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Safety and Efficacy of Olorinab, a Peripherally Acting, Highly Selective, Cannabinoid Type 2 Receptor Agonist in a Phase 2a Study in Chronic Abdominal Pain Associated With Crohn's Disease

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INTRODUCTION

- Patients with Crohn's disease (CD) commonly report abdominal pain, which has significant consequences for patient quality of life[1,2]
  - In 41% of patients with CD, pain, bloating, and erratic bowel habits persist despite apparent remission of inflammation[3]
  - Abdominal pain is severe enough to require pain-specific treatment in many cases[1]
  - Current treatment options for abdominal pain in patients with CD include non-steroidal analgesics (eg, acetaminophen), antidepressants (eg, tricyclic antidepressants), and opioids, but these strategies have demonstrated limited efficacy and/or unfavorable adverse event (AE) profiles[4]
- The cannabinoid type 2 receptor (CB_2) plays a modulatory role in the endocannabinoid system and has the potential to provide analgesia for pain associated with CD potentially without the liabilities of other pain therapeutics[5]
  - CB_2 has been shown to be upregulated in the gastrointestinal tract during intestinal inflammation[6] and to modulate visceral sensitivity in animal models[5]
- Olorinab (APD371) is a full agonist of CB_2 and was shown to activate endogenous CB_2 in primary rat splenocytes, human leukemia (HL-60) cells, and primary human B cells[7]
  - Olorinab exhibited >1000-fold selectivity for CB_2 over CB_1,[7,8] which minimizes potential for activation of CB_1 located in the brain, and sustained efficacy in several animal models of chronic pain, including inflammatory bowel disease[7,8]
  - Olorinab is peripherally acting, showing low blood-brain barrier penetration in rats,[8] which minimizes potential for psychoactive effects and addiction
- Olorinab was generally safe and well tolerated in healthy volunteers in a single dose up to 400 mg and in multiple doses up to 200 mg three times a day (TID)[7,9]

OBJECTIVES

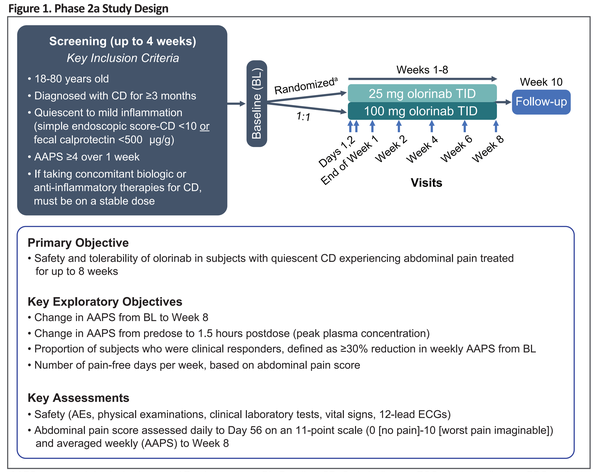
- To evaluate the effects of olorinab in subjects with mild or quiescent CD experiencing abdominal pain

METHODS

Study Design

- In an open-label, parallel-group, multicenter phase 2a study, eligible subjects with quiescent CD experiencing abdominal pain were randomly assigned 1:1 to receive 25 or 100 mg oral olorinab TID for up to 8 weeks (**Figure 1**), with a primary efficacy endpoint of change in weekly average abdominal pain score (AAPS) on a 0-10 Likert scale between Baseline and Week 8

Figure 1. Phase 2a Study Design



AAPS, average abdominal pain score; AE, adverse event; BL, Baseline; CD, Crohn's disease; ECG, electrocardiogram; PRO, patient-reported outcomes; TID, 3 times per day.
[a]Randomization was stratified by sex.

Statistics

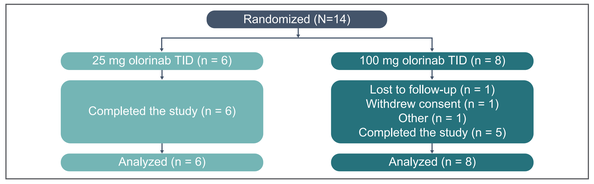
- Statistical comparisons of AAPS were performed only between Baseline and Week 4 and Baseline and Week 8 using trough and peak assessments for each dose cohort and for all subjects

RESULTS

Demographics and Baseline Characteristics

- 11 subjects completed the study including the Week 10 follow-up visit (**Figure 2**)

Figure 2. Subject Disposition



TID, 3 times a day.

