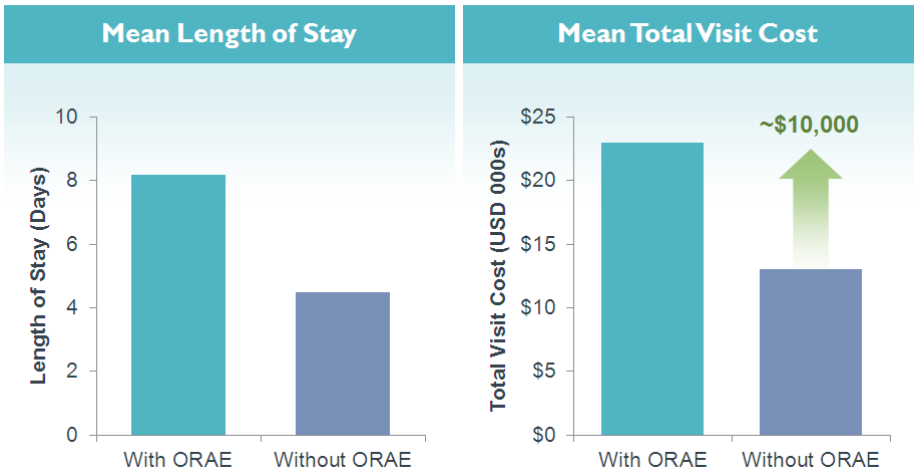
Current long-acting approaches

Oral administration of opioids such as Vicodin or Xolox in the immediate postoperative setting is limited by their slower onset of action and less efficacy than IV administration. The most common postoperative IV opioid administration modality is patient-controlled analgesia (PCA) pumps.

More than 15M PCA pumps are used in the U.S every year. Despite its popularity, current PCA pumps still leave plenty of room for improvement. Regardless of the route of administration, the active analgesic is still an opioid (morphine) with all the same risks, complications, and costs. In addition, all patients are tethered to an IV post, which delays ambulation and recovery. Any opioids related AEs will slow down the discharge process further and increase hospital related costs. Even though PCA is by definition 'controlled by patients,' these devices require considerable amount of time from hospital staffs to setup and monitor: nurses need to program the devices, set up IV access, educate patients, and frequently monitor the pump usage. Despite laborious efforts from staffs, mis-programming of devices and interruptions of usage due to technical issues are still common.

Cost for 3-days therapy on opioid IV PCA can easily exceed $500, excluding any impact of potential opioid-related adverse events. CDC report in 2006 found 48% of morphine PCA patients reported opioid-related AE's (and 8% had respiratory depression). In a recent study by Gan et al, ORAEs are found to increase the length of stay in hospital by 2.7 days, and they resulted in $10,000 higher total hospital cost per patient per visit.

Figure 13: ORAEs significantly increase length of hospital stay and costs



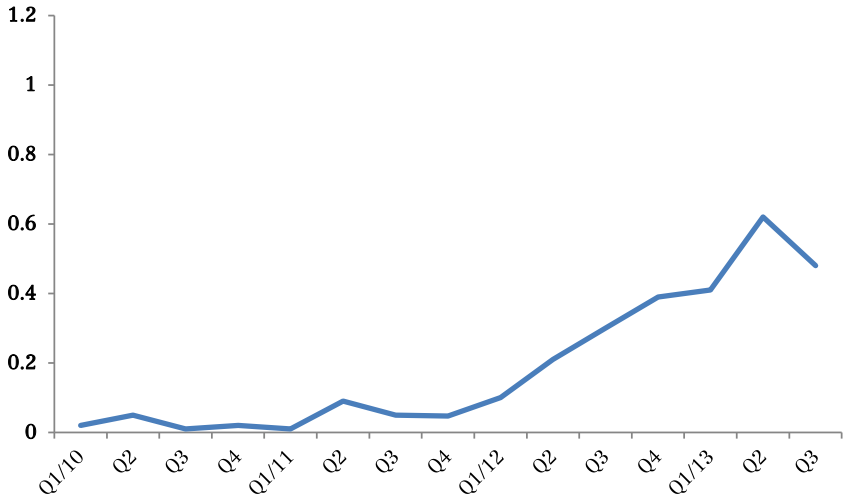
Source: Gan, 2012

Recent commercial launches in postoperative pain

Caldolor - an IV formulation of ibuprofen designed primarily for use in the hospital setting was launched in September 2009. Caldolor is approved as an injectable product in the US for postoperative pain management. Caldolor have been shown in multiple clinical trials to be safe and effective in reducing both pain and fever in 1,400 hospitalized patients.

Phase 3 trial data showed patients given 400 or 800mg of Caldolor every 6 hours reported lower post-surgical pain intensity in the first 24 hours (SPID 24) while also reducing morphine use. Clinical trials including critically ill and non-critically ill patients with fever showed temperature reduction in active versus placebo. No serious adverse events were deemed drug related.

Figure 14: Caldolor sales ($M)

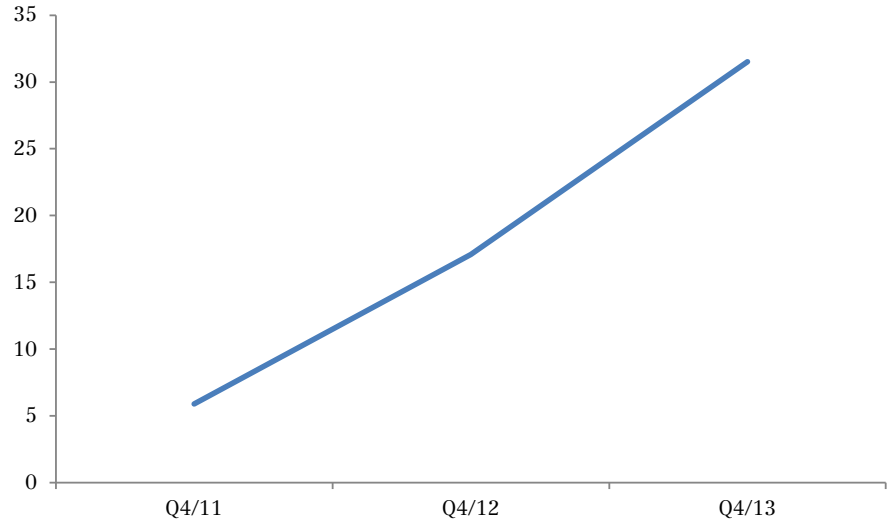


Source: Bloomberg and Canaccord Genuity research

Ofirmev - an IV formulation of acetaminophen targeted at patients suffering from acute postoperative pain. Cadence Pharmaceuticals' Ofirmev was launched in January 2011.

In a Phase 3 101 patient study in hip or knee replacement surgery, 1000 mg of Ofirmev every six hours was statistically superior to placebo for reduction of pain intensity over 24 hours (SPID24, $p<0.01$) with significantly less morphine consumption (33% over 24 hours, $p<0.01$). In a second 244 patients study in abdominal laparoscopy, Ofirmev 1000 mg every six hours, or 650 mg every four hours, showed a significant reduction in SPID24 versus placebo ($p<0.02$). In an adult volunteer study with induced fever, a single dose of Ofirmev 1000 mg showed a statistically significant reduction in temperature through six hours in versus placebo ($p<0.01$), with an 15 minute onset of pain relief. Ofirmev was well tolerated across multiple safety trials assessing a range patient and surgery types.

Figure 15: Ofirmev sales ($M)

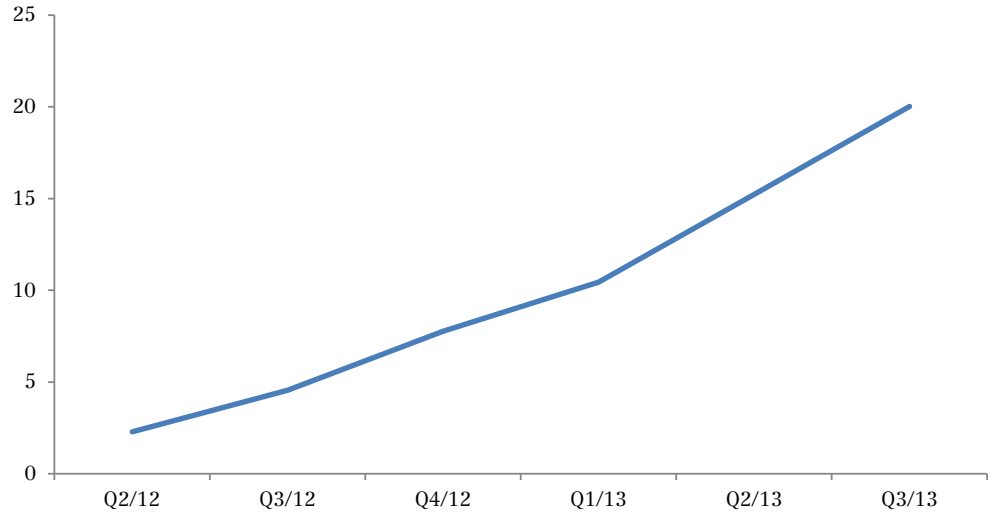


Source: Bloomberg and Canaccord Genuity research

Exparel - a multivesicular liposomal encapsulated, timed-release bupivacaine for pain management in in the postoperative setting that launched in April 2012. A single intraoperative injection given at the close of surgery delivers postsurgical pain control with reduced opioid requirements for up to 72 hours, making it a potentially suitable choice for patients who need effective pain management in the first few days after surgery, when pain is most severe.

