P139

Olorinab, a Peripherally Restricted, Highly Selective Agonist of the Cannabinoid Receptor Type 2 for the Management of Visceral Pain in Inflammatory Bowel Disease (IBD)—Preclinical and Early Clinical Development

Beatriz Lindstrom, PharmD, PhD,[1] Jon Ruckle, MD,[2] Stewart Turner, PhD,[1] Kathe Stauber, PhD,[1] Stuart M. Brierley, PhD,[3]
Brett A. English, PharmD, PhD,[1] Bruce R. Yacyshyn, MD[4]

[1]Arena Pharmaceuticals, Inc, San Diego, CA, USA; [2]Pacific Pharma Group, LLC, Tacoma, WA, USA; [3]Visceral Pain Research Group, Flinders University, SAHMRI, Adelaide, SA, Australia; [4]University of Cincinnati, Cincinnati, OH, USA

INTRODUCTION

- In patients with IBD, abdominal pain is reported up to 60% of the time and is associated with lower quality of life[1]
  - Even in apparent remission of inflammation, pain, bloating, and erratic bowel habits are noted in 25%-46% of patients[2]
  - Abdominal pain is severe enough to require pain treatment in most cases[1]
- There is an unmet need for effective non-opioid treatment options for abdominal pain in patients with IBD[1]
- The cannabinoid receptor type 2 (CB_2) provides an attractive target for abdominal pain associated with IBD[3,4]
  - CB_2 is expressed throughout the gastrointestinal tract and may be upregulated in states of disease[3,4]
  - CB_2 agonists decreased visceral hypersensitivity in preclinical models of colitis[5,6]
- 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[7,8]
  - Olorinab showed low blood-brain barrier penetration in rats[8]
- Olorinab is in clinical development for visceral pain associated with gastrointestinal diseases[7,9]

OBJECTIVE

- Provide an overview of the effects of olorinab in animal and human studies

NON-CLINICAL METHODS

Animal models: induction of colitis and treatment

- Colitis was induced in mice and rats by rectal administration of trinitrobenzenesulphonic acid (TNBS), as described in Hughes et al[10]
- No procedure was done in control animals
- Olorinab or vehicle was administered by oral gavage twice daily for 5 days in healthy animals and twice daily for 5 days in animals with colitis, starting 1 day before induction of colitis

Animal models: assessment of pain in vivo and visceral afferent activity ex vivo

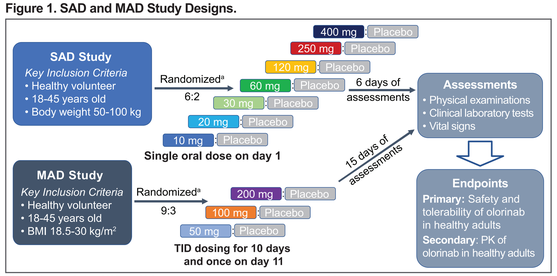
- Noxious distension of the colorectum triggers the visceromotor response (VMR), a nociceptive brainstem reflex causing contraction of the abdominal muscles,[11] which was used as an indicator of pain
  - After TNBS treatment in rats, colorectal distension (CRD) was induced using a barostat, and VMR was measured in vivo using an amplifier connected to an analog-to-digital converter
- Single-unit extracellular recordings from splanchnic colonic afferent nerves were performed ex vivo as previously described[10]
- Measurements of in vivo colonic pain and ex vivo colonic afferent mechanosensitivity were conducted on day 5 following instillation of TNBS

CLINICAL METHODS

Phase 1 clinical study designs

- In 2 double-blind, placebo-controlled, phase 1 studies, healthy young adult male and female volunteers were randomly assigned to receive either a single ascending dose (SAD; 10-400 mg) or multiple ascending doses (MAD; 50-200 mg 3 times daily [TID] for 10 days) of oral olorinab or placebo (**Figure 1**)

Figure 1. SAD and MAD Study Designs.



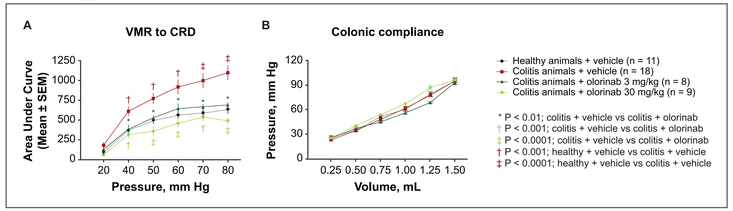
BMI, body mass index; MAD, multiple ascending dose; PK, pharmacokinetics; SAD, single ascending dose; TID, 3 times daily.
[a]Subsequent cohorts were dosed upon adequate safety findings from the previous cohort.

