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Cara Therapeutics

Biotechnology

US Equity Research
9 January 2015

BUY

PRICE TARGET US$20.00
Price (8-Jan) US$10.47
Ticker CARA-NASDAQ

52-Week Range (US$):	7.76 - 22.49
Avg Daily Vol (M) :	0.2
Market Cap (US$M):	237
Shares Out., FD (M) :	22.7
Average Price Target (US$):	23.60
Cash (US$M):	58.39
Short Interest :	244,609
2015E Cash Burn (US$M):	41
# of analysts :	5

FYE Dec	2013A	2014E	2015E	2016E
Sales (US$M)	12.0	3.3	4.0	5.0
EPS Adj&Dil (US$)	(0.72)	(0.98)	(1.37)	(2.01)

Quarterly Sales	Q1	Q2	Q3	Q4
2013A	-	-	-	-
2014E	0.2A	1.0A	1.1A	1.0
2015E	1.0	1.0	1.0	1.0
2016E	-	-	-	-

Quarterly EPS Adj&Dil	Q1	Q2	Q3	Q4
2013A	-	-	-	-
2014E	(0.21)A	(0.15)A	(0.28)A	(0.34)
2015E	(0.35)	(0.37)	(0.39)	(0.26)
2016E	-	-	-	-

Source: FactSet

CARA is a clinical-stage biotech company focused on developing novel kappa opioid receptor agonists for postoperative pain managemenet.

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Initiation of Coverage

Cara - May have the holy grail alternative to opioids

While still the single largest pharma market in volume terms, a potent alternative to opioids for pain has remained elusive. Cara seems to have found the most promising candidate - a highly selective κappa-opioid receptor agonist - CR854. The company is working on two formulations of the drug: 1) IV, going into Ph3, for acute/postoperative pain; and 2) oral, entering Ph2, as a step-down therapy for postoperative pain and for chronic pain.

Investment highlights

- **Potentially as good as opioids, without the side effects.** With more than seven Ph1 and 2 trials already completed, there's good evidence that '854 has none of the opioid side effects with equi-potent efficacy. If this continues to play out in Ph3 trials, it could become a blockbuster.
- **CR854 overcomes hurdles faced by older generation of κ agonists.** Drug companies have been exploring κ agonists for years with little success primarily due to their penetration into the blood-brain barrier, giving rise to a slew of CNS side effects (primarily dysphoria and hallucinations). In contrast, '854 remains in the periphery because it is a highly charged 4 amino acid peptide, and hence avoids all of the adverse events of its predecessors.
- **Potential for favorable scheduling.** In the recently-completed Human Liability Trial, IV '845 showed to have statistically significant lower "drug liking" scores than pentazocine, a Schedule IV opioid. This suggests that CR845 could become the first Schedule V or non-scheduled opioid for postoperative pain.
- **Catalysts**. The Ph3 IV trial in post surgical pain should start in early 2015 after the official end of Ph2 meeting with the FDA and be completed by year-end. The Ph2 oral study should also start in early 2015 and read out in early 2016. There is also an ongoing pruritis study due to be completed in early 2015.
- **Target sensitivity analysis**. We have certainly seen our fair share of pain drug trials and the κ drugs in general have virtually all failed. For this reason, we use a very high 45% discount rate in deriving our $20 target. However, if the Ph3 IV and/or the Ph2 oral trials are successful, we would argue very strongly that a much lower discount rate should be applied. This sensitivity table can be seen on page 4 of this note, and for example a 25% discount rate would yield a $43 stock – all else equal.

Valuation

We use a discounted P/E model to derive our $20 price target; we apply a 25x multiple to our 2020 EPS estimate of $5.21 discounted at 45% for 5 years. Risks include: failure to hit primary endpoint in IV CR845 Ph3 trial, unfavorable scheduling and/or failure to gain FDA approval.

INVESTMENT THESIS

Our Cara investment thesis hinges on the assumptions that its lead program IV CR845 will initiate Ph3 trial in postoperative pain and oral CR845 will initiate a Phase 2 proof-of-concept trial in 2015. We like the stock for several reasons:

1. **CR845 is a pure kappa opioid receptor agonist with limited opioid side effects but with comparable efficacy.** By acting only on the κ-opioid receptor, CR845 is mostly devoid of side effects commonly seen in the standard Mu agonists, such as euphoria, respiratory depression, nausea and vomiting. Two Ph2b clinical trials have been conducted to date, demonstrating impressive efficacy.

    a) Laparoscopic hysterectomy – In this 203-patient study, those in the CR845/CR845 group exhibited a statistically-significant reduction in pain over a 24hr period compared to placebo, as indicated by $SPID_{0-24}$. There was also a 45% reduction in morphine usage, 50% lower incidence of nausea and 80% less vomiting.

    b) Bunionectomy – In this 51-patient study, pain reduction was statistically significant over 24, 36 and 48hr periods in the CR845-treated "Completer" group compared to placebo. Given how painful the procedure is, no difference in mean fentanyl use was observed between treatment and placebo groups. However, the incidence of opioid-related adverse events (AEs) of nausea and vomiting was 60% and 80% lower respectively during the 48 hour period after randomization, a result that's believed to be a direct effect of κ-opioid receptor agonism.

2. **Cara understands why previous attempts in developing κ agonists failed.** In the late 1980s and 1990s, a variety of κ agonists were created to explore their anti-nociceptive and anti-inflammatory effects. None were successful clinically however, primarily due to a lack of efficacy and/or occurrences of central nervous system AEs as a result of drug molecules crossing the blood brain barrier. Since CR845 is restricted to the periphery and highly specific to the κ-opioid receptor, it has shown good efficacy and safety profile, with the most common AE being transient facial tingling, dizziness and fatigue.

3. **Despite the size of the pain management market and their side effects, opioids still account for >70% of all the prescriptions written in the US.** Per IMS, the US pain market was ~$18B in 2012; μ-opioid receptor agonists are the most prescribed drugs, in spite of their side effects and abuse potential, which in the postoperative setting alone, account for ~$5B in additional costs. Further, there's little innovation in the development of new analgesics, with most approvals limited to reformulations. Drug candidates that are in the clinical stage are also composed mostly for reformulations of existing opioids and NSAIDs, which are known to be less potent than opioids. Therefore, we believe a sizable unmet need exists in the pain space, and if approved, CR845 could be an attractive alternative to patients and physicians as it addresses issues associated with current opioids.

4. **CR845 could become the first Schedule V or non-scheduled peripheral opioid for postoperative pain.** In October 2014, Cara announced positive results from Human Abuse Liability trial of IV CR845. It demonstrated highly statistically significant lower drug liking scores compared to pentazocine, a Schedule IV comparator. We believe this is important on two fronts:

    a) This data suggests the potential for CR845 to be a Schedule IV or lower opioid for postoperative pain, which presently is dominated by short-acting opioids with Schedule II or III designations.

b) On August 22, 2014, the Drug Enforcement Administration (DEA) rescheduled hydrocodone combination products from Schedule III to II to combat drug abuse. As a result, restrictions on prescription and dispensing practices will be tightened, creating opportunities for manufactures to raise prices. Hence we believe that physicians will be incentivized to prescribe alternatives that are more safe and cost-effective.

5. **The CR845 franchise could hit the $1B sales mark in 2020 with <10% in market share.** According to the National Hospital Discharge Survey, >40M inpatient surgeries are performed each year. In the outpatient setting, ~240M Rxs were opioid analgesics. Assuming that 75% of patients require postoperative pain medications, and Rxs grow at ~1% annually, we model the sales of IV and oral CR845 being >$1B in 2020, with the former achieving 8% market share and the latter at 0.2%.

6. **Strong balance sheet.** Cara ended Q3/14 with $58.4M in cash and cash equivalents, which is sufficient to fund operations for another 18 months. However, we've modeled a capital raise of ~$56M in 2015 to support the advancement of IV CR845 in Ph3.

VALUATION - $20 PRICE TARGET

Since Cara is unlikely to be profitable until 2018, we believe a discounted P/E multiple valuation methodology is appropriate. We use our 2020 EPS estimate of $5.21 (third year of profitability) and a P/E multiple of 25x, and discount that back five years at 45% to derive a one-year forward price target of $20.

Figure 1: Price target sensitivity analysis

2020 EPS:	$5.21		Multiple				
Period:	5.0		15.0x	20.0x	25.0x	30.0x	35.0x
		35.0%	$17	$23	$29	$35	$41
		40.0%	$15	$19	$24	$29	$34
	Discount	45.0%	$12	$16	$20	$24	$28
		50.0%	$10	$14	$17	$21	$24
		55.0%	$9	$12	$15	$17	$20

	2018	2019	2020	2021
PE multiple	25.0x	25.0x	25.0x	25.0x
EPS	$0.17	$2.58	$5.21	$6.49
Total	4.28	64.55	130.31	162.27
Discount Rate	45%	45%	45%	45%
Discount Years	3.0	4.0	5.0	6.0
Price Target	$1	$15	$20	$17
Current price:	$9.98	$9.98	$9.98	$9.98
	(85.9%)	46.3%	103.7%	74.9%

Source: Canaccord Genuity estimates

REVENUE AND MARKET MODEL

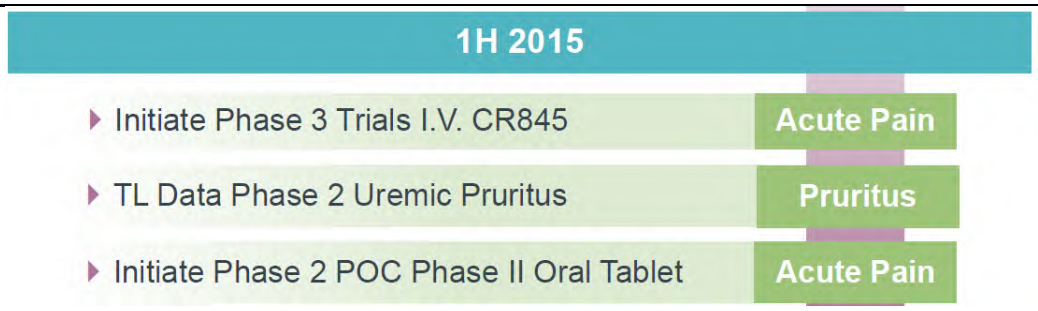
Cara's lead program is the IV form of CR845 for treating acute/postoperative pain. Oral CR845 is currently advancing into Ph2, and it targets chronic pain in an outpatient setting. CR701 is a preclinical peripherally-acting cannabinoid receptor agonist that has shown remarkable efficacies in models of inflammatory and neuropathic pain.

