P418

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

Peter D.R. Higgins,[1] Daniel Ginsberg,[2] Kye Gilder,[3] Brandon Walsh,[3] Brett English,[3] Stewart Turner,[3] Preston Klassen,[3] Stephen Hanauer,[4] Charles Barish,[5] Bruce Yacyshyn[6]

[1]University of Michigan, Ann Arbor, Michigan, USA; [2]MultiCare Institute for Research and Innovation, Tacoma, Washington, USA; [3]Arena Pharmaceuticals, Inc, San Diego, California, USA; [4]Northwestern University, Chicago, Illinois, USA; [5]University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA; [6]University of Cincinnati, Cincinnati, Ohio, USA

INTRODUCTION

- Abdominal pain is commonly reported in patients with Crohn's disease (CD) and has significant consequences for patient quality of life[1,2]
  - Pain, bloating, and erratic bowel habits persist in 41% of patients with CD 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 analgesics (eg, acetaminophen), antidepressants (eg, selective serotonin reuptake inhibitors, tricyclic antidepressants), and opioids, but these strategies have demonstrated limited efficacy and/or unfavorable adverse event profiles[4]
- The cannabinoid receptor type 2 (CB_2) has the potential to provide analgesia in CD pain without the pitfalls 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 HL-60 cells, and primary human B cells[7]
  - Olorinab exhibited >1000-fold selectivity for CB_2 over CB_1 and sustained efficacy in several animal models of chronic pain including inflammatory bowel disease[7,8]
  - Olorinab is peripherally restricted, showing low blood-brain barrier penetration in rats,[8] which minimizes potential for addiction
- Olorinab was generally safe and well tolerated in healthy volunteers in a single oral dose up to 400 mg and in multiple oral doses up to 200 mg three times a day (TID)[7,9]

OBJECTIVES

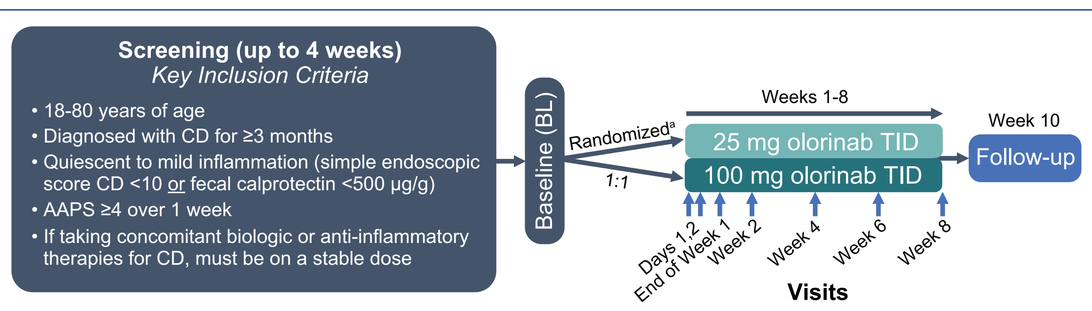
- To evaluate the safety, tolerability, and efficacy of olorinab in subjects with mild or quiescent CD experiencing abdominal pain

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 an 11-point 0-10 Likert scale between Baseline and Week 8

Figure 1. Phase 2a study design



AAPS, average abdominal pain score; AE, adverse event; CD, Crohn's disease; ECG, electrocardiogram; TID, 3 times per day.
[a]Randomization stratified by sex.

Statistics

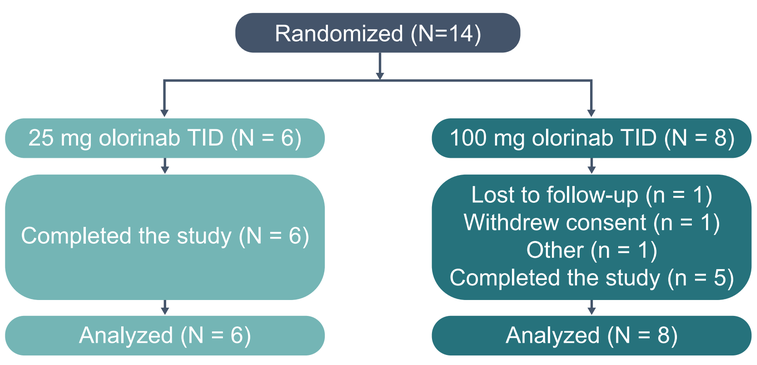
- Statistical comparisons of AAPS were performed only between Baseline and Week 4 and Baseline and Week 8 using trough and peak assessments for each dose cohort and for all subjects

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 (**Table 1**) and 12 of 14 subjects were on active treatment for CD

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

- Adverse events (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 (100 mg) 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	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]