NON-CLINICAL RESULTS

Animal models of colitis: visceral hypersensitivity and colonic compliance

- Rats with TNBS-induced colitis displayed visceral hypersensitivity (enhanced VMR) to CRD without changes in colonic compliance (**Figure 2**)
- Olorinab reversed heightened visceral sensitivity in animals with colitis but had no effect on colonic compliance (**Figure 2**)

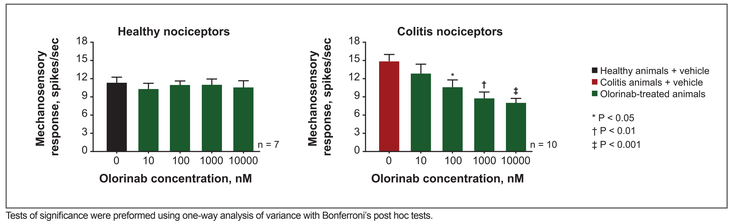
Figure 2. Olorinab Treatment (3 and 30 mg/kg) Prevented Visceral Hypersensitivity (A) Without an Effect on Colonic Compliance (B) in Rats with Colitis.



CRD, colorectal distension; SEM, standard error of the mean; VMR, visceromotor response.
All post hoc statistical comparisons used the generalized estimating equation with least significant difference.

- Healthy control rats treated with olorinab (30 mg/kg) did not show altered visceral sensitivity to CRD or changes in colonic compliance (data not shown)
- In single-unit extracellular recordings from mechanosensitive nociceptors, olorinab reduced colonic hypersensitivity in animals with colitis (**Figure 3**)

Figure 3. Olorinab Reduces Colonic Nociceptor Hypersentitivity in Mice With Colitis.



Tests of significance were preformed using one-way analysis of variance with Bonferroni's post hoc tests.

CLINICAL RESULTS

Phase 1 clinical studies

Subjects

- 56 healthy volunteers were enrolled in the SAD study and 36 healthy volunteers were enrolled in the MAD study
- Demographics and baseline characteristics were similar across treatment groups within each study (**Table 1**)

Table 1. Demographics and Baseline Characteristics in the SAD and MAD Studies

	SAD Study									MAD Study				
		Olorinab									Olorinab			
Parameter	Placebo[a] n = 14	10 mg n = 6	20 mg n = 6	30 mg n = 6	60 mg n = 6	120 mg n = 6	250 mg n = 6	400 mg n = 6	Placebo[a] n = 9	50 mg TID n = 9	100 mg TID n = 9	200 mg TID n = 9	All Subjects n = 36
Age, mean (SD), years	29.9 (7.4)	25.3 (5.6)	27.8 (8.5)	25.3 (5.6)	25.5 (3.3)	27.0 (5.5)	22.0 (2.5)	22.7 (3.2)	33.6 (9.2)	34.6 (8.2)	33.0 (7.4)	31.9 (9.8)	33.3 (8.4)
Race, n (%)													
Black or African American	1 (7.1)	0	0	0	0	0	0	0	2 (22.2)	5 (55.6)	6 (66.7)	5 (55.6)	18 (50.0)
White	13 (92.9)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	5 (83.3)	7 (77.8)	3 (33.3)	2 (22.2)	3 (33.3)	15 (41.7)
Multiple or other	0	0	0	0	0	0	0	1 (16.7)	0	1 (11.1)	1 (11.1)	1 (11.1)	3 (8.3)
Female, n (%)	7 (50.0)	4 (66.7)	3 (50.0)	3 (50.0)	3 (50.0)	3 (50.0)	2 (33.3)	4 (66.7)	6 (66.7)	6 (66.7)	5 (55.6)	4 (44.4)	21 (58.3)
Weight, mean (SD), kg	74.7 (8.0)	69.6 (14.0)	73.7 (9.6)	70.9 (10.7	74.1 (13.8)	75.4 (13.8)	85.5 (9.8)	76.2 (12.8)	71.4 (9.5)	79.4 (16.3)	75.9 (11.7)	76.1 (18.1)	75.7 (14.0)
BMI, mean (SD), kg/m²	26.3 (1.9)	24.1 (3.4)	25.0 (3.2)	25.2 (5.3)	24.7 (3.5)	26.5 (3.3)	27.6 (3.7)	27.5 (3.2)	25.9 (2.3)	26.8 (3.0)	26.7 (2.3)	25.4 (3.7)	26.2 (2.8)

BMI, body mass index; MAD, multiple ascending dose; SAD, single ascending dose; SD, standard deviation; TID, 3 times a day.
[a]Placebo subjects were pooled across cohorts.

Safety and tolerability

- 45 treatment-emergent adverse events (TEAEs) were reported by 22 subjects (39.3%) in the SAD study (**Table 2**)
  - 91.1% were mild in severity, and 53% were deemed unrelated to the study drug
  - Of the most common TEAEs (**Table 2**), dry mouth and somnolence were only reported in the higher dose groups (250 mg and 400 mg)

Table 2. Summary of AEs Reported in ≥5% of Subjects Who Received Olorinab in the SAD Study