Figure 2: Cara pipeline

Product Candidate (Class)	Indication	Status	Commercial Rights
IV CR845 (kappa opioid)	Acute Pain	Phase 3 planning	▸ Cara (worldwide ex. below) ▸ Maruishi (Japan) ▸ CKD Pharma (S.Korea)
Oral CR845	Acute/Chronic Pain	Phase 1a/b complete	▸ Cara (worldwide ex. below) ▸ Maruishi (Japan) ▸ CKD Pharma (S.Korea)
Oral (IV) CR845	Pruritus (Uremic)	Phase 2 ongoing	▸ Cara (worldwide ex. below) ▸ Maruishi (Japan) ▸ CKD Pharma (S.Korea)
Oral CR701 (cannabinoid)	Neuropathic Pain	Preclinical	▸ Cara (worldwide)
Japanese License for CR845 in Dialysis-related Pruritus*			

Source: Company presentation

Figure 3: Upcoming milestones



Source: Company presentation

Our market model is built on the assumption that CR845 IV will receive FDA approval for treating postoperative pain in the hospital setting in 2016; we also assume that EU approval will occur a year later. Assuming all goes well, the drug will be commercialized in the US in 2017 through a focused, hospital-based sales force of ~80 reps. The plan is for both oral CR845 and ex-US commercialization to be partnered, and for now, we've modeled Cara receiving 20% of sales as royalty. Cara has already entered into collaboration agreements for both IV and oral CR845 with Maruishi Pharmaceuticals in Japan and Chong Kun Dang Pharmaceutical Corp. in South Korea, which provide them the exclusive right to develop and market CR845 for certain indications within those territories. As of December 31, 2013, Cara had

received approximately $24 million in payments in connection with these collaborations

While more than 40M inpatient surgeries are performed in the US, Cara believes ~36M will be appropriate for IV CR845. We then assume that the number of procedures will grow at 0.1% annually, and 75% of such patients require some form of pain management after the operation. For oral CR845, our projection is based on the total number opioids Rxs, which is ~240M. On pricing, we have made the following assumptions given that CR845 is likely to be a volume-driven product: 1) we assign $90 per patient for the IV formulation when used inside the hospital, growing at 3% annually; 2) we assign $30 per patient for the IV formulation when used in the outpatient setting, growing at 3% annually; and 3) since oral CR845 is designed for outpatient use, we believe it should be priced on-par with currently available postoperative branded oral analgesics like Opana and Oxycontin – $130 per Rx per month, which is ~ $1,500 per year, also growing at 3% a year.

Figure 4: Revenue estimates

(In millions)

	CR845							Other Revenues		Total Revenue
	US Revenue				EU Revenue					
	IV	Oral	To Cara	Royalty	End-User	To Cara	Royalty	License Fees	Collaborative Revenue	
2012								$0.0	$0.2	**$0.2**
2013								$9.6	$2.3	**$12.0**
2014E								$0.3	$3.0	**$3.3**
2015E								$0.0	$4.0	**$4.0**
2016E								$1.0	$4.0	**$5.0**
2017E	$60.0							$1.0	$4.0	**$65.0**
2018E	$123.7				$60.0	$12.0	20%		$2.0	**$137.7**
2019E	$193.1	$187.3	$37.5	20%	$127.4	$25.5	20%			**$256.0**
2020E	$268.0	$779.4	$155.9	20%	$230.6	$46.1	20%			**$470.0**
2021E	$348.8	$1,013.6	$202.7	20%	$423.9	$84.8	20%			**$636.3**
2022E	$435.7	$1,265.3	$253.1	20%	$551.5	$110.3	20%			**$799.1**
2023E	$529.2	$1,535.6	$307.1	20%	$688.8	$137.8	20%			**$974.1**
2024E	$629.6	$1,825.7	$365.1	20%	$836.4	$167.3	20%			**$1,162.1**
2025E	$737.4	$2,136.7	$427.3	20%	$994.8	$199.0	20%			**$1,363.7**
2026E	$853.0	$2,469.8	$494.0	20%	$1,164.8	$232.95	20%			**$1,579.9**
% Growth										
18E/17E	106.2%									**111.9%**
19E/18E	56.2%									**86.0%**
20E/19E	38.8%	316.1%			81.0%	81.0%				**83.6%**
21E/20E	30.1%	30.0%			83.9%	83.9%				**35.4%**
22E/21E	24.9%	24.8%			30.1%	30.1%				**25.6%**
23E/22E	21.5%	21.4%			24.9%	24.9%				**21.9%**
24E/23E	19.0%	18.9%			21.4%	21.4%				**19.3%**
25E/24E	17.1%	17.0%			18.9%	18.9%				**17.4%**
26E/25E	15.7%	15.6%			17.1%	17.1%				**15.9%**

Source: Canaccord Genuity estimates

Figure 5: CR845 market model

Cara Market Model	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E
IV CR845												
Annual Inpatient Surgical Procedures	36,000,000	36,036,000	36,072,036	36,108,108	36,144,216	36,180,360	36,216,541	36,252,757	36,289,010	36,325,299	36,361,624	36,397,986
% Requiring Post-Op Pain Management	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
Annual Outpatient Surgical Procedures	25,000,000	25,025,000	25,050,025	25,075,075	25,100,150	25,125,250	25,150,376	25,175,526	25,200,701	25,225,902	25,251,128	25,276,379
% Requiring Post-Op Pain Management	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*	*75%*
Addressable Inpatient Patient Population	27,000,000	27,027,000	27,054,027	27,081,081	27,108,162	27,135,270	27,162,406	27,189,568	27,216,758	27,243,974	27,271,218	27,298,489
Addressable Outpatient Patient Population	18,750,000	18,768,750	18,787,519	18,806,306	18,825,113	18,843,938	18,862,782	18,881,644	18,900,526	18,919,427	18,938,346	18,957,284
price per dose			$15	$15	$16	$17	$17	$18	$19	$20	$20	$21
doses per inpatient			6	6	6	6	6	6	6	6	6	6
doses per outpatient			2	2	2	2	2	2	2	2	2	2
cost per inpatient			$90	$93	$96	$100	$104	$108	$113	$117	$122	$127
cost per outpatient			$30	$31	$32	$33	$35	$36	$38	$39	$41	$42
% inpatients treated			*2.0%*	*4.0%*	*6.0%*	*8.0%*	*10.0%*	*12.0%*	*14.0%*	*16.0%*	*18.0%*	*20.0%*
% outpatients treated			*2.0%*	*4.0%*	*6.0%*	*8.0%*	*10.0%*	*12.0%*	*14.0%*	*16.0%*	*18.0%*	*20.0%*
# inpatients			541,081	1,083,243	1,626,490	2,170,822	2,716,241	3,262,748	3,810,346	4,359,036	4,908,819	5,459,698
# outpatients			375,750	752,252	1,129,507	1,507,515	1,886,278	2,265,797	2,646,074	3,027,108	3,408,902	3,791,457
revenue for inpatients			$48.7	$100.4	$156.8	$217.7	$283.2	$353.8	$429.7	$511.3	$598.8	$692.7
revenue for outpatients			$11.3	$23.2	$36.3	$50.4	$65.6	$81.9	$99.5	$118.4	$138.6	$160.3
IV CR845 Revenue ($M)			**$60.0**	**$123.7**	**$193.1**	**$268.0**	**$348.8**	**$435.7**	**$529.2**	**$629.6**	**$737.4**	**$853.0**
Oral CR845												
Number of TRx's per year for opioids	240,000,000	242,400,000	244,824,000	247,272,240	249,744,962	252,242,412	254,764,836	257,312,485	259,885,609	262,484,465	265,109,310	267,760,403
% Treated with Oral CR845				*0.005%*	*0.05%*	*0.20%*	*0.25%*	*0.30%*	*0.35%*	*0.40%*	*0.45%*	*0.50%*
Patients Treated with Oral CR845				12,364	124,872	504,485	636,912	771,937	909,600	1,049,938	1,192,992	1,338,802
Annual Cost ($130/Rx/month)				$1,500	$1,500	$1,545	$1,591	$1,639	$1,688	$1,739	$1,791	$1,845
Oral CR845 End-User Sales ($M)				**$18.5**	**$187.3**	**$779.4**	**$1,013.6**	**$1,265.3**	**$1,535.6**	**$1,825.7**	**$2,136.7**	**$2,469.8**
Royalty Rate				*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*
Oral CR845 Royalty Revenue ($M)				**$3.7**	**$37.5**	**$155.9**	**$202.7**	**$253.1**	**$307.1**	**$365.1**	**$427.3**	**$494.0**
US Revenue			**$60.0**	**$127.4**	**$230.6**	**$423.9**	**$551.5**	**$688.8**	**$836.4**	**$994.8**	**$1,164.8**	**$1,347.0**
European Sales												
EU End-User Sales				**$60.0**	**$127.4**	**$230.6**	**$423.9**	**$551.5**	**$688.8**	**$836.4**	**$994.8**	**$1,164.8**
Royalty Rate				*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*	*20.0%*
EU Royalty Revenue ($M)				**$12.0**	**$25.5**	**$46.1**	**$84.8**	**$110.3**	**$137.8**	**$167.3**	**$199.0**	**$233.0**
TOTAL REVENUE ($M)			**$60.0**	**$139.4**	**$256.0**	**$470.0**	**$636.3**	**$799.1**	**$974.1**	**$1,162.1**	**$1,363.7**	**$1,579.9**
% growth				*132%*	*84%*	*84%*	*35%*	*26%*	*22%*	*19%*	*17%*	*16%*

