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CB-5945 0.25 mg Twice Daily is Associated with Significantly Increased Spontaneous Bowel Movement and Greater Proportion of Responders Compared with Placebo in Patients on Chronic Opioid Therapy for Noncancer Pain

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ABSTRACT

Introduction: Although opioids are widely used for managing chronic pain, central and peripheral adverse events (AEs) are common. Unlike other adverse effects, opioid-induced constipation (OIC), a predominantly peripheral effect, persists for the duration of therapy and may lead to pain management disruptions. Gastrointestinal mu opioid receptor (MOR) binding is primarily responsible for OIC, although contribution from enteric delta opioid receptors (DOR) is likely. CB-5945, a MOR and DOR antagonist, is under development for OIC and associated abdominal symptoms in patients on chronic opioid therapy for noncancer pain.
Methods: CB-5945 0.25 mg and 0.1 mg twice daily (BID) were evaluated in a randomized, double-blind, placebo-controlled, Phase 2 study. The primary endpoint was change in spontaneous bowel movements (SBMs) over 4 weeks. Other endpoints included overall SBM responders (patient with ≥ 3 SBMs/week and ≥ 1 SBM/week from baseline for 3 of 4 weeks), spontaneous complete BMs (SCBMs), opioid consumption, pain scores, trough plasma - concentrations, and treatment-emergent AEs (TEAEs).
Results: 131 patients were randomized (mean age = 50 years). Mean OIC duration ranged from 3.4-5.7 years, baseline mean morphine equivalent total daily dose was 248-273 mg, and back pain was the most common pain condition. Mean SBM change from baseline was 1.44 (placebo BID), 1.96 (0.1 mg BID), and 3.42 (0.25 mg BID), with treatment difference changes of 0.51 (P = 0.2979) and 1.98 (P = 0.0003) in the 0.1-mg and 0.25-mg groups, respectively. 26% (placebo), 28% (0.1 mg BID), and 56% (0.25 mg BID; P = 0.005) of patients were overall responders. Mean treatment difference change in SCBMs was 0.18 (P = 0.1634; 0.1 mg BID) and 1.45 (P = 0.0013; 0.25 mg BID). There were no clinically-relevant changes in opioid consumption, pain scores, nor evidence of CNS effects. Mean steady state CB-5945 trough concentrations were 264.4 pg/mL (0.1 mg BID) and 572.8 pg/mL (0.25 mg BID). The most commonly reported AE was upper respiratory tract infection (placebo, 14%; 0.1mg, 7%; 0.25 mg,7%). The proportion of patients with ≥ 1 GI TEAEs was < 10% across groups with the lowest proportion in the 0.25-mg BID dose (placebo, 9.3%; 0.1 mg, 7.0%; 0.25 mg, 4.4%). The vast majority were rated as mild with none rated as severe.
Conclusion: Clinically meaningful, statistically significant improvement in SBM frequency with a highly favorable GI tolerability was observed after CB-5945 0.25mg BID treatment. Phase 3 trials are planned with this dose.

INTRODUCTION

- Chronic noncancer pain is common[1]
  - Back pain, osteoarthritis, fibromyalgia, headache, neuropathy
- Management requires a multimodal approach with opioids playing an integral role in therapy[1]
  - Opioid use has sharply increased over the past decade, in part based on the imperative to inquire about and manage pain reported by patients[1,2]
- Although opioids are effective for managing pain, they are associated with both central and peripheral side effects[2,3]
- Constipation is the most common, and often most debilitating side effect, associated with chronic opioid use (opioid-induced constipation; OIC)[2-5]
  - ≤ 80% of patients with ≥ 1 side effects consistent with opioid-induced bowel dysfunction (constipation, nausea, vomiting, abdominal bloating/pain and gastro-esophageal reflux)
  - Refractory, not "tolerance sensitive"
  - May lead to pain management disruptions
  - Adverse effect on Health-related quality of life
- Long-term treatment options are limited

OBJECTIVE

- To compare 2 different dose levels (0.10 and 0.25 mg twice daily [BID]) of CB-5945 with placebo for the treatment of OIC in patients taking long-term opioid therapy for chronic noncancer pain

METHODS

- Randomized, double-blind, placebo-controlled trial **(Figure 1)**

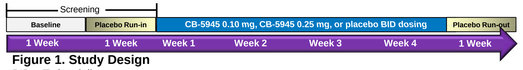

Figure 1. Study Design
BID = Twice daily.

- 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)
  - Time to first BM and SBM
  - BM diaries (comfort and satisfaction scores)
  - Rescue laxative use
- Steady-state trough plasma concentrations were collected
- 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 patient-reported outcomes measure (Chronic Opioid-related Gastrointestinal GI Symptom Scale; CORGISS) designed to assess other opioid-related GI symptoms associated with OIC was validated in this study

RESULTS

- 131 patients were included in the study **(Table 1)**
  - Morphine equivalent total daily dose ranged from 30 to 1,284 mg
  - Mean duration of OIC was 4.6 years
  - Back pain was the most common pain condition (58%)

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)
Age, mean years ± SD	49.7 ± 11.06	50.3 ± 11.98	49.6 ± 9.75
Race, n (%)			
White	31 (72.1)	30 (69.8)	31 (68.9)
Black	12 (27.9)	11 (25.6)	14 (31.1)
Asian	0	2 (4.7)	0
Males, n (%)	20 (46.5)	23 (53.5)	25 (55.6)
BMI, mean kg/m^2 ± SD	30.9 ± 5.64	30.7 ± 5.87	29.6 ± 5.05
METDD, mean mg ± SD	247.6 ± 280.22	273.4 ± 275.31	271.1 ± 303.94

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

- Mean steady state CB-5945 plasma trough concentrations were 264.4 pg/mL (0.1 mg BID) and 572.8 pg/mL (0.25 mg BID)

RESULTS (Cont.)