- Demographics and baseline characteristics were similar across treatment groups and 12 of 14 subjects were on active treatment for CD (**Table 1**)

Table 1. Demographics and Baseline Characteristics

	Olorinab 25 mg TID n = 6	Olorinab 100 mg TID n = 8	Overall N = 14
Age, mean (SD), years	35.0 (10.8)	36.9 (15.2)	36.1 (13.1)
Female, n (%)	4 (66.7)	4 (50.0)	8 (57.1)
Race, n (%)			
White	5 (83.3)	7 (87.5)	12 (85.7)
Black	0	1 (12.5)	1 (7.1)
American Indian or Alaskan Native	1 (16.7)	0	1 (7.1)
Weight, mean (SD), kg	82.8 (17.8)	87.8 (22.3)	85.7 (19.9)
BMI, mean (SD), kg/m^2	30.8 (7.7)	29.2 (5.7)	29.9 (6.4)
Time since diagnosis, mean (SD), years	15 (6.4)	8.8 (8.9)	11.4 (8.3)
Location of CD, n (%)			
Ileum	3 (50.0)	7 (87.5)	10 (71.4)
Colon	4 (66.7)	5 (62.5)	9 (64.3)
Rectum	1 (16.7)	2 (25.0)	3 (21.4)
Perianal	1 (16.7)	2 (25.0)	3 (21.4)
Baseline AAPS, mean (SD)	5.8 (1.3)	5.5 (2.0)	5.6 (1.7)
On active treatment for CD, n %	5 (83.3)	7 (87.5)	12 (85.7)

AAPS, average abdominal pain score; BMI, body mass index; CD, Crohn's disease; SD, standard deviation; TID, 3 times a day.

Safety and Tolerability

- AEs were reported in 67% (4/6) of subjects who received 25-mg olorinab TID and in 75% (6/8) of subjects who received 100-mg olorinab TID (**Table 2**)
  - AEs were generally mild to moderate and limited in duration
  - The only 2 serious AEs (interstitial lung disease, acute interstitial pneumonitis) occurred in the same subject (receiving 100-mg dose) and were not considered treatment-related (Table 2)

Table 2. Summary of Adverse Events

	Olorinab 25 mg TID n = 6	Olorinab 100 mg TID n = 8	Overall N = 14
Subjects with ≥1 AE, n (%)	4 (67)	6 (75)	10 (71)
AE preferred term reported by ≥2 subjects, n (%)			
Drug hypersensitivity	1 (17)	1 (13)[a]	2 (14)
Hypomagnesemia	0	2 (25)[a]	2 (14)
Pain in extremity	0	2 (25)	2 (14)
CNS AEs, n (%)	0	3 (38)	3 (21)
Dizziness	0	1 (13)	1 (7)
Headache	0	1 (13)	1 (7)
Somnolence	0	1 (13)	1 (7)
Subjects with ≥1 serious AE,[a,b] n (%)	0	1 (13)[a]	1 (7)[a]
Interstitial lung disease	0	1 (13)[a]	1 (7)[a]
Acute interstitial pneumonitis	0	1 (13)[a]	1 (7)[a]

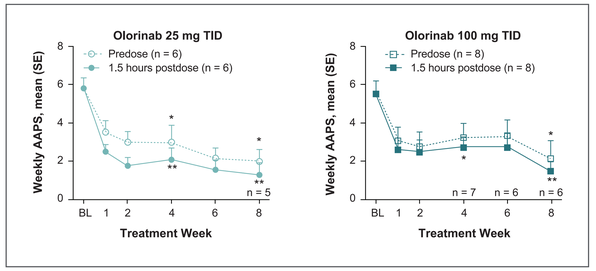
AE, adverse event; CNS, central nervous system; TID, 3 times a day.
[a]1 subject receiving olorinab 100 mg TID reported 20 AEs, including 2 serious AEs that were not considered treatment-related.
[b]Serious: Common Terminology Criteria for Adverse Events, grades 3-5.
Each subject is counted only once within each system organ class and preferred term.
AEs were coded using Medical Dictionary for Regulatory Activities, version 21.0.