Source: Canaccord Genuity estimates

POSTOPERATIVE PAIN MANAGEMENT

Surgical pain is a result of tissue inflammation or direct nerve injury. Tissue trauma releases local inflammatory signals to heighten sensitivity in the injured area or allodynia (misperception of pain to non-noxious stimuli). Pain perception can be directly interfered by medications that target signal propagation such as lidocaine, or anti-inflammatory agents like NSAIDs. Specifically, such effects can be achieved by blocking the neuronal transmission or release of substance P, calcitonin gene-related peptide, aspartate, glutamate and GABA.

Figure 6: Transduction, transmission and modulation targets for pain management

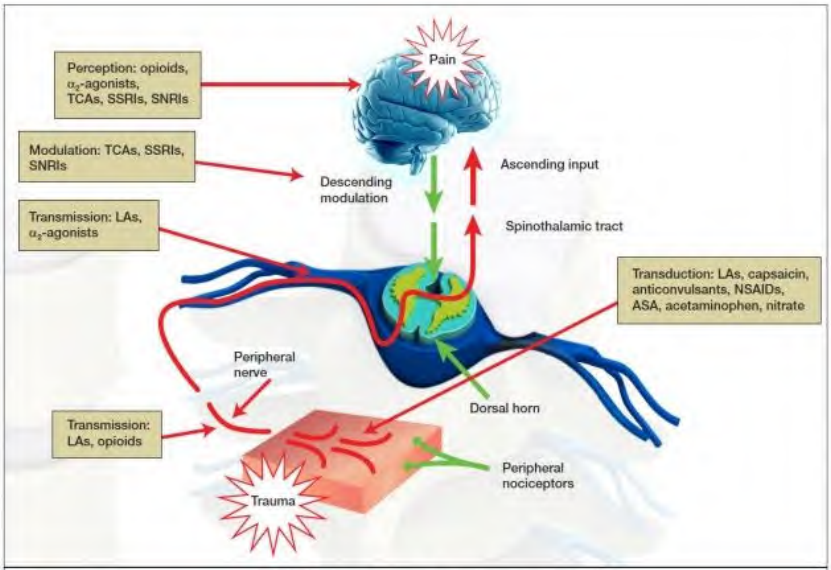


Figure 1. Transduction, transmission, and modulation targets of pain management drugs.
ASA, aspirin; **CNS**, central nervous system; **GABA**, γ-aminobutyric acid; **LAs**, local anesthetics; **NMDA**, *N*-methyl-D-aspartate; **NSAID**, non-steroidal anti-inflammatory drugs; **SC**, subcutaneous; **SNRI**, serotonin norephinephrine reuptake inhibitors; **SSRI**, selective serotonin reuptake inhibitors; **TCA**, tricyclic antidepressant

Source: Kehlet H and Dahl JB. *Anesth Analg.* 1993;77(5):1048-1056; Scholz J and Woolf CJ. *Nat Neurosci.* 2002;5(suppl):1062-1067; Gregory TB and Settles K. Perioperative Pain Plan: Why is it Needed: http://www.practicalpainmanagement.com/treatments/interventional/injections/perioperative-pain-plan-why-it-needed

Postoperative IV medications

1. Parenteral opioids
    - Morphine, hydromorphone and fentanyl are the most commonly used ones;
    - Fentanyl is ~80-100x more potent than morphine;
    - Use of acetaminophen or an NSAID with opioids reduces narcotic requirement;
    - Sufentanil, alfentanil and remifentanil are derivatives of fentanyl. Sufentanil is 10x more potent than fentanyl, and alfentanil is 1/5 to 1/10 the potency of fentanyl. Sufentanil isn't used very frequently due to

its high cost. Remifentanil isn't advised for patients who have renal or hepatic insufficiencies.

2. Exparel
    - A relatively new entrant to the market marketed by Pacira that is an extended release version of bupivacaine – an anesthetic, not an analgesic.
3. NSAIDs
    - Used to reduce the need for opioids;
    - Ketorolac, celecoxib, etoricoxib, parecoxib.
4. IV ketamine
    - A noncompetitive inhibitor of NMDA receptor;
    - Reduces sensitive to pain and opioid tolerance.
5. IV lidocaine
    - Major benefit is seen following abdominal surgery, leading to substantial improvements in pain scores in the immediate postoperative period;
    - Most common AE is CNS toxicity, but is rare.
6. IV acetaminophen
    - Used when oral or rectal administration is not possible;
    - Its addition to NSAID regimens can improve pain control;
    - Gained FDA approval by Cadence, which was recently purchased by Mallinkrodt.

Postoperative oral analgesics

1. Acetaminophen
2. Narcotics
    - Codeine, oxycodone
3. NSAIDs
    - Ibuprofen, diclofenac, ketoprofen
4. α-2 receptor agonists
    - Reduces effects of opioid withdrawal
    - Clonidine, dexmedetomidine
5. Anticonvulsants
    - Gabapentin and pregabalin are effective in managing chronic neuropathic pain;
    - Reduce opioid-related side effects;
    - One disadvantage is dose-dependent sedation.

OPIOID RECEPTORS

There are three types of opioid receptors expressed in the central nervous system (CNS) and peripheral nervous system (PNS) – μ, δ and κ. While μ receptor agonists are still the standard of care in treating mod-to-severe pain, they positively modulate mood via the release of dopamine within the ventral striatum, contributing to their abuse potential. Other unwanted side effects include respiratory depression, constipation, dependence and urinary retention.

Figure 7: Proposed distribution, pharmacology and function of subtypes of MOP, DOP and KOP receptors

Pharmacological subtypes	No. of genes	IUPHAR classification	Distribution	Possible discriminatory ligands	Other relevant ligands	Function/effect
μ_1	One	MOP	Brain, spinal cord, periphery	Naloxonazine (antagonist)	Morphine (agonist), TRIMU-5 (antagonist), β-FNA (antagonist), Dihydromorphine (agonist), Naloxone (antagonist), Nalorphine (anagonist) Codeine (agonist), Oxycodone (↓agonist)	Analgesia
μ_2		MOP	Brain, spinal cord, periphery	TRIMU-5 (agonist), M6G (agonist)	Morphine (↓ agonist)*, naloxone (↓ antagonist)*, Dihydromorphine (↓ agonist)*, β-FNA (antagonist), M6G (agonist), heroin (agonist), Naloxonazine (↓ antagonist)	Analgesia, GI transit, respiratory depression, itching
μ_3		MOP	Immune cells, amygdala, peripheral neural, CV endothelial cells	(opioid peptide insensitivity)	Morphine (↓agonist)*, naloxone (↓ antagonist)*, dihydromorphine (↓ agonist)*, β-FNA (antagonist), M6G (↓agonist)*	Various including NO release
δ_1	One	DOP	Brain, periphery	DPDPE (agonist), BNTX (antagonist), DALCE (antagonist)	Enkephalin (agonist), deltorphin-D (agonist), naltrexone (antagonist)	Analgesia, cardioprotection
δ_2		DOP	Brain and spinal	Deltorphin-II (agonist), DSLET (agonist) 5-NTII (antagonist), Naltriben (antagonist)	Enkephalin (agonist), deltorphin-D (agonist), naltrexone (antagonist), deltorphin-II (agonist)	Analgesia, cardioprotection, thermoregulation
κ_{1a}	One	KOP	Brain (nucleus accumbens, neocortex, cerebellum)	Dynorphin A (agonist), U50,488H (agonist)	nor-BNI (antagonist), U69,593 (agonist),	Analgesia, feeding
κ_{1b}		KOP		Dynorphin B (agonist), α-neoendorphin (agonist)		
κ_{2a}		KOP	Brain (hippocampus, thalamus, brainstem)	Leu-enkephalin (antagonist), oxycodone (agonist)	nor-BNI (↓antagonist)*, bremazocine (agonist)	Analgesia, diuresis, neuroendocrine
κ_{2b}		KOP				
$\kappa_3^{\#}$		KOP	Brain	NalBzOH	Nalorphine (agonist), nor-BNI (↓antagonist)*	Spinal analgesia, peripheral effects

Source: Dieis, N et al. Opioid receptor subtypes: fact or artifact? *British Journal of Anesthesia.* 107(1): 8-18 (2011)

On the other hand, κ receptor agonists don't elicit the aforementioned side effects, and may even have potential in treating inflammatory pain, neuropathic pain, visceral pain, and rheumatoid arthritis. Pfeiffer et al. studied extensively on the acute effects of the κ receptor agonist MR2033 and found that those treated with the lower dose reported increased anxiety and discomfort. Those on the higher dose reported severe temporal and spatial disturbances, hallucinations, depersonalization and loss of self-control. Therefore, while peripheral κ receptor agonists can be potent analgesics, central activation induces a slew of undesirable psychiatric side effects. To circumvent this, modifications that restrict CNS penetration was explored during the late 1980s and 1990s. These include ICI204448, GR94839 and asimadoline. Asimadoline's diffusion across the blood-brain barrier (BBB) is limited by p-glycoprotein. Clinically, patients who were on the higher dose (10mg orally) had reported increase in pain intensity post-surgery. Peptidic κ agonists E-2078 and SK-9709 were also developed under the hypothesis that a peptide would be less likely to cross the BBB; however, the peptidic fragments did cross. As a result, all these compounds were discontinued and no pure κ receptor agonists have yet to receive FDA approval.