Primary Efficacy Results

- Mean change in SBMs from baseline for treatment weeks 1 – 4 was 1.44, 1.96, and 3.42 in the placebo, 0.1-mg, and 0.25-mg groups, respectively, with a significant treatment difference noted in the 0.25-mg group **(Figure 2)**

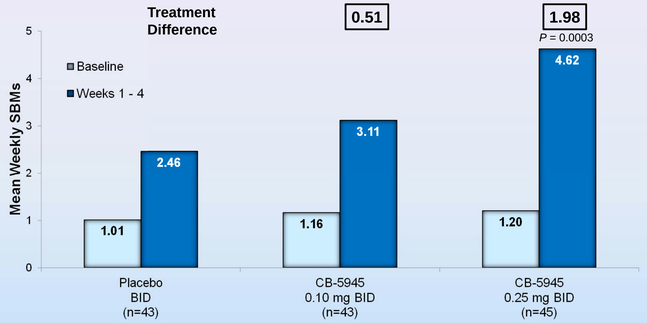

Figure 2. Treatment Difference in SBM Frequency
BID = Twice daily; SBM = Spontaneous bowel movement.
Note: Treatment difference = Mean of the individual changes in treatment differences (CB-5945 – placebo).

Secondary Efficacy Results

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

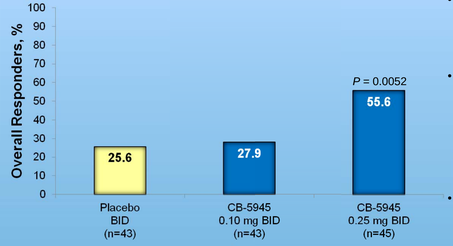

Figure 3. Proportion of Overall SBM Responders
BID = Twice daily; SBM = Spontaneous bowel movement.
SBM responders = patients with ≥ 3 SBMs/week and an increase of at least 1 SBM over baseline for 3 of the 4 weeks of treatment.

- Mean change in SCBMs from baseline was 0.78 , 0.97, 2.24 in the placebo, 0.1-mg, and 0.25-mg group, with a significant treatment difference noted in the 0.25-mg group (P = 0.0013)
- Median time to first BM
  - 45 hours, placebo
  - 25 hours, CB-5945 0.1 mg
  - 16 hours, CB-5945 0.25 mg
- Median time to first SBM
  - 49 hours, placebo
  - 36 hours, CB-5945 0.1 mg
  - 21 hours, CB-5945 0.25 mg
- After 4 weeks of treatment
  - BM comfort scores were generally less severe and improvement of BM satisfaction scores was greater in the 0.25-mg group compared with baseline and compared with placebo
  - Greater increase in % of patients who reported much better than usual or better than usual satisfaction with their BM quality in the 0.25-mg group compared with placebo
- Rescue laxative use 14% in the placebo BID group compared with 7% in the 0.25-mg BID group

Safety Results

- Overall, 23% to 26% of patients had 1 or more treatment-emergent AEs (TEAEs)
  - Upper respiratory tract infection was the most commonly reported TEAEs (14%, placebo BID; 7%, CB-5945 0.1 mg BID; 7%, CB-5945 0.25 mg BID)
    - Majority mild, no ne
  - 2 serious AEs occurred in the 0.25-mg 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)
- Majority of gastrointestinal TEAEs were mild , no severe **(Table 2)**
- No clinically relevant changes in pain scores or opioid consumption, COWS scores, SOWS scores, 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)
Any GI disorder (SOC)	4 (9.3)	3 (7.0)	2 (4.4)
Abdominal pain	1 (2.3)	1 (2.3)	1 (2.2)
Nausea	1 (2.3)	0	1 (2.2)
Vomiting	0	1 (2.3)	1 (2.2)
Abdominal pain, upper	0	1 (2.3)	0
Diarrhea	0	1 (2.3)	0
Dyspepsia	1 (2.3)	0	0
Oral discomfort	0	1 (2.3)	0
Toothache	1 (2.3)	0	0

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

CONCLUSIONS

- Clinically meaningful, statistically significant improvement in SBM frequency with favorable GI tolerability was observed after CB-5945 0.25mg BID treatment
  - Trends in other OIC symptoms favored CB-5945 compared with placebo
- Low and comparable incidence of TEAEs and GI-related TEAEs compared with placebo with most mild in severity
  - No evidence of reversal of opioid analgesia
  - Gradual restoration of normal bowel motility may improve GI tolerability
- Validation of the patient-reported outcome measure in ongoing
- Phase 3 trials with the 0.25-mg dose are anticipated to initiate in 2012

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