The safety of Exparel has been evaluated in over 1300 subjects across 21 clinical trials. Locally administered Exparel, from 66 mg to 532 mg, at the surgical incision site was evaluated in 10 randomized, double-blind clinical studies with 823 patients undergoing various surgical procedures. In its Phase 4 study, Exparel showed a 64mg mean reduction in opioid consumption (P<0.0001). In addition, the patients on Exparel reduced their hospital stay by 24 hours (p=0.0019) that resulted in a $1,782 reduction in healthcare cost. Most importantly, only 8% of the patients in the treatment group experience ORAEs, versus 41% in the IV opioid-based PCA group (p=0.0019).

Figure 16: Exparel sales ($M)



Source: Bloomberg and Canaccord Genuity research

CR845 IN ACUTE POSTOPERATIVE PAIN

CARA is developing the peripherally acting kappa opioid receptor agonist CR845 in IV formulation for moderate-to-severe acute pain in the postoperative setting. CARA intends to bring about a novel class of potent pain management agents that target the body's peripheral nervous system without triggering the common AEs associated with currently available pain therapeutics. CARA's Phase 3 ready CR845 showed significant pain relief and a favorable safety and tolerability profile in three Phase 2 clinical trials in patients with acute postoperative pain. We expect CARA to initiate Phase 3 registrational trials in H2/14. We also think CARA will be able to advance the oral version of CR845, or oral CR845, which recently completed a Phase 1 trial that successfully demonstrated the feasibility to deliver CR845 orally.

Prescription pain management is an $8.3B market in the US

According to IMS Health, revenues of pain management drugs in the US exceeded $18.2 billion in 2012. Opioid analgesics represented 71% of the 341 million prescriptions written in 2012 and accounted for more than $8.3 billion in sales. Opioid analgesics decrease the sensation of pain by stimulating mu, delta and/or kappa opioid receptors. All of these receptors are involved in the modulation of pain signals. The most widely used opioid analgesics such as morphine, fentanyl and hydromorphone, act primarily through the activation of mu opioid receptors in the CNS. However, because of the wide expression of mu opioid receptors throughout the brain, morphine and other mu opioid agonists also trigger a characteristic pattern of adverse "central" side effects that include nausea, vomiting, pruritus, and respiratory depression. Mu opioids have also been demonstrated to induce euphoria, which may lead to misuse, abuse and potential addictions.

CR845: a potent analgesic without any of the past baggage

CR845 is designed to achieve pain relief by preferentially stimulating kappa, rather than mu, opioid receptors. Moreover, CR845 was constructed with specific chemical characteristics that restrict its entry into the CNS that and limit CR845's mechanism of action to kappa opioid receptors in the peripheral nervous system. Activation of kappa receptors in the CNS is also known to result in severe side effects such as acute psychiatric disorders, which led to the ultimate failure of ADL 10-0101. Since CR845 is designed to modulate pain signals without activating receptor of any kind in the CNS, it is not expected to produce any hallucination or euphoria. Based on the clinical trials and preclinical studies CARA has completed to date, we believe CR845, if approved, will be an attractive treatment option for both patients and physicians for managing moderate-to-severe acute pain.

Strong scientific rationale for IV CR845 in postoperative setting

CARA's lead product candidate is an IV formulated CR845 for the treatment of acute pain in a hospital setting. IV CR845 has been well tolerated and demonstrated consistent efficacy in three randomized, double-blind, placebo-controlled Phase 2 clinical trials. Two of these trials were in patients undergoing a laparoscopic hysterectomy, a soft tissue pain model, and a third trial was in patients undergoing a bunionectomy, a hard tissue surgical procedure.

Administration of IV CR845 resulted in statistically significant reductions in pain intensity, as measured by the sum of pain intensity difference, or SPID, an endpoint recommended by the FDA. In addition, IV CR845 exhibited an ability to decrease the opioid-related adverse events (ORAEs) such as nausea, vomiting, or respiratory depression in both surgical models. According to research conducted by Gan et al at Duke University, postoperative AEs associated with currently approved opioids increase the length stay in the hospital and increases the total cost of caring for those patients. Therefore, we think IV CR845, if supported by clinical data generated in subsequent Phase 3 trials, has compelling clinical and pharmacoeconomic benefit.

CR845 has a strong safety track record

CR845 has a clean safety profile that is documented in four Phase 1 and three Phase 2 studies. CR845 has been administered to over 300 human subjects at single or repeat doses ranging from 0.002 mg/kg to 0.125 mg/kg over a 24 hour period as IV infusion, IV bolus injection, or oral capsule.

The most common treatment-emergent AEs across evaluated populations were transient facial tingling, dizziness, and fatigue. In addition, aquaresis, the transient increase in urine output in the absence of electrolyte loss, was also observed, and it was accompanied by asymptomatic, clinically benign elevations in plasma sodium in some subjects. No clinically significant change in EKG characteristics was observed in any of the participants. Importantly, there was no reported incidence of the characteristic CNS-related AEs, such as acute psychiatric side effects, typically seen in prior-generation CNS-active kappa agonists.

Compelling clinical data for CR845

IV CR845 has shown robust efficacy and tolerability in three randomized, double-blind, placebo-controlled Phase 2 clinical trials in patients undergoing laparoscopic hysterectomy

(soft tissue) and bunionectomy (hard tissue) surgery. In the laparoscopic hysterectomy and bunionectomy clinical trials, administration of CR845 led to statistically significant reductions in pain intensity, measured by summed pain intensity differences (SPID).

Phase 2b Laparoscopic Hysterectomy (CLIN2002)

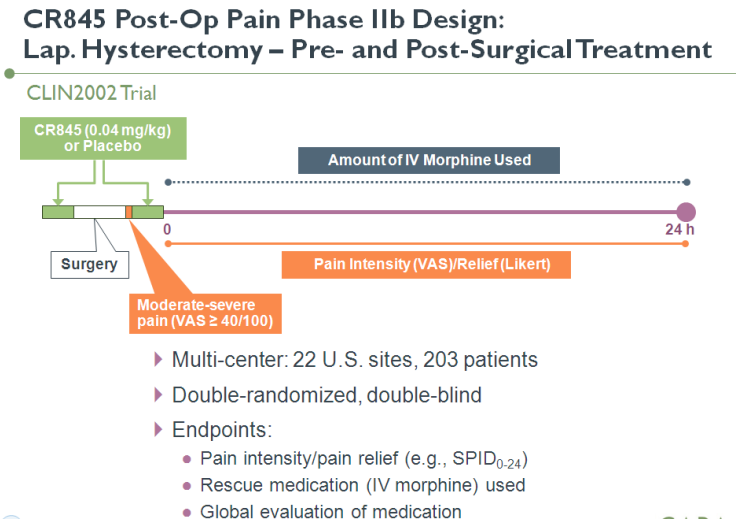
The Phase 2b trial of CR845 in laparoscopic hysterectomy was conducted in 203 patients across 22 sites in the US. The trial enrolled female patients between the age of 21 and 65 undergoing elective laparoscopic hysterectomy. Patients were administered either placebo or one dose of 0.04 mg/kg IV CR845 preoperatively. Following surgery, if they were stable and had a pain intensity score $\geq$ 40 on a 100 point pain scale based on the visual analog scale (VAS) they were then re-randomized to receive either placebo or another dose of 0.04 mg/kg IV CR845. Efficacy was measured using 24 hour pain intensity differences (SPID24).

More than 600,000 hysterectomies are performed in the US each year, making it one of the most common surgical procedures. Hysterectomies typically result in intense pain requiring significant postoperative analgesic care, typically beginning with local anesthetic infusion and ongoing administration of opioids for several days. As such, laparoscopic hysterectomy is a suitable model for soft tissue pain. We think the data generated from this representative model will be informative and well-regarded by the FDA.

Summed pain intensity difference (SPID)

Pain intensity (PI) is measured at various times by asking patients to rate their pain on a 100-point pain scale. Pain intensity difference (PID) is the difference between the PI measured prior to treatment and at subsequent times of measurement. Summed pain intensity difference (SPID) is the time-weighted sum of all of the PID scores, from the pretreatment level to a subsequent time of measurement. Both PID and SPID are meaningful endpoints recognized by the FDA for acute pain clinical trials. Other endpoints in CLIN2002 included the amount of morphine consumption over 24 hours, time-specific total pain relief and global evaluation of study medication. 183 out of 203 patients in CLIN2002 received a postoperative dose. We note that two subjects did not record baseline pain scores and were not included in calculated PID and SPID values.