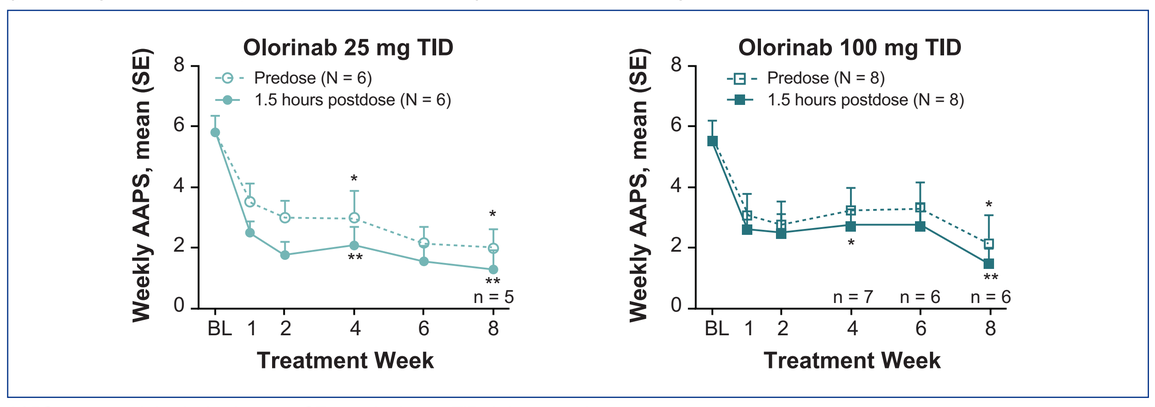
AE, adverse event; CNS, central nervous system; TID, 3 times a day.
[a]1 subject receiving olorinab 100 mg TID reported 20 AEs, including 2 serious AEs that were not considered treatment related.
[b]Serious: Common Terminology Criteria for Adverse Events, grades 3-5.
Each subject is counted only once 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 both treatment groups (25 mg, n = 5, $P = 0.0043$; 100 mg, n = 6, $P = 0.0036$; overall, n = 11, $P < 0.001$)

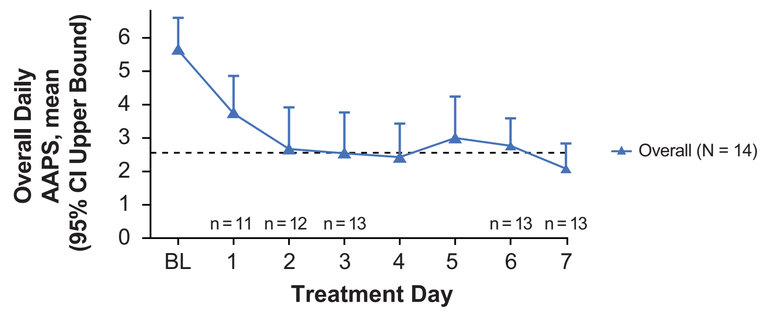
Figure 3. Weekly average abdominal pain scores measured at trough olorinab plasma concentration (predose) and at peak plasma concentration (1.5 hours postdose)



AAPS, average abdominal pain score; 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**)

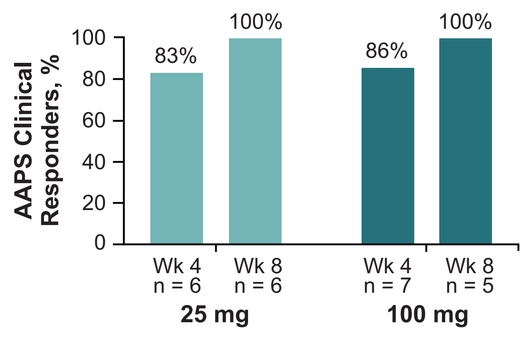
Figure 4. Daily average abdominal pain score during the first week of treatment with olorinab (all subjects combined, 25 mg and 100 mg TID)



AAPS, average abdominal pain score; BL, Baseline; CI, confidence interval; TID, 3 times per day.

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

Figure 5. Proportion 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.

CONCLUSIONS

- Olorinab was generally safe and well tolerated in subjects with mild to quiescent CD experiencing abdominal pain
- AEs were mostly mild-moderate; the only 2 SAEs (in the same subject) were not considered related to study treatment
- This exploratory open-label study provided evidence for an improvement in abdominal pain without any apparent psychotropic effects, although interpretation is limited by small sample size and lack of placebo control
- These data support additional clinical studies with more robust designs

REFERENCES

1. Zeitz J et al. *PLoS One*. 2016;11:e0156666; 2. Docherty MJ et al. *Gastroenterol Hepatol (N Y)*. 2011;7:592-601. 3. Halpin SJ, Ford AC. *Am J Gastroenterol*. 2012;107:1474-1482; 4. Srinath AI et al. *Ther Adv Gastroenterol*. 2012;5:339-357; 5. Wright KL et al. *Br J Pharmacol*. 2008;153:263-270; 6. Wright KL et al. *Gastroenterology*. 2005;129:437-453; 7. Adams JW et al. Poster presented at the American Pain Society Scientific Summit; March 4-6, 2018; Anaheim, California. #100; 8. Han S et al. *ACS Med Chem Lett*. 2017;8:1309-1313; 9. Jones RCW et al. Poster presented at the American Pain Society Scientific Summit; March 4-6, 2018; Anaheim, California. #286.

ACKNOWLEDGMENTS

We thank the patients who participated in this research, as well as the study staff. Medical writing assistance was provided by ApotheCom, San Francisco, CA, and was funded by Arena Pharmaceuticals, Inc.

Poster presented at the 14th Congress of ECCO – Inflammatory Bowel Diseases; March 6-9, 2019; Copenhagen, Denmark