CR845

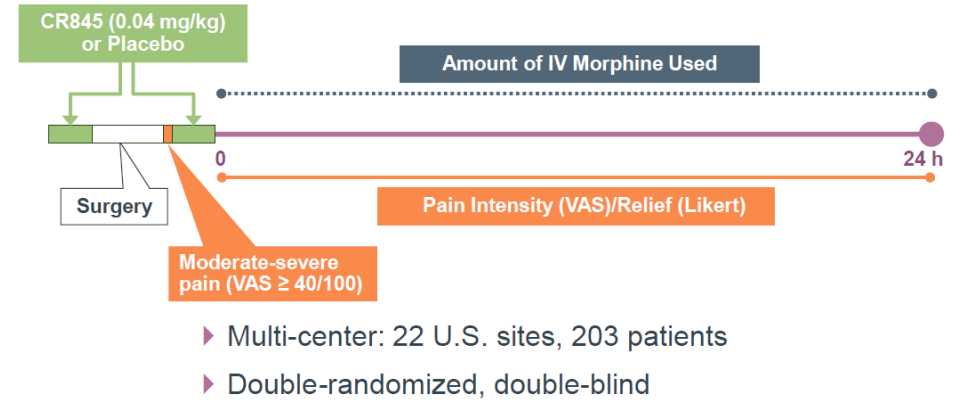
CR845 is a κ receptor agonist designed to act only in the periphery, thereby eliminating side effects and abuse associated with μ receptor activation. The IV formulation is Cara's most advanced product candidate intended for treating acute mod-to-severe pain in a hospital setting. The oral version would be used for chronic pain or/and as a step-down therapy in hospitalized patients prepared for discharge.

CR845's efficacy and safety have been demonstrated in 7 clinical trials, including four Ph1s and three Ph2s. The drug has been administered in >300 subjects at single or repeated doses ranging from 0.002mg/kg to 0.125mg/kg over 24hr in forms of IV infusion, IV bolus injection or oral capsule. CR845 was generally well-tolerated, with the most common AE being transient facial tingling, dizziness, fatigue and aquaresis. Most importantly, there weren't any cases of CNS-related side effects that are typical of the older generation of drugs in this class.

Phase 2b Clinical Data

CLIN2002 was a Ph2b trial conducted in female patients scheduled for laparoscopic hysterectomy under general anesthesia. Patients were dosed with 0.04mg/kg IV CR845 preoperatively, followed by surgery. If deemed medically stable and had pain intensity score ≥40 out of 100, these patients were re-randomized to receive placebo or one dose of IV CR845. Efficacy was measured using time-specific 24hr pain intensity difference, which was assessed by having the patient to rate their pain on a 100-point scale, where "0" is absence of pain and "100" is maximal pain. The summed pain intensity difference (SPID) is the time-weighed sum of all pain intensity difference scores, from the pretreatment level to 24hr after the pretreatment baseline measure in this particular trial. Of the 203 patients who participated in the trial, 183 received a post-operative dose.

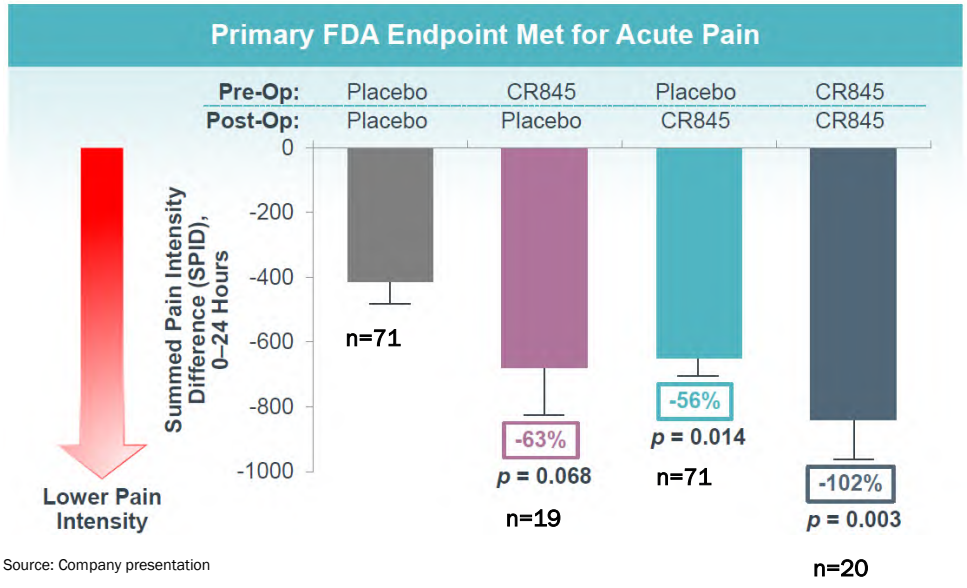
Figure 8: CLIN2002 trial design – laparoscopic hysterectomy



Source: Company presentation

Both CR845/CR845 and placebo/CR845 cohorts showed statistically significant pain reduction over 24hr, in comparison to the placebo/placebo group (P≤0.05). Moreover, the CR845/CR845 group exhibited statistically significant improvements for the 0-4, 0-8 and 0-16hr time intervals, and the CR845/placebo and placebo/CR845 groups exhibited statistically significant decreases in pain for the 0-8 and 0-16hr time intervals, compared to placebo. Given that most laparoscopic hysterectomies take less than 60 minutes to complete, this suggests that the CR845/C845 treatment paradigm could provide pain relief for up to 24hr.

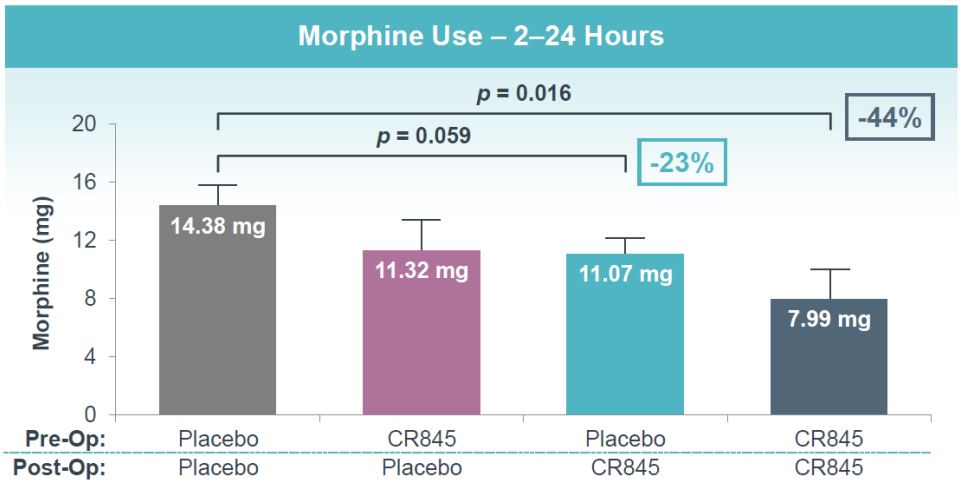
Figure 9: CR845 significantly reduced post-op pain



Source: Company presentation

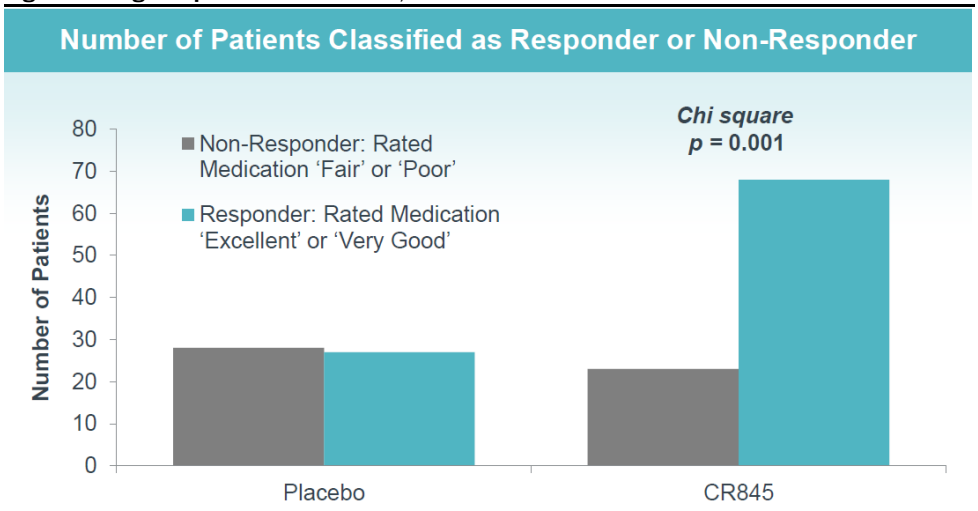
IV morphine was available as a rescue medication in the trial. As indicated in the figure below, CR845/CR845 and CR845/placebo groups used ~44% and ~23% less morphine respectively, relative to the placebo/placebo group.