Figure 17: Ph2b laparoscopic hysterectomy trial design



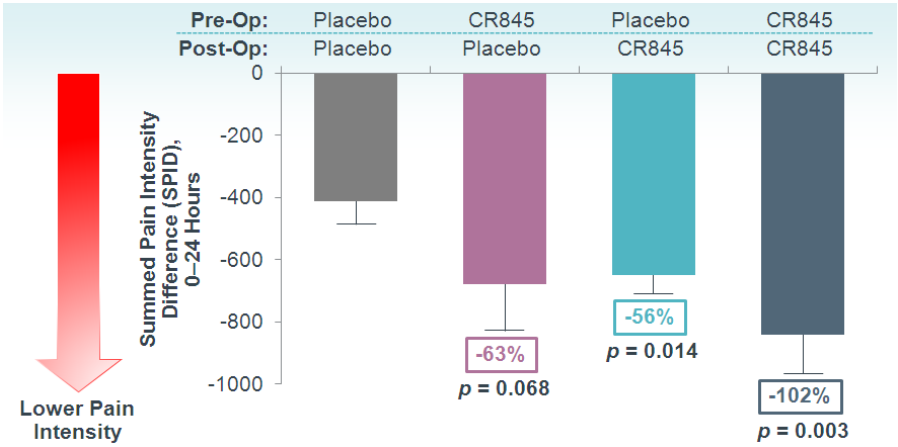
	Study to evaluate analgesic effect of IV administration of kappa agonist CR845 for hysterectomy surgery
NCT ID	NCT01361568
Design	Randomized, placebo controlled, double blind
Enrollment	203
Dosing	CR845 0.04 mg/kg single intravenous dose administered postoperatively for pain
Key inclusion criteria	• Female, 21 to 65 years of age • Scheduled for elective laproscopic hysterectomy under general anesthesia • Negative result on serum pregnancy test at screening and negative urine pregnancy test at baseline • Negative urine drug screen for drugs of abuse at screening at baseline • American Society of Anesthesiologists risk class 1 to 3 • BMI between 17 and 40
Key exclusion criteria	• Has known allergies to opioids, or hypersensitivity to other materials (such as infusion line) or medications to be used in the study; • Has a known or suspected history of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)-diagnosed alcohol, opiate or other drug abuse or dependence within 12 months prior to screening; • Is unable to refrain from alcohol consumption for the Treatment Period; • Is scheduled to undergo a hysterectomy that will utilize any type of robotic technology and/or a concomitant surgical procedure that would produce a significantly greater degree of surgical trauma than the laparoscopic hysterectomy or laparoscopic assisted vaginal hysterectomy alone; • Has taken non-opioid analgesics (NSAIDs within 12 hours of the Baseline assessments; • Has taken any opioid analgesics or used systemic steroids within 4 days of surgery OR has previously used opiates chronically for a period of ≥3 months; • Has used antipsychotics, antiepileptics, sedatives, hypnotics, or antianxiety agents, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants for < 30 days prior to surgery or had a dose change within the previous 30 days; • Has taken any prescription or over-the-counter medication within 3 days prior to surgery that, in the opinion of the Investigator, is expected to confound the analgesic response; • Has taken herbal agents or nutraceuticals (i.e., chaparral, comfrey, germander, gin bu huan, kava, pennyroyal, skullcap, St. John's wort, or valerian) 7 days prior to surgery; • In the opinion of Investigator shows clinical signs of hypovolemia; • Has an oxygen saturation < 92% on room air at Screening or prior to receiving the first infusion of study drug; • Has any history of clinically significant cardiovascular disease, • Has a clinically significant abnormal electrocardiogram (ECG) or a history of additional risk factors for torsades de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome); • Has a history of any serious medical conditions • Has serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or gamma glutamyl transferase (GGT) >2.5 x the upper limit of normal (ULN) at screening; • Has bilirubin, blood urea nitrogen (BUN), or creatinine >1.5 x the reference ULN at Screening; • Has abnormally low hemoglobin < 10 mg/dl at Screening; • Has serum sodium levels > 146 mmol/L at Screening; • Has impaired renal function (creatinine clearance [CrCl] < 50 ml/min) at Screening; • Has a positive test for human immunodeficiency virus (HIV) or known history of HIV infection; • Has received another investigational drug within 30 days of scheduled surgery; • Has a significant chronic pain condition in areas unrelated to the operative site at the time of Screening that in the Investigator's opinion could confound the interpretation of study results
Primary endpoint	Total morphine consumption in the first 24 hours in patients who are re-randomized in the postoperative period
Secondary endpoint	Efficacy of CR845 compared to placebo in reducing pain following laparoscopic hysterectomy / effect of CR845 compared to placebo on the use of rescue opioid analgesics during the postoperative period / proportion of patients requiring rescue morphine within the first 4 hours following completion of the surgical procedure
Powering	Over 90% powered to show a difference with p<0.05

Source: Company presentation

Four treatment groups results from the pre/postoperative randomization: CR845/CR845, PBO/CR845, CR845/PBO, PBO/PBO.

The CR845/CR845 group exhibited a statistically significant reduction in SPID over a 24-hour time period, compared to the Placebo/Placebo group ($p \leq 0.01$). The Placebo/CR845 group also showed a statistically significant improvement in SPID24 compared to the Placebo/Placebo group ($p \leq 0.05$). The CR845/Placebo group had an improved SPID24 score compared to the Placebo/Placebo group, but this difference was not statistically significant ($p = 0.014$). Due to the small number of patients in the trial, we don't think the narrowly missed p-value compromises the overall strength of the data set.

Figure 18: Ph2b trial in lap. hysterectomy - SPID24 following postoperative treatment

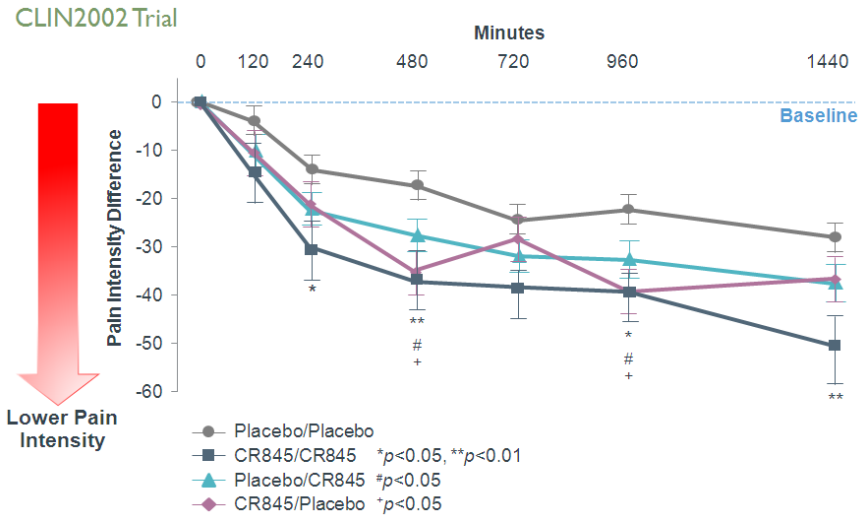


Source: Company filings

The CR845/CR845 group showed a statistically significant 3.5-fold improvement in mean SPID values compared to the Placebo/Placebo group after 4 hours ($p \leq 0.05$). In addition, over the 0-8, 0-12 and 0-16 time periods, patients in the Placebo/CR845 group also demonstrated meaningful reduction in pain intensity compared to the Placebo/Placebo group ($p \leq 0.05$).

The mean PID from baseline at each time interval was numerically superior across all groups that received one or both doses of IV CR845 relative to the Placebo/Placebo group. Patients in the CR845/CR845 group showed a 60% reduction in pain intensity at 24 hours ($p \leq 0.01$) and statistically significant improvements at 4, 8 and 16 hour intervals ($p \leq 0.05$, $p \leq 0.01$ and $p \leq 0.05$, respectively). Patients received one dose of CR845 also showed statistically significant decreases in pain intensity at the 8 and 16 hour interval ($p \leq 0.05$).

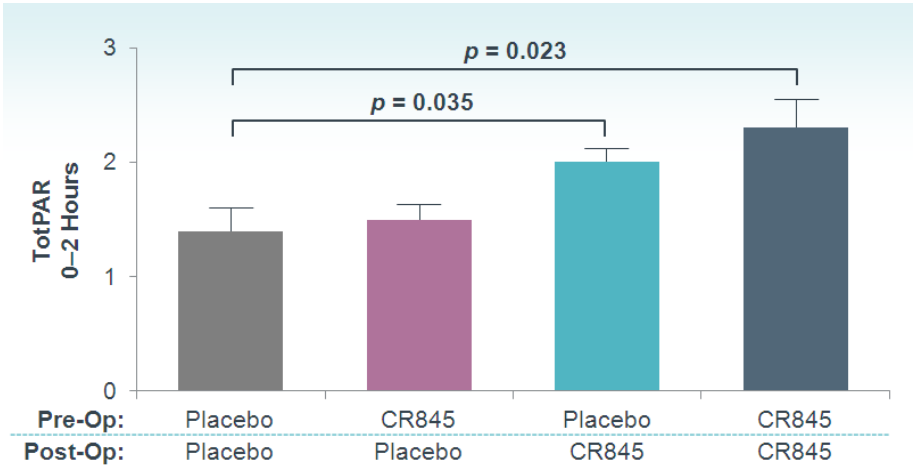
Figure 19: Ph2b trial in lap. hysterectomy - pain intensity difference across treatment groups



Source: Company filings

At the same time intervals at which PI measurements were recorded, the perceived pain relief scores from patients were also recorded using a 5 point subjective Likert scale (0-4). The "TotPAR" score is short for the "total pain relief score," and it is an endpoint commonly used in acute pain trials recognized by the FDA. Mean TotPAR scores were higher across all intervals for groups that received at least one dose of CR845 than the Placebo/Placebo group. The patients in the CR845/CR845 group and Placebo/CR845 showed statistically significant pain relief compared to the Placebo/Placebo group within the first 2 hours following postoperative randomization ($p \leq 0.05$).