- No subjects discontinued the study because of AEs
- No clinically significant changes in vital signs (including heart rate and blood pressure) or clinical safety laboratory results were observed

Effects on Abdominal Pain

- The AAPS was significantly improved from Baseline at Weeks 4 and 8 in both treatment groups (**Figure 3**)
  - 11 subjects with a mean Baseline AAPS of 6.0 provided Week 8 AAPS data
  - Mean change in AAPS from Baseline to the time of peak concentration (1.5 hours postdose) during Week 8 was –4.6 in all subjects (11-point scale, n = 11, $P < 0.001$) and –4.6 in both treatment groups (25 mg, n = 5, $P = 0.0043$; 100 mg, n = 6, $P = 0.0036$; overall, n=11; $P < 0.001$)

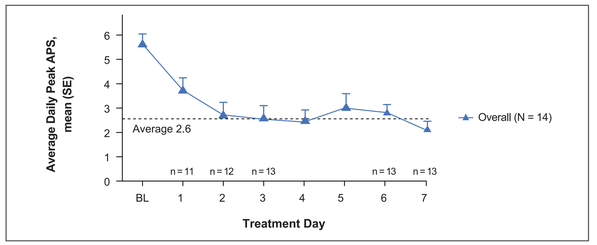
Figure 3. Weekly Average Abdominal Pain Scores Measured at Trough Olorinab Plasma Concentration (predose) and at Peak Plasma Concentration (1.5 hours postdose)



AAPS, average abdominal pain score; BL, baseline; SE, standard error; TID, 3 times per day.
*$P < 0.05$; **$P < 0.01$.

- Among all subjects (N = 14), mean AAPS was reduced from 5.6 at Baseline to 2.6 within 2 days of treatment, and remained relatively stable for the rest of the first week of treatment (**Figure 4**)
- Pain scores at 1.5 h postdose were consistently lower than predose pain scores, which correlates with peak and trough serum concentrations

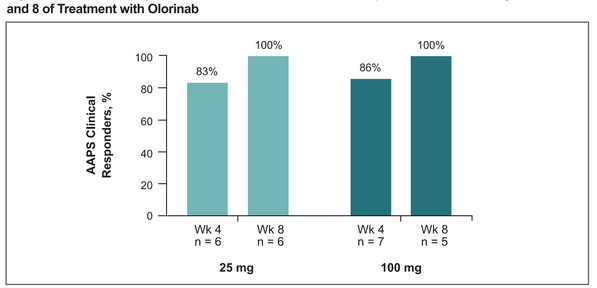
Figure 4. Average Daily Peak Abdominal Pain Score During the First Week of Treatment with Olorinab (all subjects)



AAPS, average abdominal pain score; BL, baseline; CI, confidence interval; SE, standard error; TID, 3 times per day.

- Clinical response in AAPS (≥30% reduction) was seen in 85% (11/13) of all subjects with evaluable data at Week 4 and 100% (11/11) at Week 8 (data by dose in **Figure 5**)

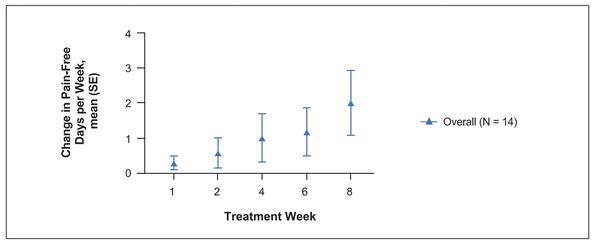
Figure 5. Portion of Subjects Who Demonstrated a Clinical Response[a] in AAPS During Weeks 4 and 8 of Treatment with Olorinab



AAPS, average abdominal pain score.
[a]A clinical responder is defined as a subject with ≥30% reduction from Baseline in weekly AAPS.

- No subjects required any rescue medications for breakthrough pain for the study duration
- No subjects at Baseline had a pain-free day; the mean increase in pain-free days at Week 8 was 2 days per week among all subjects (25 mg, 1.6, n = 5; 100 mg, 2.3, n = 6) (**Figure 6**)

Figure 6. Mean Change in Pain-Free Days Per Week From Baseline[a] (all subjects)



SE, standard error.
[a]The mean number of pain-free days per week at baseline was 0.

CONCLUSIONS

- Olorinab demonstrated a favorable safety profile in subjects with mild to quiescent CD experiencing abdominal pain
- AEs were mostly mild-moderate; the 2 serious adverse events (in the same subject) reported were not considered related to study treatment
- No subject required rescue medication for pain and, on average, subjects experienced more pain-free days over the course of the 8-week study
- This exploratory open-label study provides evidence for an improvement in abdominal pain without any apparent psychoactive effects, although interpretation is limited by a small sample size and lack of placebo control
- Olorinab may provide a future therapeutic approach for chronic abdominal pain in CD

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DISCLOSURES

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