Figure 10: Significantly reduced post-op narcotic use



Source: Company presentation

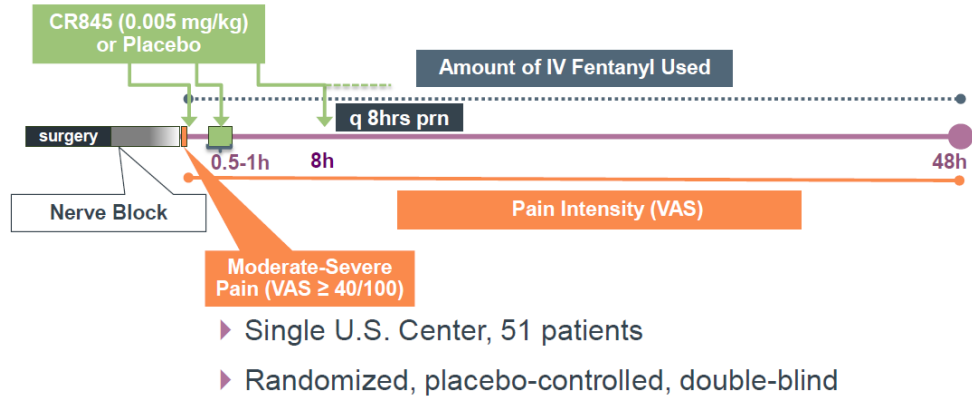
Figure 11: High response rate to CR845, reflective of a lack of CNS side effects



Source: Company presentation

CLN2003 was a 51-patient trial assessing the efficacy of CR845 in managing pain after bunionectomy (bunion removal). This procedure is generally very painful; typically the patient would need local anesthesia and continuous administration of opioids for several days. Patients were randomized into CR845 or placebo groups, in a 2:1 ratio after reporting moderate-to-severe pain as defined as pain intensity score of ≥40 on the 100-point scale. After an initial dose of 0.005mg/kg, additional doses were allowed every 8hr up to 48hr.

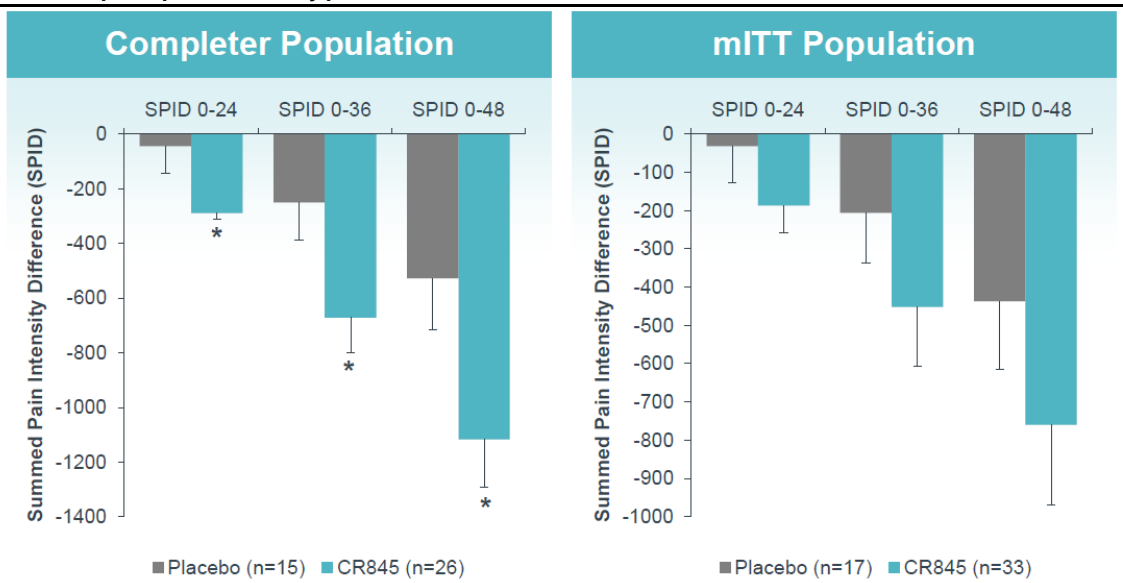
Figure 12: CLIN2003 trial design – bunionectomy, repeat dose postoperative treatment



Source: Company presentation

Results were analyzed for the "Completers" population, which includes only patients who completed the trial, and the modified Intent-to-Treat (mITT), population, which includes Completers and all patients who discontinued the trial (non-Completers, but received at least one dose of the drug). In the Completers group, CR845 treatment significantly reduced SPID score over the initial 24hr ($SPID_{0-24}$; $p<0.05$), over 36hr ($SPID_{0-36}$, $p<0.03$), and over 48hr ($SPID_{0-48}$, $p<0.03$), when compared to placebo. Although the Completer analysis is more indicative of the drug's efficacy, the mITT analysis reflects the variability that will be encountered, which would help to determine the actual number of patients needed for Ph3. Fentanyl was available upon request, but no difference in mean usage was seen between CR845 and placebo groups, suggesting that it's not as potent as fentanyl, but should be on-par with morphine.

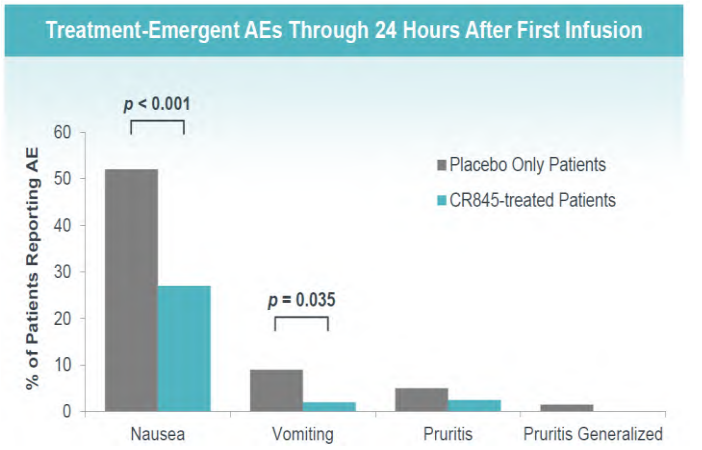
Figure 13: CR845 reduces post-op bunionectomy pain



Source: Company presentation

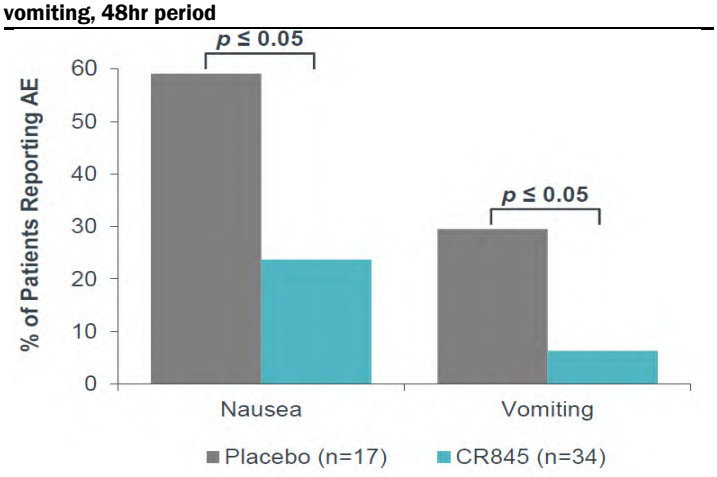
As a reflection of CR845's mechanism of action (a pure κ-opioid receptor agonist), those treated with the drug experienced lower incidences of opioid-related AEs – nausea, vomiting and pruritus. In the bunionectomy trial, although mean fentanyl use between the treatment groups wasn't noteworthy, it's believed that the resulting decrease in AEs is due to direct anti-nausea and anti-vomiting effects.

Figure 14: CR845 Ph2 hysterectomy study: significant reduction in opioid-related AEs



Source: Company presentation

Figure 15: CR825 Ph2 bunionectomy study: suppression of nausea and vomiting, 48hr period



Source: Company presentation

While there may be some concern over the fact that the mean plasma sodium level in CR845-treated patients were elevated by ~3% over 24hr from baseline level, we note that this is *not* supraphysiological. This can be easily remedied with oral water or sodium-free/low IV fluid.