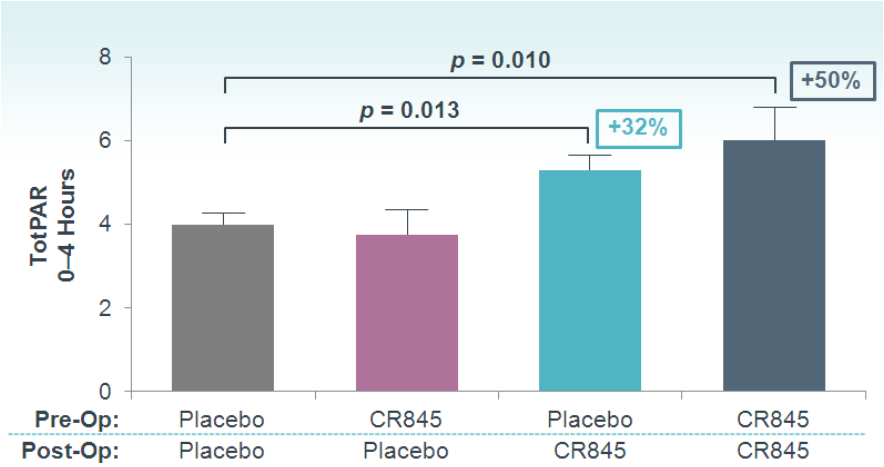
Figure 20: Ph2b trial in lap. hysterectomy - CR845 showed significant total pain relief (2 hrs)



Source: Company filing

Statistically significant improvements in TotPAR were also reported in the CR845/CR845 and Placebo/CR845 groups compared to the Placebo/Placebo group for the 0-4 ($p<0.01$), 2-4 ($p<0.04$, $p<0.03$ for CR845/CR845 and Placebo/CR845 respectively) and 0-8 ($p<0.02$) hour intervals. In addition, the improvement in mean TotPAR also reached statistical significance for the 0-12 hour interval for the CR845/CR845 group ($p \leq 0.05$).

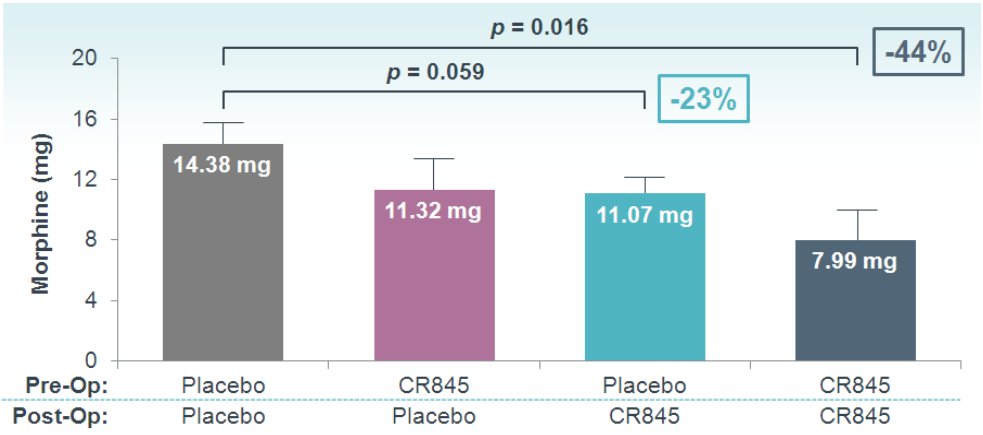
Figure 21: Ph2b trial in lap. hysterectomy - CR845 showed significant total pain relief (4 hrs)



Source: Company presentation

IV morphine was the rescue therapy in CLIN2002 to all patients upon request. Morphine consumption per treatment group in the 2-24 hour period, after patients leave the post-anesthesia care unit indicated that patients in the CR845/CR845 group used approximately 44% less morphine than those in the Placebo/Placebo group ($p \leq 0.05$), and patients in the Placebo/CR845 and CR845/Placebo groups used approximately 23% less morphine than those in the Placebo/Placebo group.

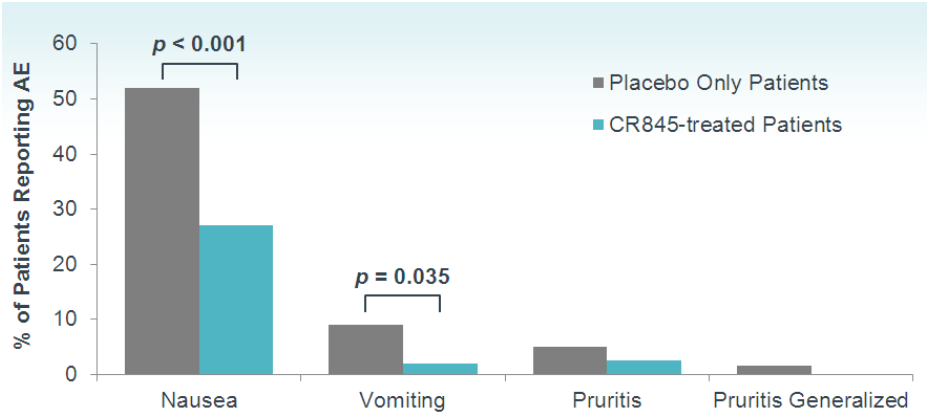
Figure 22: Ph2b trial in lap. hysterectomy - CR845 reduced postoperative morphine use



Source: Company presentation

In addition, patients on CR845 had a statistically significant lower incidence of opioid-related AEs through 24 hours after the first infusion. The incidence of nausea was reduced by approximately 50% (only 26.1% of patients administered CR845 experienced nausea as compared to 51.2% for placebo, $p \leq 0.001$) and the incidence of vomiting was reduced by nearly 80% (only 1.7% of patients administered CR845 experienced vomiting, as compared to 8.3% for placebo, p=0.035). There was also less pruritus reported in patients on CR845. Since ORAE is associated with delayed discharge and increased hospital-related spending, we think CR845 not only has a strong safety and tolerability profile, but may offer a compelling pharmacoeconomic benefit for both the providers and payors.

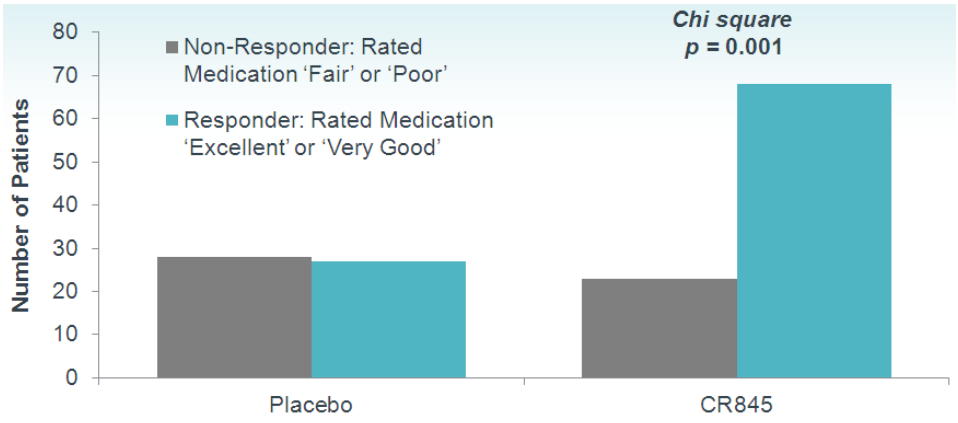
Figure 23: Ph2b trial in lap. hysterectomy - patients on CR845 have significantly less ORAEs



Source: Company presentation

The responder analysis indicated that a higher ratio of patients IV CR845 were characterized as "responders" compared to those on placebo (p = 0.001). Responders included patients who rated their medication "excellent" or "very good" and non-responders are those who rated their medication "fair" or "poor". We think the meaningful reduction in nausea and vomiting reported in patients on CR845 and their low overall pain intensity scores at the end of the study period contributed to patients' greater satisfaction with IV CR845 treatment compared to placebo.

Figure 24: Ph2b trial in lap. hysterectomy – high response rate to CR845

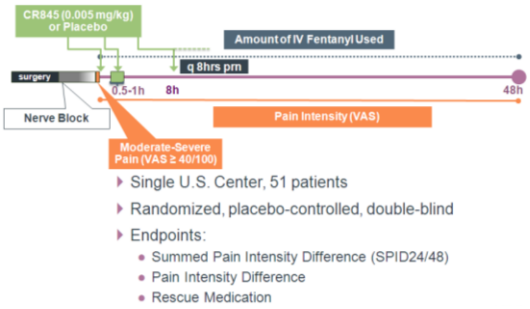


Source: Company presentation

In CLIN2002, IV administration of 0.04 mg/kg of CR845 was well tolerated. The placebo and CR845 treatment patient groups showed a similar overall incidence of treatment-emergent AEs of mild to moderate severity. The most common AEs were nausea, hypotension, flatulence, hypernatremia, and headache. The increase in blood sodium levels observed in CR845 treatment groups was likely a result of the aquaretic effect of IV CR845. In subsequent trials, fluid replacement with water or I.V. solutions with low or no sodium were used and no hypernatremia was reported.

