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CB-5945 (Formerly ADL5945), a Potent Orally Bioavailable Peripheral Opioid Receptor Antagonist, Improves Bowel Motility With a Low Incidence and Severity of Gastrointestinal Adverse Effects in a Dose-dependent Manner; Results of 2 Phase 2 Trials in Patients with Opioid-induced Constipation

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ABSTRACT

Opioids are a mainstay for managing chronic pain, however central and peripheral adverse effects often limit their utility. Mu opioid receptor (MOR) binding is primarily responsible for opioid-induced constipation (OIC) and gastrointestinal (GI) symptoms; the delta OR (DOR) may also play a similar role.
CB-5945, a MOR and DOR antagonist, is under development for the treatment of OIC and associated abdominal symptoms in patients on chronic opioid therapy for persistent noncancer pain.

Randomized, double-blind, placebo-controlled, Phase 2 studies compared CB-5945 dosed once- (0.25mg QD) or twice-daily (0.1mg BID and 0.25mg BID) with placebo based on spontaneous bowel movement (SBM) change over treatment weeks 1-4. Other endpoints included overall SBM responders (patient with ≥3 SBMs/week and ≥1 SBM/week from baseline for 3 of 4 weeks), opioid consumption, pain scores, and adverse events (AEs).

131 patients (BID) and 81 patients (QD) were randomized. Mean OIC duration ranged from 3.4-6.9 years; back pain was the most common pain condition. Mean SBM change from baseline was 1.44 (placebo BID), 1.40 (placebo QD), 1.96 (0.1mg BID), 2.58 (0.25mg QD), and 3.42 (0.25mg BID), with a mean treatment difference change of 0.51 (*P*=0.2979), 1.18 (*P*=0.0118), and 1.98 (*P*=0.0003) in the 0.1-mg BID, 0.25-mg QD, and 0.25-mg BID groups, respectively. 26-28% of patients (placebo cohorts), 28% (0.1mg BID), 43% (0.25mg QD), and 56% (0.25mg BID; *P*=0.005) were overall responders. There were no changes in opioid consumption or pain scores and no evidence of CNS effects. The most commonly reported AEs were abdominal pain (QD; 10% across groups) and upper respiratory tract infection (BID; placebo,14%; 0.1mg,7%; 0.25mg,7%). Incidence of GI-related AEs was low and comparable across groups; most of mild severity.

Significant, clinically-meaningful improvement in SBM frequency was observed after CB-5945 treatment, with the 0.25-mg BID dose demonstrating the most favorable benefit-to-risk profile. Phase 3 trials are planned.

INTRODUCTION

- Chronic noncancer pain (CNCP) is common and accounts for a large burden on the healthcare system [1]
- Opioids play integral part in multimodal management strategy for CNCP[1]
  - Use has substantially increased over the past decade, in part based on supportive guidelines and the recognition that pain is frequently inadequately treated[1,2]
- Although opioids can be effective for managing chronic pain, they are associated with both central and peripheral side effects that can limit their utility[2,3]
- Constipation is the most common, and often most debilitating peripheral side effect associated with chronic opioid use (opioid-induced constipation; OIC)[2-5]
  - ≤ 80% of patients experience ≥ 1 side effects consistent with opioid-induced bowel dysfunction (constipation, nausea, vomiting, abdominal bloating/pain and gastro-esophageal reflux)
  - Tolerance usually does not develop to OIC and associated symptoms
  - May lead to pain management disruptions
  - Adverse effect on Health-related quality of life
  - Long-term treatment options are limited
- Mu opioid receptor (MOR) binding is primarily responsible for OIC and associated gastrointestinal (GI) symptoms[6,7]
  - Delta OR (DOR) may also play a role
- CB-5945, a MOR and DOR antagonist, is under development for OIC and associated abdominal symptoms in CNCP patients on long-term opioid therapy

OBJECTIVE

- To compare twice daily (0.10 and 0.25 mg BID) and once-daily (0.25 mg QD) dosing of CB-5945 with placebo for the treatment of OIC in patients on opioid therapy for chronic noncancer pain

METHODS

- 2 randomized, double-blind, placebo-controlled trials **(Figure 1)**

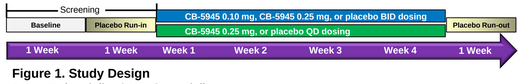

Figure 1. Study Design
BID = Twice daily; QD = Once daily.