Phase 3 clinical development plan

Cara is planning to advance into Ph3 in 2015 for IV CR845 in patients suffering from acute pain in hospital settings. Based on FDA's guidance for analgesic indications, two successful trials in nociceptive pain, one in visceral and one in nonvisceral pain, are generally considered to be adequate. Cara believes that the primary endpoint should be the change in SPID at either 24 or 48 hours compared to placebo; this is appropriate because: 1) recent trials of acute pain drugs that led to FDA approval used either SPID 24 or SPID 48 as endpoints; and 2) the FDA guided that "*for parenteral drugs used in the postoperative period, the primary efficacy period should be no less than 24 hours for one trial and 48 hours for the second trial".* In addition to the two pivotal Ph3s, Cara is considering running one supportive Ph3 with CR845 dosed before and after surgery in patients undergoing laparoscopic hysterectomy or bunionectomy. All patients will have access to morphine rescue medication, and trial designs will be similar to Ph2 trials:

- Randomized, double-blind and placebo-controlled;
- At least 600 female patients for postoperative pain after laparoscopic hysterectomy; at least 600 male or female patients for postoperative pain after bunionectomy; and at least 450 patients with postoperative pain following either laparoscopic hysterectomy or bunionectomy for the third trial;
- Patients will be assigned to receive one of three doses of IV CR845 or placebo;
- Second endpoints will include total pain relief score (TOPAR) at 24hr and/or 48hr, morphine use and occurrence of nausea and vomiting.

Figure 16: Postoperative pain drugs in development

Drug	Company	Mechanism of Action	Status
Oxycodon IR	Purdue Pharma	Formulation designed with the intent to deter intranasal and IV abuse	NDA submitted
Bupivacaine controlled release	Durect	Bupivacaine base (12%) in a controlled-release matrix	NDA submitted
Bupivacaine implant	Innocoll	Biodegradable and bioresorbable matrix of purified fibrillar collagen impregnated with bupivacaine	Ph3
Tapentadol IR	Grunenthal	μ-opioid receptor agonist and norepinephrine reuptake inhibitor	Ph3
Etoricoxib	Merck	COX-2 selective inhibitor	Ph3
Dexketoprofen/tramadol	Menarini Ricerche	NSAID, μ opioid receptor activator, serotonin and norepinephrine reuptake inhibitor	Ph3
Dexibuprofen	Gebro Pharma GmbH	NSAID	Ph3
Indomethacin	Iroko/iCeutica	NSAID	Ph3
Diclofenac injection	IBSA	New 1ml volume formulation	Ph3
Morphine-6-glucuronide	CeNeS Pharmaceuticals	Morphone metabolite	Ph3
Ketorolac intranasal	Daiichi Sankyo	NSAID	Ph3
OMS-103HP	Omeros Corp.	Amitriptyline, oxymetazoline, ketoprofen	Ph3
Meloxicam IV	Elan Drub Delivery	NSAID	Ph3
TRV 130	Trevena	IV G protein biased ligand that targets the μ opioid receptor	Ph2
Dexmedetomidine	Orion	Selective α2-agonist	Ph2
Cebranopadol	Grunenthal	Nociceptin/orphanin FQ peptide receptor and the μ opioid receptor activator	Ph2
E52862	Esteve	δ1 receptor antagonist	Ph2
AYX 1	Adynxx	EGR1 inhibitor	Ph2
SAF 312	Novartis	TRPV cation channel antagonist	Ph2
Ropivacaine ER	Encore Therapeutics	Non-liposomal phospholipid gel formulation of ropivacaine	Ph2
XEN2174	Xenome	Norepinephrine transporter inhibitor	Ph2
KAI1678	Amgen	Protein kinase C ε inhibitor	Ph2
CB189625	Cubist	Selective TRPA1 antagonist	Ph1
VVZ149	Vivozon	Serotonin 2A and glycine transporter 2 inhibitor	Ph1
BI 1026706	Boehringer Ingelheim	COX-2 inhibitor	Ph1
Celecoxib IV	Acusphere	NSAID	Ph1

Source: Bloomberg; Company websites; Canaccord Genuity Research

INTELLECTUAL PROPERTY

Both CR845 and CR701 were discovered in-house. Cara owns a total of six US patents covering composition of matter and methods of use for CR845, and is expected to expire no earlier than November 12, 2027. The company also owns two issued patents covering CR701, which are due after 2028.

Figure 17: Summary of Cara's issued US patents

Compound	Patent #	Name	Type	Expiration	Extensions
CR845	7,402,564	Synthetic peptide amides	Composition of matter	2022	N/A
	7,713,937	Synthetic peptide amides and dimeric forms thereof	Composition of matter	2024	N/A
	7,727,963	Synthetic peptide amides	Composition of matter	2024	N/A
	7,842,662	Synthetic peptide amide dimers	Composition of matter	2024	168 days
	8,217,007	Synthetic peptide amides	Method of use	2026	57 days
	8,236,766	Uses of synthetic peptide amides	Method of use	2026	360 days
	8,486,894	Uses of synthetic peptide amides	Method of use	2026	417 days
	8,536,131	Synthetic peptide amides and dimers thereof	Composition of matter	2027	86 days
CR701	7,517,874	Substituted imidazo[1,5-a][1,4]diazepines and imidazo[1,5-a]pyrazines as cannabinoid receptor agonists for the treatment of pain	Composition of matter	2023	N/A
	8,431,565	Substituted imidazoheterocycles	Method of use	2027	945 days

Source: Company reports; USPTO

MANAGEMENT

Derek Chalmers, Ph.D. – CEO, President and Director

Dr. Chalmers is one of the founders of Cara. He has 19+ years of experience in the biotechnology industry. He co-founded Arena Pharmaceuticals and served as its VP and Executive Director from 1997 to 2004.

Michael E. Lewis, Ph.D. – Chief Scientific Advisor

Dr. Lewis is one of the founders of Cara. He has five years of experience in opioid research at NIH and the University of Michigan. He is one of the co-founders of Cephalon and Adolor Corporation. He is also an inventor or a co-inventor of 15 issued US patents.

Frédérique Menzaghi, Ph.D. – VP Research and Development

Dr. Menzaghi is one of the founders of Cara. She has 20+ years of drug development and management experience in biotechnology. Prior to Cara, she held business development and research roles at Psychogenics Inc., Arena Pharmaceuticals, Eli Lilly, Merck and Johnson & Johnson.

Josef Schoell – CFO

Mr. Schoell joined Cara in 2006. He has 20+ years of financial and accounting experience. Prior to Cara, he was a consultant with Robert Half Management Resources. From 1995 to 2002, he was the CFO and VP Finance of American Biogenetic Sciences.

Joseph Stauffer – Chief Medical Officer

From 2004 to 2009, Dr. Stauffer was the CMO at Alpharma Pharmaceuticals. Previously, he was the Global Medical Director at Abbott. Dr. Stauffer completed his residency training in Anesthesiology and Critical Care Medicine at Johns Hopkins University Hospital.

Figure 18: Cara balance sheet

(In millions)	Dec-12	Dec-13	Mar-14	Jun-14	Sep-14
ASSETS					
Current Assets:					
Cash & cash equivalents	1.1	12.4	67.0	62.8	58.4
Accounts receivables	0.0	0.1	0.0	0.5	0.1
Inventory	0.0	0.0	0.0	0.0	0.0
Prepaid expenses & other current assets	0.1	2.1	1.1	1.7	0.9
Total Current Assets	1.2	14.6	68.2	65.1	59.4
Property, Plant, & Equipment, net	3.6	2.8	2.6	2.4	2.3
Restricted cash	0.7	0.7	0.7	0.7	0.7
TOTAL ASSETS	**5.5**	**18.1**	**71.6**	**68.2**	**62.4**
Working Capital					
LIABILITIES & STOCKHOLDERS EQUITY					
Current Liabilities					
Accounts payable and accrued expenses	0.9	2.0	2.3	2.5	4.1
Notes payable, net of discount - related parties	0.5	0.0	0.0	0.0	0.0
Current portion of deferred revenue	0.0	3.5	3.4	3.1	1.9
Current portion of long-term debt	0.3	0.0	0.0	0.0	0.0
Total current liabilities	1.7	5.4	5.8	5.6	6.1
Long-term Liabilities					
Related party debt, including accrued interest	1.4	1.1	1.1	1.0	0.9
Other liabilities	0.0	0.0	0.0	0.0	0.0
Total Liabilities	3.1	6.6	6.8	6.6	7.0
Stockholders' Equity					
Preferred stock	58.5	65.6	0.0	0.0	0.0
Common stock	0.0	0.0	0.0	0.0	0.0
Additional paid-in capital	1.2	8.4	130.5	131.0	131.3
Accumulated deficit	(59.4)	(62.5)	(65.8)	(69.5)	(76.0)
Other	2.1	0.0	0.0	0.0	0.0
Treasury Stock	0.0	0.0	0.0	0.0	0.0
Total stockholders' equity	2.4	11.5	64.7	61.6	55.3
TOTAL LIABILITITES AND EQUITY	**5.5**	**18.1**	**71.6**	**68.2**	**62.4**