Phase 2 Bunionectomy (CLIN2003)

Figure 25: Phase 2 bunionectomy trial design



	A Phase 2 study to evaluate analgesic effect of IV CR845 for pain following bunionectomy surgery
NCT ID	NCT01789476
Design	Randomized, placebo controlled, double blind
Enrollment	51
Dosing	CR845 of 0.005 mg/kg per dose. The initial dose is administered upon reaching a qualifying pain intensity score and followed by a supplemental dose, if requested by patient for pain. Additional doses can be administered every 8 hours up to 48 hours
Key inclusion criteria	• Males and females aged 18 years or older; • Scheduled for elective primary unilateral first metatarsal bunionectomy surgery (osteotomy and internal fixation) with no collateral procedures; • Females physically incapable of childbearing potential (postmenopausal for more than 1 year or surgically sterile) or practicing an acceptable method of contraception (hormonal, barrier with spermicide, intrauterine device, vasectomized partner, or abstinence). Subjects using hormonal birth control must have received at least 1 cycle of treatment prior to randomization. All females of childbearing potential must have a negative pregnancy test and not be breast feeding at Baseline; • Negative urine drug screen for drugs of abuse at Screening and at Baseline; a positive drug screen result may be permitted if the patient has been on a stable dose of an allowed medication for >30 days (antipsychotics, antiepileptics, sedatives, hypnotics, or antianxiety agents, selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants) or >3 months (opioid analgesics or systemic steroids); • American Society of Anesthesiologists (ASA) risk class of I to II; • Body weight <170 kg
Key exclusion criteria	• Has known allergies to opioids, unless has subsequently tolerated other opioids and in the opinion of the PI could tolerate study drug; • Has a known or suspected history of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)-diagnosed alcohol, opiate or other drug abuse or dependence within 12 months prior to screening; • Is unable to refrain from alcohol consumption for a period beginning 24 hours prior to surgery through the end of the Treatment Period; • Has taken non-opioid analgesics (including cyclooxygenase-2 [COX-2] inhibitors) or nonsteroidal anti-inflammatory drugs (NSAIDs) within 12 hours of the Baseline assessments; • Has taken any opioid analgesics or used systemic steroids within 4 days of surgery OR has been using opiates chronically for a period of < 3 months; (Note: Patients on stable chronic opioids for ≥ 3 months will need to discontinue them for 4 days prior to surgery); • Has used antipsychotics, antiepileptics, sedatives, hypnotics, or antianxiety agents, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants for < 30 days prior to surgery or had a dose change within the previous 30 days; • Has taken any prescription or over-the-counter medication within 4 days prior to surgery that, in the opinion of the Investigator, is expected to confound the analgesic response; • Has taken herbal agents or nutraceuticals (i.e., chaparral, comfrey, germander, jin bu huan, kava, pennyroyal, skullcap, St. John's wort, or valerian) during any of the 7 days prior to surgery; • Has any clinically significant condition or a significant laboratory abnormality that would, in the Investigator's or designee's opinion, preclude study participation • Has received another investigational drug within 30 days of scheduled surgery.
Primary endpoint	Time-specific VAS difference-the 24 hour summed pain intensity differences (SPID24)
Secondary endpoint	Efficacy of CR845 compared to placebo in reducing pain following bunionectomy / effect of CR845 compared to placebo on the use of rescue opioid analgesics during the postoperative period
Powering	Over 90% powered to show a difference with p<0.05

Source: Company presentation

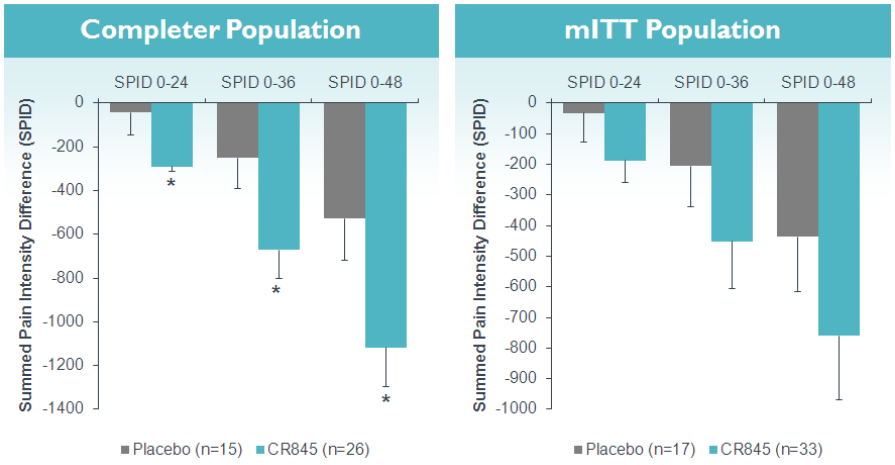
A bunionectomy is a common surgical procedure to remove a joint enlargement at the base of the big toe and includes both bone and soft tissue. The procedures generally result in intense pain that require significant postoperative analgesic care that involves pain management with strong opioid treatment for several days. As such, bunionectomy is a suitable model for investigating pain management agents in hard tissue pain and we think the data generated from this representative hard tissue pain model will be informative and well-regarded by the providers, the payors, and the FDA.

CLIN2003 was a randomized, double-blind, placebo-controlled trial conducted with 51 patients following bunionectomy surgery at a single site in the US. The trial enrolled patients of both genders, ages 18 years and older, who are scheduled for elective bunionectomy under regional anesthesia.

Patients were randomized 2:1 into CR845 or placebo after reporting a pain intensity score > 40 on a 100-point pain scale. The IV CR845 were administered at a dose of 0.005 mg/kg, and additional doses on an as-needed basis 30-60 minutes thereafter, but no more frequently than every 8 hours through a 48-hour dosing period.

Results for completers and the mITT population were analyzed in CLIN2003. In the Completer group, CR845 treatment resulted in a statistically significant reduction in pain intensity compared to placebo at 24, 36, and 48 hours ($p<0.05$, $p<0.03$, $P<0.03$, respectively). Improvements in SPID scores in the CR845 group versus placebo were also evident across the same time periods when analyzing the mITT population of Completers together with non-Completers.

Figure 26: Phase 2 bunionectomy trial - CR845 reduces postoperative bunionectomy pain



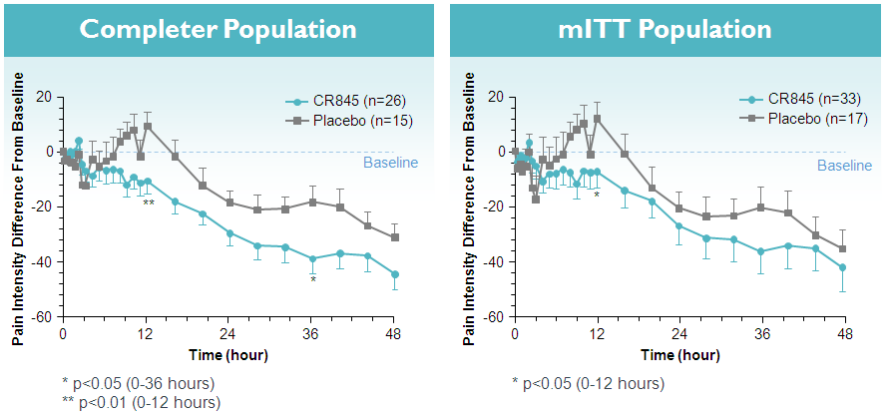
Source: Company presentation

The strong treatment effect trend in completer analysis is, in our opinion, indicative of the efficacy of IV CR845, while the mITT analysis indicated the real-world variability that physicians will likely face in the mITT populations. We think CARA is talking this into consideration and using it to determine the appropriate number of patients for its Phase 3 clinical trials.

In addition, mean PID from baseline at each time interval was higher across the 48 hour trial period in the CR845 group relative to the placebo group for both the Completer and

mITT populations. Statistically significant reductions in pain intensity differences in the CR845 group versus placebo were evident in the 12 hour interval for both the Completer and mITT populations ($p \leq 0.01$, $p \leq 0.05$ respectively) and for the 36 hour interval for the Completer populations ($p \leq 0.05$). This trend is consistent with the SPID endpoints.

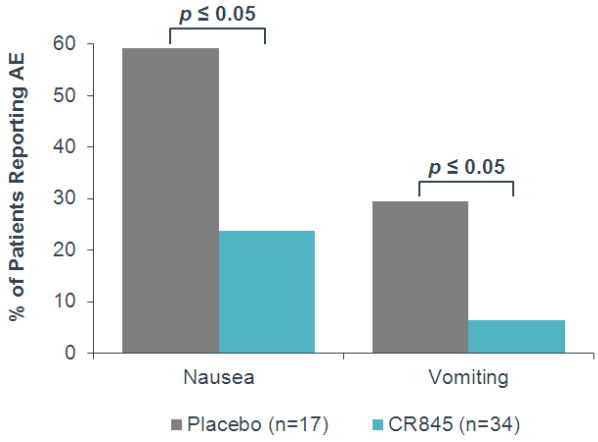
Figure 27: Phase 2 bunionectomy trial - pain intensity difference over 48 hours



Source: Clinicaltrials.gov

Fentanyl the recue therapy for CLIN2003 and it is available to all patients upon request. While there was no difference in mean fentanyl use between the placebo and CR845 groups, the incidence of ORAEs such as nausea and vomiting was significantly reduced by 60% and 80% ($p \leq 0.05$) in patients who received CR845 compared to placebo during the 48 hour treatment period. We think this result supports the scientific rationale that CR845 is able to reduce nausea and vomiting through its kappa opioid agonist mechanism of action.

Figure 28: Phase 2 bunionectomy trial - CR845 suppresses nausea and vomiting



Source: Company presentation

CR845 was well tolerated at 0.005 mg/kg. The most frequent AEs seen with treatment was transient facial tingling and somnolence. There was no evidence of acute psychiatric side

effects or hallucineations observed with prior-generation kappa opioid agonists active in the CNS.

Figure 29: Summary of AEs in Phase 2 bunionectomy trial

	PBO	CR845
Nervous System		
Dizziness	4 (23.5%)	10 (29.4%)
Paresthesia	0	10 (29.4%)
Somnolence (mild or mod.)	0	7 (20.6%)
• Likely related		0
• Possibly related		4 (11.8%)
• Unlikely related		3 (8.8%)
Increased Blood Sodium*		
155 mM or greater	0	0
150 mM threshold	0	1 (2.9%)

Source: Company presentation

Phase 2a Laparoscopic Hysterectomy (CLIN2001)

CLIN2001 trial was the proof-of-concept trial for CR845 in postoperative pain and it enrolled 114 patients undergoing laparoscopic hysterectomy.

In the first cohort of the trial, two single doses of IV CR845 (0.008 mg/kg; 0.024 mg/kg) were studied versus placebo in 68 patients on background IV PCA morphine. >50% of the all patients did not request rescue medication 4 hours after randomization while only 30% of placebo patients required no narcotic for 24 hours after randomization. Still, the pain magnitude the day after surgery was too small to allow separation between groups, therefore no clinical conclusions regarding the efficacy of CR845 was made.