- Primary endpoint
  - Change from baseline in weekly average spontaneous bowel movements (SBMs) during 4-week treatment period compared with placebo
- Secondary endpoints included
  - SBM responders
  - Spontaneous complete bowel movement (SCBMs)
  - Rescue laxative use
- Safety was monitored via adverse event collection, opioid consumption, pain scores, Clinical Opiate Withdrawal Scales (COWS), Subjective Opiate Withdrawal Scales (SOWS), laboratory tests, vital signs, and ECG readings
- A recently developed patient-reported outcomes measure (Chronic Opioid-related Gastrointestinal GI Symptom Scale; CORGISS) designed to assess opioid-related GI symptoms was included for validation

RESULTS

- 212 patients were included in both studies **(Table 1)**
  - Morphine equivalent total daily dose ranged from 30 to 1,284 mg
  - Mean duration of OIC ranged from 3.4 – 6.9 years
  - Back pain was the most common pain condition (57%)

Table 1. Baseline Demographics

Characteristic	Placebo BID (n = 43)	CB-5945 0.10 mg BID (n = 43)	CB-5945 0.25 mg BID (n = 45)	Placebo QD (n = 41)	CB-5945 0.25 mg QD (n = 40)
Age, mean years ± SD	49.7 ± 11.06	50.3 ± 11.98	49.6 ± 9.75	51.9 ± 10.54	51.6 ± 11.00
Race, n (%) White Black Asian	 31 (72.1) 12 (27.9) 0	 30 (69.8) 11 (25.6) 2 (4.7)	 31 (68.9) 14 (31.1) 0	 27 (65.9) 13 (31.7) 1 (2.4)	 29 (72.5) 11 (27.5) 0
Males, n (%)	20 (46.5)	23 (53.5)	25 (55.6)	13 (31.7)	12 (30.0)
BMI, mean kg/m^2 ± SD	30.9 ± 5.64	30.7 ± 5.87	29.6 ± 5.05	31.7 ± 6.51	30.2 ± 5.26
METDD, mean mg ± SD	248 ± 280.2	273 ± 275.3	271 ± 303.9	226 ± 304.6	178 ± 182.6

BID = Twice daily; BMI = Body mass index; METDD = Morphine equivalent total daily dose; SD = Standard deviation.

Primary Efficacy Results

- Mean change in SBMs from baseline for treatment weeks 1 – 4 was 1.44 in the placebo BID group, 1.40 in the placebo QD group, 1.96 in the 0.1-mg BID group, 2.58 in the 0.25-mg QD group, and 3.42 in the 0.25-mg group, with a significant mean treatment difference changes associated with the 0.25 mg QD and 0.25 mg BID doses **(Figure 2)**

RESULTS (Cont.)

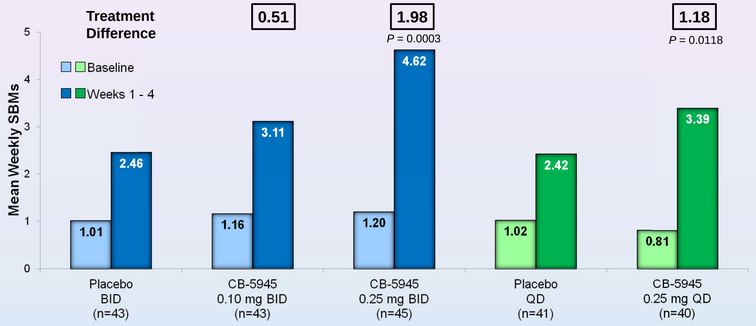

Figure 2. Treatment Difference in SBM Frequency
BID = Twice daily; QD = Once daily; SBM = Spontaneous bowel movement.
Note: Treatment difference = Mean of the individual changes in treatment differences (CB-5945 – placebo).

Secondary Efficacy Results

- 30% absolute difference compared with placebo in overall SBM responders in the 0.25-mg BID group **(Figure 3)**
  - Proportion of weekly responders for the 0.25-mg BID group remained consistent, ranging from 58% to 69% across 4 weeks of treatment

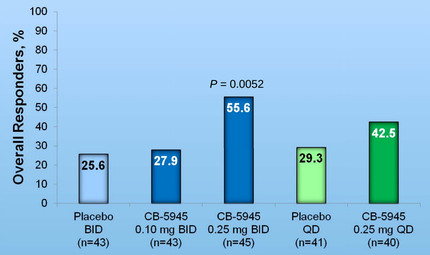

Figure 3. Proportion of Overall SBM Responders
BID = Twice daily; QD = Once daily; SBM = Spontaneous bowel movement.
Overall SBM responder = patients with ≥ 3 SBMs/week and an increase of at least 1 SBM over baseline for 3 of the 4 weeks of treatment.