Source: Company reports

Figure 19: Cara statement of cash flow

(In millions except per share amount)	Dec-12	Dec-13	Mar-14	Jun-14	Sep-14
	12 mo	12 mo	3 mo	6 mo	9 mo
CASH FLOWS FROM OPERATING ACTIVITIES					
Net income (loss)	(6.3)	(4.0)	(3.4)	(7.0)	(13.6)
Depreciation & Amortization	1.0	0.8	0.2	0.4	0.6
Other non-cash adjustments	0.4	3.8	0.4	0.7	0.8
Amortization of financing costs	0.0	0.1	0.0	0.0	0.0
Accrued interest and amortization of beneficial conversion feature on promissory notes	0.0	3.6	0.0	0.0	0.0
Loss/(gain) on sale of property and equipment	0.3	0.0	0.0	0.0	0.0
Share-based compensation	0.1	0.1	0.4	0.8	1.0
Change in fair value of liability under license agreement	(0.0)	(0.0)	0.0	0.0	0.0
Other	0.0	0.0	0.0	(0.1)	(0.2)
Change in opearing assets & liabilities	(1.1)	2.2	(0.3)	(1.4)	0.3
Restricted Cash	0.3	0.0	0.0	0.0	0.0
Accounts receivable	0.0	(0.0)	0.0	(0.5)	(0.0)
Prepaid expenses & other assets	0.1	(1.7)	(0.4)	(0.6)	0.2
Accounts payable and accrued expenses	(1.3)	0.7	0.2	0.1	1.6
Deferred revenue	0.0	3.5	(0.1)	(0.4)	(1.5)
Deferred rent	(0.2)	(0.2)	(0.1)	0.0	0.0
Net Cash from Operations	**(6.0)**	**2.8**	**(3.1)**	**(7.3)**	**(11.8)**
CASH FLOWS FROM INVESTING ACTIVITIES					
Purchases of fixed assets, net	0.5	(0.0)	0.0	(0.0)	(0.0)
Purchase of short-term investments, net	0.0	0.0	0.0	0.0	0.0
Net Cash from Investing	0.5	(0.0)	0.0	(0.0)	(0.0)
CASH FLOWS FROM FINANCING ACTIVITIES					
Proceeds from issuance of preferred stock	0.4	7.6	0.0	0.0	0.0
Proceeds from issuance of common stock and options excercises	0.1	0.0	0.0	0.0	0.1
Payment of long term debt principle	(0.4)	(0.3)	0.0	0.0	0.0
Proceeds from secured promissory notes & credit facility	2.5	1.5	0.0	0.0	0.0
Proceeds from public offering, net	0.0	0.0	57.8	57.8	57.8
Other credit/debt financing	0.0	(0.3)	0.0	0.0	0.0
Financing Costs	(0.0)	(0.1)	0.0	0.0	0.0
Net Cash from Financing	2.5	8.4	57.8	57.8	57.9
Foreign exchange rate effect	0.0	0.0	0.0	0.0	0.0
Net Increase in Net Cash	**(3.0)**	**11.2**	**54.7**	**50.5**	**46.0**
Net Cash at beginning of year	4.1	1.1	12.4	12.4	12.4
Short term investments.					
Net Cash/Investments, End of Period	**1.1**	**12.4**	**67.0**	**62.8**	**58.4**

Source: Company reports

Figure 20: Cara complete P&L

	TOTAL REVS	COGS	Gross Profit	Margin % rev	R&D	% rev	SG&A	% rev	Total OpEx	Op Income	% rev	Total	Pretax Inc	% rev	Non-GAAP Total Adjust.	Inc. Tax Rate		GAAP Net Income	Adj. Net Income	% rev	GAAP EPS (diluted)	Adj. EPS (diluted)	Diluted shares
2012	**$0.2**	0.0	0.2	100%	4.6	2583%	2.8	1589%	7.4	(7.2)	nm	(0.1)	(7.3)	nm	0.0	0.0	0%	(7.3)	(7.3)	nm	**($2.21)**	**($2.20)**	3.3
2013	**$12.0**	0.0	12.0	100%	8.7	73%	3.5	29%	12.2	(0.2)	nm	(3.8)	(4.0)	nm	0.1	0.0	0%	(3.1)	(3.0)	nm	**($0.74)**	**($0.72)**	4.1
2014E	**$3.3**	0.0	3.3	100%	19.1	586%	5.9	181%	25.0	(21.7)	nm	0.1	(21.6)	nm	0.8	0.0	0%	(21.5)	(20.8)	nm	**($1.01)**	**($0.98)**	21.0
1QE	**$1.0**	0.0	1.0	100%	7.5	nm	2.0	nm	9.5	(8.5)	nm	0.0	(8.5)	nm	0.3	0.0	0%	(8.5)	(8.2)	nm	**($0.37)**	**($0.35)**	23.2
2QE	**$1.0**	0.0	1.0	100%	8.0	nm	2.0	nm	10.0	(9.0)	nm	0.0	(9.0)	nm	0.3	0.0	0%	(9.0)	(8.7)	nm	**($0.38)**	**($0.37)**	23.4
3QE	**$1.0**	0.0	1.0	100%	8.5	nm	2.0	nm	10.5	(9.5)	nm	0.0	(9.5)	nm	0.3	0.0	0%	(9.5)	(9.2)	nm	**($0.40)**	**($0.39)**	23.6
4QE	**$1.0**	0.0	1.0	100%	9.0	nm	2.0	nm	11.0	(10.0)	nm	0.0	(10.0)	nm	0.3	0.0	0%	(10.0)	(9.7)	nm	**($0.26)**	**($0.26)**	37.6
2015E	**$4.0**	0.0	4.0	100%	33.0	nm	8.0	nm	41.0	(37.0)	nm	0.1	(36.9)	nm	1.2	0.0	0%	(36.8)	(35.7)	nm	**($1.41)**	**($1.37)**	27.0
2016E	**$5.0**	0.0	5.0	100%	50.0	1000%	15.0	300%	65.0	(60.0)	nm	0.1	(59.9)	nm	1.9	0.0	0%	(59.8)	(58.0)	nm	**($2.08)**	**($2.01)**	38.6
2017E	**$65.0**	12.0	53.0	82%	55.0	85%	50.0	77%	105.0	(52.0)	nm	0.1	(51.9)	nm	3.1	0.0	0%	(51.9)	(48.8)	nm	**($1.28)**	**($1.20)**	40.6
2018E	**$137.7**	18.5	119.1	87%	55.6	40%	60.0	44%	115.6	3.6	nm	0.1	3.7	nm	3.4	0.0	0%	3.7	7.1	nm	**$0.09**	**$0.17**	41.6
2019E	**$256.0**	19.3	236.7	92%	56.1	22%	75.0	29%	131.1	105.6	nm	0.1	105.7	nm	3.9	0.0	0%	105.8	109.7	nm	**$2.49**	**$2.58**	42.5
2020E	**$470.0**	26.8	443.2	94%	56.7	12%	90.0	19%	146.7	296.6	nm	0.1	296.7	63.1%	3.2	74.2	25%	222.6	225.8	48.0%	**$5.14**	**$5.21**	43.3
2021E	**$636.3**	34.9	601.4	95%	57.2	9%	108.0	17%	165.2	436.2	68.6%	0.1	436.3	68.6%	3.1	152.7	35%	283.7	286.8	45.1%	**$6.42**	**$6.49**	44.2
2022E	**$799.1**	43.6	755.5	95%	57.8	7%	129.6	16%	187.4	568.1	71.1%	0.1	568.2	71.1%	3.4	0.0	38%	568.3	571.7	71.5%	**$12.61**	**$12.68**	45.1
2023E	**$974.1**	52.9	921.2	95%	58.4	6%	155.5	16%	213.9	707.3	72.6%	0.1	707.4	72.6%	4.0	268.8	38%	438.6	442.6	45.4%	**$9.54**	**$9.63**	46.0
2024E	**$1,162.1**	63.0	1099.1	95%	59.0	5%	186.6	16%	245.6	853.5	73.4%	0.1	853.6	73.5%	4.6	324.4	38%	529.2	533.8	45.9%	**$11.29**	**$11.38**	46.9
2025E	**$1,363.7**	73.7	1290.0	95%	59.6	4%	223.9	16%	283.5	1006.5	73.8%	0.1	1006.6	73.8%	5.3	382.5	38%	624.1	629.4	46.1%	**$13.05**	**$13.16**	47.8
2026E	**$1,579.9**	85.3	1494.6	95%	60.2	4%	268.7	17%	328.9	1165.7	73.8%	0.1	1165.8	73.8%	6.1	443.0	38%	722.8	728.9	46.1%	**$14.82**	**$14.94**	48.8
% Growth																							
14E/13E					120.0%		67.5%		104.9%														
15E/14E					72.7%		35.8%		64.0%														
16E/15E					51.5%		87.5%		58.5%														
17E/16E					10.0%		233.3%		61.5%														
18E/17E	**111.9%**	54.7%	124.8%		1.0%		20.0%		10.0%														
19E/18E	**86%**	4.1%	98.8%		1.0%		25.0%		13.5%														
20E/19E	**84%**	38.8%	87.2%		1.0%		20.0%		11.9%														
21E/20E	**35%**	30.1%	35.7%		1.0%		20.0%		12.7%														
22E/21E	**26%**	24.9%	25.6%		1.0%		20.0%		13.4%	30.2%			30.2%					100.3%	99.3%		96.4%	95.4%	
23E/22E	**22%**	21.5%	21.9%		1.0%		20.0%		14.1%	24.5%			24.5%					-22.8%	-22.6%		-24.3%	-24.1%	
24E/23E	**19%**	19.0%	19.3%		1.0%		20.0%		14.8%	20.7%			20.7%					20.7%	20.6%		18.3%	18.3%	
25E/24E	**17%**	17.1%	17.4%		1.0%		20.0%		15.4%	17.9%			17.9%					17.9%	17.9%		15.6%	15.6%	
26E/25E	**16%**	15.7%	15.9%		1.0%		20.0%		16.0%	15.8%			15.8%					15.8%	15.8%		13.5%	13.5%	

Source: Canaccord Genuity estimate; Company reports

Figure 21: Cara summary P&L

($ In millions, except per share amount)