In the second cohort, 46 patients were given a single dose of CR845 at 0.04 mg/kg or placebo within three hours after surgical recovery. In this group, CR845 patients showed statistically significant pain intensity reductions up to six hours after infusion versus placebo ($p \leq 0.05$). IV PCA morphine use was 49% lower in the CR845 group versus placebo, which was sustained for 12 hours ($p \leq 0.01$) with a concomitant reduction in nausea and vomiting.

The results for this POC trial showed that CR845 could reduce pain intensity and morphine consumption in postoperative settings and informed the study timeline and design of the larger Phase 2 clinical trial, CLIN2002, described in the prior section.

Figure 30: Phase 2a laparoscopic hysterectomy trial design

	Study to evaluate analgesic effect of IV administration of CR845 after bunionectomy surgery
NCT ID	NCT00877799
Design	Randomized, placebo controlled, double blind
Enrollment	114
Dosing	Cohort 1 - CR845 - I.V. 0.008 mg/kg single dose 24 hours post-surgery Cohort 1 - CR845 - I.V. 0.024 mg/kg single dose 24 hours post-surgery Cohort 1 - Matched Placebo single I.V. within 24 hours post-surgery Cohort 2 - CR845 - I.V. 0.040 mg/kg single dose within 3 hours post-surgery Cohort 2 - Placebo Comparator 2 - Matched Placebo single I.V. within 3 hours post-surgery
Key inclusion criteria	• The patients will have an elective laparoscopic-assisted hysterectomy under general anesthesia. • The patient's preoperative health is graded as the American Society of Anesthesiologists (ASA) risk class of I to III
Key exclusion criteria	• The patient has a history of known allergies to opioids • The patient is currently taking opioid analgesics chronically or took opioid analgesics on at least 4 days during the week before surgery. • Patients having additional procedures (such as those involving the bladder) at the same time as the laparoscopic-assisted hysterectomy. • Patients taking short-acting oral analgesics (eg, acetaminophen, aspirin, ibuprofen, ketorolac) within 6 hours before administration of study drug; long-acting nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, naproxen, oxaprozin, piroxicam, celecoxib) within 3 days before administration of study drug; systemic steroids within 72 hours before administration of study drug; or any opioid analgesics or tramadol daily for greater than 10 days of the last 30 days before administration of study drug. • Patients taking the following herbal agents or nutraceuticals within 7 days prior to beginning of the study: chapparal, comfrey, germander, gin bu huan, kava, pennyroyal, skullcap, St. John's wort, or valerian. • Patients with clinically significant cardiovascular disease, or cardiac arrhythmias, or significant major risk factors for cardiovascular disease such as poorly controlled hypertension, poorly controlled hypercholesterolemia, poorly controlled diabetes mellitus or serious medical conditions, such as cancer. • Patient has a history of hepatitis B or C or HIV infection with positive hepatitis B surface antigen (HBsAg), or anti-hepatitis C virus (HCV) antibody test.
Primary endpoint	Analgesic efficacy measured by patient's self-reported pain level at rest after surgery (after single dose administration)
Secondary endpoint	Time to onset of analgesic efficacy / Time specific and total level of pain relief / Duration of analgesia / Time specific pain intensity difference from baseline and total level of pain relief / Time and requirement for rescue medication including survival curve of patients requesting rescue medication / Patient satisfaction with study medication with the patient Global evaluation scale / Vital signs, clinical laboratory parameters, ECG / Incidence of adverse events / Sedation as measured by Ramsay sedation scale / Anti-inflammatory effects (measured by quantification of serum TNF alpha and serum IL-6
Powering	Over 90% powered to show a difference with $p<0.05$

Source: clinicaltrials.gov

CR845: Phase 1 Clinical Trials and Pre-clinical Studies

In addition to the three Phase 2 clinical trials, the safety of CR845 has been demonstrated across four Phase 1 trials and CR845 was well tolerated in all of these trials. The most common AEs across evaluated populations were transient facial tingling or numbness, dizziness, fatigue and aquaresis.

Figure 31: CR845 showed broad spectrum activity in multiple types of preclinical pain models

	Method	Species	ED50 (IV, mg/kg)	Duration of action
Somato – Visceral inflammatory pain	Acetic Acid Writhing: somatic and visceral pain	Mouse	0.07	> 18 hours
Chronic inflammatory pain	Complete Freund's Adjuvant: mechanical hyperalgesia	Rat	0.08	> 2 hours
Acute inflammatory pain	Carrageenan: mechanical hyperalgesia	Rat	0.3	> 1 hour
Neuropathic pain	L5/6 Spinal Nerve Ligation: tactile allodynia	Rat	0.3	> 8 hours

Source: Company filing

CR845 treatment reduced acute and chronic visceral, inflammatory and neuropathic pain in a dose-dependent fashion. CR845 related analgesia was measurable within 15 minutes post-administration and lasting up to 18 hours after a single dose. CR845 also decreased production and release of pro-inflammatory mediators.

CR845 showed robust efficacy across surgical models

CR845 showed consistent statistically significant reductions in SPID 24 and 48 in both soft and hard tissue models. In addition, CR845 was able to maintain meaningful reductions in pain intensity difference 24 or 48 hours after dosing. We note that the Cohen's d for CR845 in both tissue models was between 0.5 to 0.7 and we think it signals to us early significant drug effect size. On the safety side, no respiratory depression was reported and CR845 led to consistent reductions in ORAEs. We think the combined dataset across the two distinct surgical model serves as strong basis for power analysis for Phase 3 design in both soft and hard tissue pain.

Design of upcoming pivotal Phase 3 Trials

CARA is currently planning two Phase 3 clinical trials, one in patients with soft tissue pain and the other hard tissue. We think the primary efficacy endpoints will be the change in SPID at either 24 or 48 hours as compared to placebo.

Recent trials conducted by other companies for FDA-approved acute pain drugs have run similar Phase 3 development programs in soft and hard tissue models using either SPID 24 or SPID 48 as their endpoints. CARA is also planning on running an optional supportive Phase 3 clinical trial with CR845 dosed both pre-surgery and post-surgery in patients undergoing either laparoscopic hysterectomy or bunionectomy surgery. In all three trials, patients will have access to morphine as rescue medication throughout the trial. We expect CARA to initiate the trials in H2/14 and file an NDA after data readout in Q2/15.

We think CARA's Phase 3 trial design will be similar to their sucessful Phase 2 trials:

- **CLIN3001 – registrational soft tissue model***:* 600 laparoscopic hysterectomy patients. Patients assigned to one of three IV CR845 dose or placebo. Primary efficacy endpoint will be SPID24; secondary endpoints: morphine use, SPID at other time points, TotPAR 24 hours and nausea and vomiting.
- **CLIN3002 – registration hard tissue model***:* 600 bunionectomy patients. Patients assigned to receive one of three I.V. CR845 doses or placebo. Primary efficacy endpoint will be SPID48. Secondary endpointsL morphine use, SPID at other time points, TotPAR at 24 and 48 hours, and nausea and vomiting.
- **CLIN3003 – supportive trial***:* 450 laparoscopic hysterectomy or bunionectomy patients. This trial will compare the efficacy of I.V. CR845 when dosed both pre-surgery and post-surgery as compared with only post-surgery dosing. Patients will receive CR845 both pre- and post-surgery, CR845 post-surgery only, or placebo. Primary endpoint will be SPID24 or SPID48. Secondary endpoints: morphine use, SPID at other time points, TOTPAR at 24 and 48 hours, nausea and vomiting. P. 88 of S1

Figure 32: IV CR845 Phase 3 trials design

Trials	Pivotal Trial 1	Pivotal Trial 2	Optional Supportive Trial 3
Study/ Surgical Model	CR845-CLIN3001 (Soft tissue)	CR845-CLIN3002 (Hard tissue)	CR845-CLIN3003 (Hard and/or Soft tissue)
Design	Randomized, double-blind, placebo-controlled, multicenter, parallel group study with repeated post-surgical doses in female patients with pain following an elective laparoscopic hysterectomy	Randomized, double-blind, placebo-controlled, multicenter, parallel group study with repeated post-surgical doses in female and male patients with pain following bunionectomy	Randomized, double-blind, placebo-controlled, multicenter, parallel group study with repeated post-surgical doses in patients with pain following bunionectomy
Enrollment	600 (150/group)	600 (150/group)	450 (150/group)
Primary Efficacy Endpoint	Sum of Pain Intensity Difference over 24 hours (SPID-24) (Superiority vs. Placebo)	Sum of Pain Intensity Difference over 48 hours (SPID-48) (Superiority vs. Placebo)	Sum of Pain Intensity Difference over 48 hours (SPID-48) (Superiority pre-and post-surgical doses vs. post-surgical doses)
Secondary Efficacy Endpoint	Morphine consumption, patient satisfaction, SPID-6, SPID-12, total pain relief over 24 hours (TOTPAR-24), time to first rescue pain medication, post-operative nausea and vomiting	Morphine consumption, patient satisfaction, SPID-6, SPID-12, SPID-24, total pain relief over 24 and 48 hours (TOTPAR-24 and -48), time to first rescue pain medication, post-operative nausea and vomiting	Morphine consumption, patient satisfaction, SPID-6, SPID-12, SPID-24, total pain relief over 24 and 48 hours (TOTPAR-24 and -48), time to first rescue pain medication, post-operative nausea and vomiting
Dose	• 3 doses to range between 0.25 and 2.5 mg over a 24 hour period (as per efficacious doses established in Phase 2 trials) • Post-surgical administration, fixed interval Q6h, IV bolus), • Rescue medication: morphine	• 3 Total doses to range between 0.25 and 2.5 mg over a 24 hour period (as per efficacious doses established in Phase 2 trials) • Post-surgical administration, fixed interval Q6h, IV bolus), • Rescue medication: morphine	• Pre-surgical loading dose followed by repeated single dose (Q6h, IV bolus) post-surgery, • Rescue medication: morphine

Source: Company presentation, Canaccord Genuity research.