- Mean change in SCBMs from baseline was 0.78 in the placebo BID group, 0.52 in the placebo QD group, 0.97 in the 0.1-mg BID group, 1.31 in the 0.25 QD group, and 2.24 in the 0.25-mg BID group, with a significant mean treatment difference change in the 0.25 -mg BID and 0.25-mg QD groups **(Figure 4)**

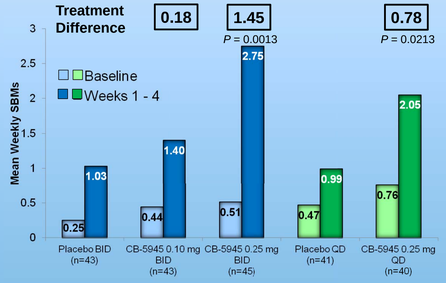

Figure 4. Treatment Difference in SCBM Frequency
BID = Twice daily; QD = Once daily; SCBM = Spontaneous complete bowel movement.

- Rescue laxative use 14% in the placebo BID group compared with 7% in the 0.25-mg BID group

Safety Results

- Overall, 27% of patients in the placebo groups, 23% in the 0.1 mg BID, 24% in the 0.25 mg BID, and 40% in the 0.25 mg QD groups had 1 or more treatment-emergent AEs (TEAEs)

Safety Results (Cont.)

- Upper respiratory tract infection was the most commonly reported TEAE in the BID trial (14%, placebo BID; 7%, 0.1 mg BID; 7%, 0.25 mg BID) and abdominal pain was the most commonly reported TEAE in the QD trial (10% in each cohort)
- Majority mild
- 2 serious AEs occurred in the 0.25-mg BID group ≥ 3 weeks after last dose of study medication and in patients at high risk and with pre-existing disease (exacerbation of chronic obstructive pulmonary disease and myocardial infarction)
- 1 serious AE/death occurred in the placebo QD group 35 days after the last dose of study medication (sudden cardiac arrest)
- GI TEAEs were low and comparable among groups; most mild **(Table 2)**
- No clinically relevant changes in pain scores, opioid consumption, COWS, SOWs, laboratory results, vital signs, ECG changes

Table 2. GI-related TEAEs

TEAE	Placebo BID (n = 43)	CB-5945 0.10 mg BID (n = 43)	CB-5945 0.25 mg BID (n = 45)	Placebo QD (n=41)	CB-5945 0.25 QD (n=40)
Any GI disorder (SOC)	4 (9.3)	3 (7.0)	2 (4.4)	6 (14.6)	6 (15)
Abdominal pain	1 (2.3)	1 (2.3)	1 (2.2)	1 (2.4)	2 (5.0)
Nausea	1 (2.3)	0	1 (2.2)	2 (4.9)	0
Vomiting	0	1 (2.3)	1 (2.2)	1 (2.4)	1 (2.5)
Abdominal pain, upper	0	1 (2.3)	0	3 (7.3)	2 (5.0)
Diarrhea	0	1 (2.3)	0	0	2 (5.0)
Abdominal distention	0	0	0	0	1 (2.5)
Dyspepsia	1 (2.3)	0	0	0	0
Oral discomfort	0	1 (2.3)	0	0	0
Toothache	1 (2.3)	0	0	0	0

BID = Twice daily; GI = Gastrointestinal; QD = Once daily; SOC = System order class; TEAE = Treatment-emergent adverse event.

CONCLUSIONS

- Clinically meaningful, statistically significant improvement in SBM and SCBM frequency with favorable GI tolerability with 0.25 mg treatment
  - Trends in other OIC symptoms favored CB-5945
- Low and comparable incidence of TEAEs and GI-related TEAEs ; most mild
  - BID dosing and gradual restoration of normal bowel motility may improve GI tolerability
  - No evidence of reversal of opioid analgesia
- A clear dose response was observed with the 0.25-mg BID dose demonstrating a highly favorable balance between efficacy and GI tolerability
- Validation of the patient-reported outcome measure in ongoing
- Phase 3 trials with the 0.25-mg BID dose are anticipated to initiate in 2012

REFERENCES

1. Chou R, et al. *J Pain* 2009;10:113-130.
2. Camilleri M. *Am J Gastroenterol 2011*;106(5):835-42.
3. Olesen AE, et al. *Adv Ther* 2011 Apr;28(4):279-94.
4. Bell TJ, et a. J Opioid Management. 2009;5(3):137-144.
5. Penning-van Beest, et al. *J Med Econ*. 2010;13:129-135.
6. Kurz A, et al. *Drugs*. 2003;63(7):649-71.
7. Holzer P. *Regulatory Peptides*. 2009;155:11-17.

This study was funded by Adolor Corporation, a wholly owned subsidiary of Cubist Pharmaceuticals

American Pain Society , Honolulu, HI

May 16 – 19, 2012