Year End: December 31	2013	1Q14	2Q14	3Q14	4Q14E	2014E	1Q15E	2Q15E	3Q15E	4Q15E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E
IV CR845	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$60.0	$123.7	$193.1	$268.0	$348.8	$435.7	$529.2	$629.6	$737.4	$853.0
Oral CR845 Royalty	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$37.5	$155.9	$202.7	$253.1	$307.1	$365.1	$427.3	$494.0
CR845 EU Royalty	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$12.0	$25.5	$46.1	$84.8	$110.3	$137.8	$167.3	$199.0	$233.0
Others	$12.0	$0.2	$1.0	$1.1	$1.0	$3.3	$1.0	$1.0	$1.0	$1.0	$4.0	$5.0	$5.0	$2.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Total Revenue	**$12.0**	**$0.2**	**$1.0**	**$1.1**	**$1.0**	**$3.3**	**$1.0**	**$1.0**	**$1.0**	**$1.0**	**$4.0**	**$5.0**	**$65.0**	**$137.7**	**$256.0**	**$470.0**	**$636.3**	**$799.1**	**$974.1**	**$1,162.1**	**$1,363.7**	**$1,579.9**
COGS	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12.0	18.5	19.3	26.8	34.9	43.6	52.9	63.0	73.7	85.3
Gross Profit	12.0	0.2	1.0	1.1	1.0	3.3	1.0	1.0	1.0	1.0	4.0	5.0	53.0	119.1	236.7	443.2	601.4	755.5	921.2	1,099.1	1,290.0	1,494.6
Gross Margin	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*81.5%*	*86.5%*	*92.5%*	*94.3%*	*94.5%*	*94.5%*	*94.6%*	*94.6%*	*94.6%*	*94.6%*
SG&A	3.5	1.4	1.5	1.5	1.5	5.9	2.0	2.0	2.0	2.0	8.0	15.0	50.0	60.0	75.0	90.0	108.0	129.6	155.5	186.6	223.9	268.7
R&D	8.7	2.2	3.2	6.2	7.5	19.1	7.5	8.0	8.5	9.0	33.0	50.0	55.0	55.6	56.1	56.7	57.2	57.8	58.4	59.0	59.6	60.2
Adj. Operating Income	**($0.2)**	**($3.4)**	**($3.7)**	**($6.6)**	**($8.0)**	**($21.7)**	**($8.5)**	**($9.0)**	**($9.5)**	**($10.0)**	**($37.0)**	**($60.0)**	**($52.0)**	**$3.6**	**$105.6**	**$296.6**	**$436.2**	**$568.1**	**$707.3**	**$853.5**	**$1,006.5**	**$1,165.7**
Adj. Operating Margin																	*68.6%*	*71.1%*	*72.6%*	*73.4%*	*73.8%*	*73.8%*
Non-Op	(3.8)	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Tax Rate						.														38.0%	38.0%	38.0%
Adj. Net Income	(3.0)	(3.3)	(3.4)	(6.4)	(7.7)	(20.8)	(8.2)	(8.7)	(9.2)	(9.7)	(35.7)	(58.0)	(48.8)	7.1	109.7	225.8	286.8	571.7	442.6	533.8	629.4	728.9
Net Margin																*48.0%*	*45.1%*	*71.5%*	*45.4%*	*45.9%*	*46.1%*	*46.1%*
GAAP EPS (diluted)	($0.74)	($0.22)	($0.16)	($0.29)	($0.35)	($1.01)	($0.37)	($0.38)	($0.40)	($0.26)	($1.41)	($2.08)	($1.28)	$0.09	$2.49	$5.14	$6.42	$12.61	$9.54	$11.29	$13.05	$14.82
Adjusted EPS (diluted)	**($0.72)**	**($0.21)**	**($0.15)**	**($0.28)**	**($0.34)**	**($0.98)**	**($0.35)**	**($0.37)**	**($0.39)**	**($0.26)**	**($1.37)**	**($2.01)**	**($1.20)**	**$0.17**	**$2.58**	**$5.21**	**$6.49**	**$12.68**	**$9.63**	**$11.38**	**$13.16**	**$14.94**
Diluted Shares (M)	4.1	15.7	22.6	22.7	22.9	21.0	23.2	23.4	23.6	37.6	27.0	38.6	40.6	41.6	42.5	43.3	44.2	45.1	46.0	46.9	47.8	48.8
Year-over-Year Growth																						
IV CR845														106%	56%	39%	30%	25%	21%	19%	17%	16%
Oral CR845																316%	30%	25%	21%	19%	17%	16%
CR845 EU Royalty															112%	81%	84%	30%	25%	21%	19%	17%
Total Revenue														**112%**	**86%**	**84%**	**35%**	**26%**	**22%**	**19%**	**17%**	**16%**
Gross Profit													*960%*	*125%*	*99%*	*87%*	*36%*	*26%*	*22%*	*19%*	*17%*	*16%*
SG&A						*68%*					*36%*	*88%*	*233%*	*20%*	*25%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
R&D						*120%*					*73%*	*52%*	*10%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*
Operating Income																	*47%*	*30%*	*24%*	*21%*	*18%*	*16%*
Net Income																	*27%*	*99%*	*(23%)*	*21%*	*18%*	*16%*
Adj. EPS																	***25%***	***95%***	***(24%)***	***18%***	***16%***	***14%***

Source: Canaccord Genuity estimates; Company reports

INVESTMENT RISKS

Clinical risk – Much of Cara's success is dependent on the approvability of the lead product IV CR845. There's no guarantee that the drug will meet the primary endpoints of the three planned Ph3 trials or show an acceptable safety profile.

Regulatory risk – While CR845 has shown to be safe and tolerable thus far, the FDA may still determine that CR845-based products require a Risk Evaluation and Mitigation Strategy (REMS) programs. If required, such a program would lead to higher costs of commercialization. In addition, currently approved μ opioids are Schedule II drugs. Even though the Human Abuse Liability trial showed that CR845 exhibited no abuse potential, it may still be classified as a scheduled substance.

Commercial risk – Upon approval, Cara plans to build its own hospital-focused marketing, sales and distribution team. If the drug doesn't achieve broad market acceptance, sales will be limited.

Financing risk – Cara ended Q3/14 with $58.4M in cash and equivalents, which according to management, is sufficient to fund operations for another 18 months. Given that the Ph3s will result in increases in cash burn, additional capital may be needed. In the event that adequate funds can't be obtained, the company may need to reduce or eliminate R&D activities or commercial efforts.

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Target Price / Valuation Methodology:

Cara Therapeutics - CARA:

We use a discounted P/E model to derive our $20 price target; we apply a 25x multiple to our 2020 EPS estimate of $5.21 discounted at 45% for 5 years.

Risks to achieving Target Price / Valuation:

Cara Therapeutics - CARA:

Clinical risk -- Cara's planned Phase 3 trials may not be successful. 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. 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.

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Rating	Coverage Universe		IB Clients
	#	%	%
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Sell	42	3.90%	0%
Speculative Buy	53	4.92%	60.38%
	1077*	100.0%	

*Total includes stocks that are Under Review

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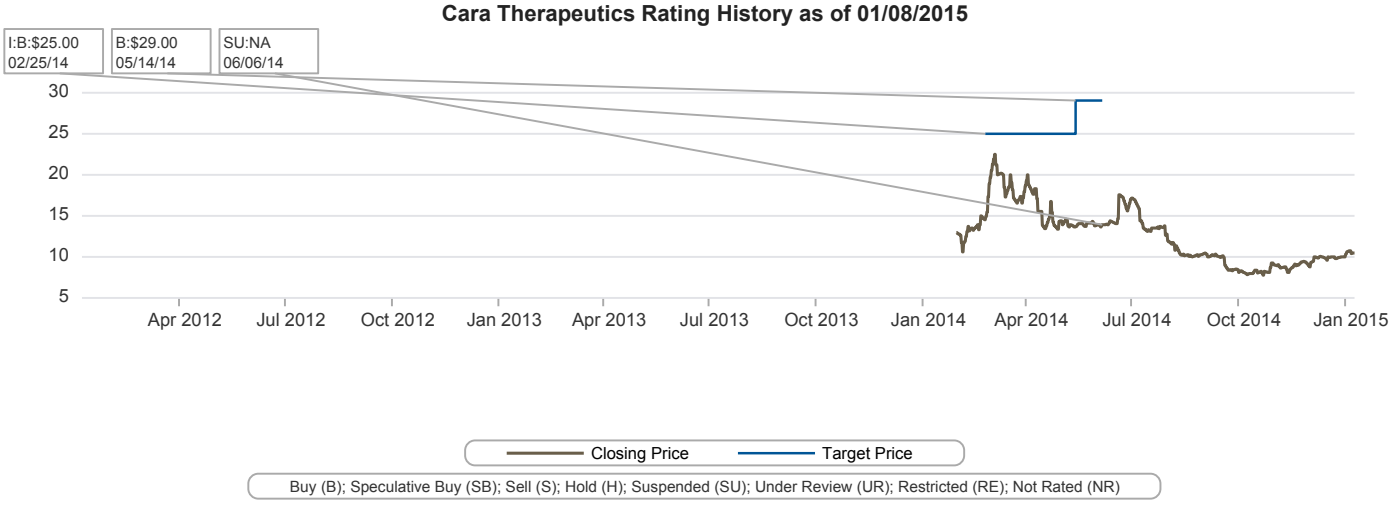

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