CARA is also planning on completing a "Human Abuse Liability Study" in 2014 to confirm the lack of CNS euphoric effects and the non-abusability of CR845. These studies are FDA-recommended and enroll non-dependent, recreational drug users to assess how likely it is that a test drug is abusable. The results of this trial would be submitted as part of the IV CR845 NDA. We think CARA will meet the 1,500 total exposures to IV CR845 across multiple planned clinical trials to initiate shortly.

Figure 33: CR845 abuse liability trial design

Expert CRO	CRL Lifetree (Lynn R. Webster, MD, board certified in anesthesiology, pain medicine and certified in addiction medicine)
Goals	To compare the relative abuse potential of IV administered CR845 to IV administered morphine in non-dependent, experienced recreational opioid users (male/female,18-55 years of age, inclusive)
Study Design	Phase 1, single center, randomized, double-blind, active and placebo-controlled, 5-way crossover design 3 study phases: screening, in-clinic (qualification and treatment periods), and telephone follow-up • To determine eligibility to enter the treatment period, subjects will first undergo a Naloxone Challenge Test (to ascertain lack of physical dependence) and Drug Discrimination Test (to ensure that subject scan tolerate and differentiate between the effects of a single dose of 10 mg IV morphine and placebo) • The Treatment period will consist of 5 consecutive dosing days, each of which will involve a single IV bolus injection of morphine, CR845 or placebo followed by a near 24 (±2) hour wash-out
Duration	Up to 41 days (up to 21days screening, 10 days in-clinic and 7 to 10 days follow-up)
Dosing	Low, therapeutic and supratherapeutic doses of CR845 (i.e., 0.3, 1 and 3 mg), placebo and Morphine sulfate (10 mg), IV bolus
Number of sites	1 US site (CRL Lifetree, Salt Lake City) with 30 planned completers
PK/PD Measures	Primary endpoint: • Drug Liking (Bipolar VAS) Secondary endpoints • Drug Effects Questionnaire (DEQ, 0-100 point unipolar VAS) (any drug effects, high, good and bad effects, sick, nausea, sleepy, dizzy, spaced out, floating, detached, and any hallucinations. • Take Drug Again Assessment (TDAA) (0-100 point bipolar VAS) • Addiction Research Center Inventory-Morphine Benzedrine Group/d-Lysergic Acid Diethylamide/Pentobarbital Chlorpromazine Alcohol Group (ARCI-MBG/LSD/PCAG) subscales • Overall Drug Liking and drug similarity (0-100 point bipolar VAS) • Alertness/Drowsiness (0-100 point bipolar VAS) • Price Value Assessment Questionnaire (PVAQ) • Pupillometry
Projected timeline	First subject / first visit: end of Q1/14 Last subject / last visit: Q2/14 Topline data: mid-2014

Source: Company presentation, Canaccord Genuity research

Oral CR845

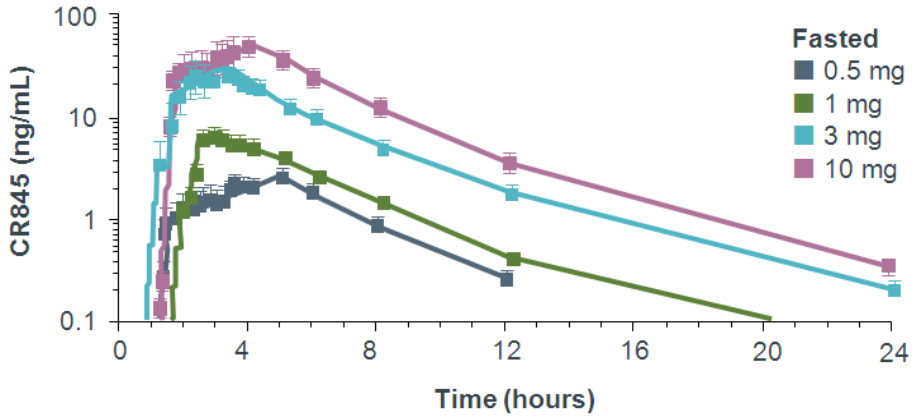
CARA is developing an oral version of CR845. We think it will capture a significant portion of the market opportunity in postoperative "step-down" therapy as patients transition from IV drugs to oral analgesics. In addition, we think oral CR845 will be useful in treating chronic condition and certain inflammatory diseases such as arthritis, irritable bowel syndrome, and pruritus. The lack of CNS side effects, including euphoria, which should preclude oral CR845 from the misuse, abuse and addiction risks associated with currently approved mu opioids.

Phase 1 trial of Oral CR845 (Study 1001-PO) was conducted in 50 male volunteers administered with an enteric-coated capsule of CR845 (0.5, 1, 3, or 10 mg) or matched placebo. Oral CR845 appeared to be 16% bioavailability. Maximal plasma concentration (Cmax) and overall exposure increased linearlyat ascending doses. The time to maximal concentration (Tmax) was 3 hours.

The increase in serum prolactin, a known biomarker of kappa receptor activation, suggests the level of exposure at all doses was sufficient to activate peripheral kappa receptors. Oral CR845 was well tolerated and all AEs were mild in nature. None of the test subjects displayed any of the dysphoric or psychotomimetic side effects that have halted the development of prior generations of centrally active kappa agonists. We think oral CR845 has confirmed kappa activity at even the lowest capsule concentrations and early favorable safety profile that supports further development

Figure 34: Oral CR845 trial design and summary of data

	Phase 1 trial of oral CR845
Enrollment	50 male volunteers
Dosing	Administration of an enteric-coated capsule of CR845 (o.5, 1, 3, or 10mg) or matched placebo
PK/PK measures	Bioavailability, maximal plasma concentration, overall exposure, time to maximal concentration
Safety endpoints	Incidence of abdominal discomfort, dysphoria, or psychotomimetic effects
Next step	Phase 1 single ascending dose and multiple ascending dose studies in Q1/14 Phase 2 POC in H2/14



Source: Company filing and Canaccord Genuity research

After the positive outcome of the POC trial, CARA has subsequently developed a tablet version of oral CR845 that is predicted to provide greater predictability with respect to the amounts of drug administered versus its concentration in the blood and its pharmacokinetic profile. CARA plans to conduct both single ascending and multiple ascending dose Phase 1 clinical trials in the H1/14 and, and, based on positive results,

initiate a Phase 2a POC trial in acute pain in the second half of 2014. Planned Phase 1 trials include.

- **CLIN1002-SAD:** Single ascending dose trial; 10 subjects per cohort - 8 Oral CR845, 2 placebo. Up to 100 subjects with doses from 0.1 mg up to 20 mg.
- **CLIN1003-SAD.** Multiple ascending dose trial with three cohorts of low, mid and high doses. 15 subjects in each cohort: 10 Oral CR845, 5 placebo.

Figure 35: Planned Ph1 SAD/MAD study for oral CR845

	CLIN1002	CLIN1003
Design	Single ascending dose	Multiple ascending dose
Enrollment	10 subjects per cohort, 10 cohorts	15 subjects per cohort, 3 cohorts
Dosing	0.1 mg to 20 mg	Low, mid, and high doses
Randomization	4 to 1 - active to placebo	2 to 1 – active to placebo

Source: Company filings and Canaccord Genuity estimates

Commercial strategy

CARA intends to build out its own sales and marketing organization to commercialize IV CR845 for acute pain in the hospital setting in the United States. With a sales force of approximately 80 sales professionals, CARA can reach a large majority of its target market. We think CARA will also build its sales and medical liaison organizations and a reimbursement infrastructure to support the ongoing sales and marketing efforts.

CARA is looking to establish partnerships for development and commercialization of IV CR845 ex-US with someone who has deep expertise in pain management. CARA already has development and commercialization agreements with Maruishi for IV CR845 and acute indications of oral CR845 in Japan and Chong Kun Dang for IV and oral CR845 in the South Korea.

CARA will continue to advance its oral formulation of CR845 past the POC stage and then seek a global development and commercialization partner. CARA believes the market for oral chronic pain management is large and requires a significant sales and marketing infrastructure that one can only find in global pharmaceutical companies. However, CARA intends to retain the rights to co-promote oral CR845 in the US for patients who receive IV CR845 in the hospital and "step-down" to the oral formulation as they leave the hospital.

CR701: CARA's imidazoheterocycle cannabinoid platform

There are two types of cannabinoid receptor, CB1 and CB2, in mammalian tissues and both of them are coupled to G proteins. Even though both receptors are expressed in central and peripheral nervous system, CB1 receptors are expressed mainly through neurons while CB2 receptors are distributed across non-neuronal tissues, particularly in immune cells. Activation of both CB1 and CB2 receptors reduces nociceptive processing in acute and chronic animal models of pain. As such, we think CR701, if pre-clinical data warrants further development, may be a strong add-on to CARA's portfolio of pain drugs.

INTELLECTUAL PROPERTY

CARA has filed for patent protection covering compositions of matter and methods of use for its drug candidates. CARA owns six issued U.S. patents and the first of which is expected to expire no earlier than 2007 that cover the compound CR845, CARA's synthetic peptide amide kappa opioid agonist, and methods of using these compounds to modulate functions of kappa opioid receptors and for the treatment of acute postoperative pain. CARA also relies on trade secrets and careful monitoring of proprietary information to protect aspects of its business that are no amenable to patent protection.

CARA's synthetic peptide amide kappa opioid agonist patent portfolio consists of eight issued U.S. patents with claims to compositions of a wide range of synthetic peptides. The CR845 patent portfolio also includes pending U.S. patent applications which claim additional uses and methods of administering CR845. Related foreign applications were filed in more than 40 other countries and national patents have been granted in 32 European countries, as well as in Australia, China, Hong Kong, Japan, Malaysia, Mexico, New Zealand, Russia, Singapore and South Africa.

CARA's wholly owned imidazoheterocycle cannabinoid compound patent portfolio includes U.S. Patent Nos. 7,517,874 and 8,431,565; and a pending U.S. patent application claiming CR701, related compounds, and methods of using these compounds. These U.S. patents are due to expire no earlier than June 20, 2028. A related international PCT application was filed and sixteen national and European and Eurasian regional patent applications have been filed based on the PCT application. The European regional patent has been granted as have national patents in Hong Kong, Israel, Malaysia, Mexico, New Zealand, Singapore and South Africa. These and any other patents resulting from the pending national patent applications, if issued, expire on June 20, 2028. In addition, CARA has patent portfolios for other cannabinoid compounds that regulate prolactin in mammals. These patent portfolios are wholly owned by CARA.

Figure 36: Summary of key CARA patents

Patent	Title	Expiration
7,402,564	Synthetic peptide amides	2032
7,713,937	Synthetic peptide amides and dimeric forms thereof	2033
7,727,963	Synthetic peptide amides	2033
7,842,662	Synthetic peptide amide dimers	2032
8,217,007	Synthetic peptide amides	2035
8,236,766	Uses of synthetic peptide amides	2034
8,486,894	Synthetic peptide amides and dimeric forms thereof	2035
8,536,131	Synthetic peptide amides and dimers thereof	2035

Source: Company reports and Canaccord Genuity estimates

MANAGEMENT TEAM

The CARA management team has a strong history of corporate leadership, development and commercialization in the biotechnology industry.

Derek Chalmers, Ph.D., D.Sc., is a co-founder of CARA. Dr. Chalmers has served as the President and Chief Executive Officer of CARA since September 2004 and has served as a member of CARA's board of directors since July 2004. Dr. Chalmers has over 19 years of experience in the biotechnology industry with increasing levels of corporate and business responsibilities. Prior to founding our company, Dr. Chalmers co-founded Arena Pharmaceuticals, Inc. (NASDAQ: ARNA), a drug discovery and development company, and served as its Vice President and Executive Director from June 1997 until May 2004. Dr. Chalmers holds a B.Sc. and Ph.D. in Pharmacology from the University of Glasgow.

Josef Schoell has served as the Chief Financial Officer of CARA since May 2006. He joined CARA in May 2005 and served as the Controller between then and May 2006. Mr. Schoell has over 20 years of financial and accounting experience, including 18 years in the biotechnology industry. From 2003 until joining CARA in May 2005, Mr. Schoell was a consultant with Robert Half Management Resources, a provider of accounting and financial professionals. From 1995 to 2002, he served as the Chief Financial Officer and Vice President of Finance, of American Biogenetic Sciences Inc. Mr. Schoell received a B.S. in Accounting from the New York University Stern School of Business and is a Certified Public Accountant. Mr. Schoell is a member of the American Institute of Certified Public Accountants and Financial Executives International.

Frédérique Menzaghi, Ph.D., is a co-founder of CARA and has served as the Vice President of Research and Development since September 2004. Dr. Menzaghi has over 20 years of drug development and management experience in biotech. From 1999 to 2003, Dr. Menzaghi served as the Research Director of In Vivo Pharmacology at Arena Pharmaceuticals, Inc. (NASDAQ: ARNA) and from 2003 to 2004, was the Vice President of Pharmacology and Business Development at Psychogenics Inc., a preclinical central nervous system service provider. Dr. Menzaghi received her Ph.D. in Neurosciences from the Louis Pasteur University, Strasbourg, France and a M.Sc. in Clinical Psychology from the University of Nancy.

Michael E. Lewis, Ph.D., is a co-founder of CARA. He has served as the Chief Scientific Advisor of CARA since September 2004 and a member of CARA's board of directors from September 2004 to July 2010. Prior to joining CARA, Dr. Lewis co-founded Arena Pharmaceuticals (NASDAQ: ARNA) and served as Arena's Chief Scientific Advisor from 1997 to 2004. He was also a director of Arena from 1997 to 2000. Prior to co-founding Arena, Dr. Lewis co-founded and served as Chief Scientific Advisor of Adolor Corporation (NASDAQ: ADLR) from 1994 to 1997. Prior to that, Dr. Lewis co-founded Cephalon, Inc. (NASDAQ: CEPH), serving as Director of Pharmacology from 1988 to 1992 and Senior Director of Scientific Affairs from 1992 to 1993. Dr. Lewis received a Ph.D. in Psychology from Clark University and postdoctoral training at the University of Cambridge, the National Institutes of Mental Health, and the University of Michigan, with a focus on opioid receptor research.

Figure 37 CARA key management members

Name	Title	Work History	Joined CARA in:
Derek Chalmers, Ph.D., D.Sc.	President and Chief Executive Officer	Arena Pharmaceuticals Neurocrine Biosciences	2004
Josef Schoell	Chief Financial Officer	Robert Half Management Resources American Biogenetic Sciences, Inc.	2005
Frédérique Menzaghi, Ph.D.	VP of Research and Development	Arena Pharmaceuticals Psycogenetics, Inc. SIBIA Neurosciences	2004
Michael E. Lewis, Ph.D.	Chief Scientific Advisor	Arena Pharmaceuticals Adolor Corporation Cephalon, Inc. PolyMedix, Inc.	2004

Source: Company reports and Canaccord Genuity estimates

Figure 38: CARA P&L

	2011A	2012A	Q1/13A	Q2/13A	Q3/13A	Q4/13E	2013E	Q1/14E	Q2/14E	Q3/14E	Q4/14E	2014E	2015E	2016E
TRV130	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Product revenues	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Grant/partnership revenue	-	1.2	3.7	3.7	3.7	3.7	14.7	-	1.00	1.00	1.00	3.0	3.0	3.0
Total revenues	**-**	**1.2**	**3.7**	**3.7**	**3.7**	**3.7**	**14.7**	**-**	**1.0**	**1.0**	**1.0**	**3.0**	**3.0**	**3.0**
Cost of goods sold		-	-	-	-	-	-	-	-	-	-			
Gross Profit	**-**	**1.2**	**3.7**	**3.7**	**3.7**	**3.7**	**14.7**	**-**	**1.00**	**1.00**	**1.00**	**3.0**	**3.0**	**3.0**
R&D expense	7.2	4.6	2.2	2.2	2.2	3.0	9.7	3.0	5.0	7.0	9.0	24.0	25.0	35.0
SG&A expense	2.4	2.8	0.8	0.8	0.8	1.0	3.5	1.1	1.1	1.2	1.2	4.6	10.0	40.0
Other operating expense	-	0.0					-	-	-	-	-	-	-	-
Total operating expense	**9.6**	**7.5**	**3.1**	**3.1**	**3.1**	**4.0**	**13.2**	**4.1**	**6.1**	**8.2**	**10.2**	**28.6**	**35.0**	**75.0**
Operating income	**(9.6)**	**(6.3)**	**0.6**	**0.6**	**0.6**	**(0.3)**	**1.5**	**(4.1)**	**(5.1)**	**(7.2)**	**(9.2)**	**(25.6)**	**(32.0)**	**(72.0)**
Net Interest/Investment income	-	-					0.0					0.0	0.0	0.0
(interest expense)	(0.1)	(0.1)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1
Other non-operating income (expense)	(0.2)	-					-					-	-	-
Interest and other, Net	(0.3)	(0.1)	-	-	-	-	-	-	-	-	-	-	-	-
Pre-tax income	**(9.8)**	**(6.3)**	**0.6**	**0.6**	**0.6**	**(0.3)**	**1.6**	**(4.1)**	**(5.1)**	**(7.2)**	**(9.2)**	**(25.6)**	**(31.9)**	**(71.9)**
Income tax expense (benefit)	-	-	-	-	-	-	-					-	-	-
Net income (loss)	**(9.8)**	**(6.3)**	**0.6**	**0.6**	**0.6**	**(0.3)**	**1.6**	**(4.1)**	**(5.1)**	**(7.2)**	**(9.2)**	**(25.6)**	**(31.9)**	**(71.9)**
Basic EPS	**(0.59)**	**(0.38)**	**0.04**	**0.04**	**0.04**	**(0.01)**	**0.09**	**(0.18)**	**(0.22)**	**(0.31)**	**(0.40)**	**(1.12)**	**(1.39)**	**(3.11)**
Diluted EPS	**(0.59)**	**(0.38)**	**0.04**	**0.04**	**0.04**	**(0.01)**	**0.09**	**(0.18)**	**(0.22)**	**(0.31)**	**(0.40)**	**(1.12)**	**(1.39)**	**(3.11)**
Basic shares outstanding	16.8	16.8	16.8	16.8	16.8	22.6	18.3	22.7	22.8	22.9	23.0	22.9	23.0	23.1
Diluted shares outstanding	16.8	16.8	16.8	16.8	16.8	22.6	18.3	22.7	22.8	22.9	23.0	22.9	23.0	23.1

Source: Company reports and Canaccord Genuity estimates

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Company	Disclosure
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