		Olorinab						
Preferred Term	Placebo n = 14	10 mg n = 6	20 mg n = 6	30 mg n = 6	60 mg n = 6	120 mg n = 6	250 mg n = 6	400 mg n = 6
AEs reported, n	4	6	1	2	2	9	5	16
Subjects reporting any AE, n (%)	3 (21.4)	3 (50.0)	1 (16.7)	1 (16.7)	2 (33.3)	5 (83.3)	2 (33.3)	5 (83.3)
Somnolence	0	0	0	0	0	0	0	4 (66.7)
Dry mouth	0	0	0	0	0	0	2 (33.3)	2 (33.3)
Dizziness	1 (7.1)	0	0	1 (16.7)	0	0	0	2 (33.3)
Diarrhea	0	1 (16.7)	0	0	0	2 (33.3)	0	0
Headache/sinus headache	0	3 (50.0)	0	0	0	0		0

AE, adverse event; SAD, single ascending dose.
Note: At each level of summarization, subjects reporting more than 1 event were only counted once. Sinus headache was determined by the opinion of the investigator, considering the details of the history and physical examination.
Medical Dictionary for Regulatory Activities, version 16.1 was used as the adverse event coding dictionary.

- 17 TEAEs were reported by 10 subjects (27.8%) in the MAD study; all were mild (**Table 3**)

Table 3. Summary of AEs Reported in Any Subject in the MAD Study

Preferred Term	Placebo TID n = 9	Olorinab 50 mg TID n = 9	Olorinab 100 mg TID n = 9	Olorinab 200 mg TID n = 9	Total Olorinab TID n = 27
Subjects reporting any AE	3 (33.3)	5 (55.6)	0	2 (22.2)	7 (25.9)
Headache	0	2 (22.2)	0	0	2 (7.4)
Nausea	0	2 (22.2)	0	0	2 (7.4)
Constipation	0	1 (11.1)	0	0	1 (3.7)
Deafness bilateral	0	1 (11.1)	0	0	1 (3.7)
Dysmenorrhea	0	1 (11.1)	0	0	1 (3.7)
Dyspepsia	0	1 (11.1)	0	0	1 (3.7)
Eructation	0	1 (11.1)	0	0	1 (3.7)
Musculoskeletal stiffness	0	1 (11.1)	0	0	1 (3.7)
Somnolence	0	0	0	1 (11.1)	1 (3.7)
Thirst	0	0	0	1 (11.1)	1 (3.7)
Back pain	1 (11.1)	0	0	1 (11.1)	1 (3.7)
Neck pain	1 (11.1)	1 (11.1)	0	0	1 (3.7)
Eyelid edema	1 (11.1)	0	0	0	0

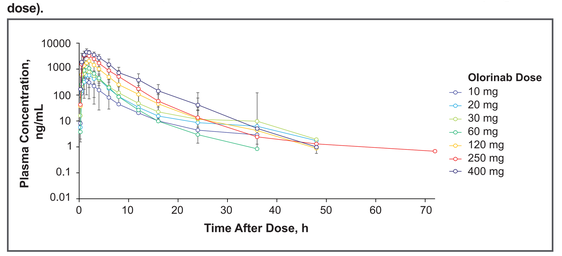
AE, adverse event; MAD, multiple ascending dose; TID, 3 times daily.
Note: At each level of summarization, subjects reporting more than 1 event were only counted once.

- Changes in supine heart rate and blood pressure were observed in healthy volunteers at the higher tested doses in the SAD (250 mg and 400 mg) and the MAD (200 mg) studies; none of the observed changes was clinically significant and no related AEs were reported

Pharmacokinetics

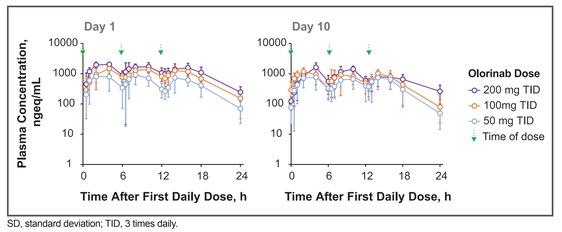
- Systemic exposure of olorinab increased in a manner that was less than dose proportional
- Renal elimination was minimal
- The median time to reach maximum plasma concentration was approximately 1.5 hours in the SAD study (**Figure 4**) and 2 to 4 hours across all dose groups and days dosed in the MAD study (**Figure 5**)
- The terminal half-life for plasma olorinab ranged from 3.11 to 4.23 hours across dose groups in the SAD study and 3.79 to 5.06 hours across dose groups in the MAD study
- After 10 days of TID dosing, there was no accumulation of olorinab in plasma
- Systemic exposures of all tested metabolites (M1-M5 in the SAD study; M1, M2, and M4 in the MAD study) increased in a less than dose proportional manner; in the MAD study the combined half-life of active metabolites (M1, M4) and olorinab ranged from 7.67 to 9.01 hours

Figure 4. Arithmetic Mean (±SD) Plasma Concentration-Time Profiles of Olorinab (single dose).



SD, standard deviation

Figure 5. Arithmetic Mean (±SD) Steady-State Plasma Concentration-Time Profiles of Olorinab (TID dosing).



SD, standard deviation; TID, 3 times daily.

CONCLUSIONS

- Olorinab showed efficacy in a rat model of colitis-induced visceral hypersensitivity
- Olorinab was generally safe and well tolerated without psychotropic AEs in healthy volunteers administered single doses up to 400 mg/kg and multiple doses up to 200 mg/kg TID
- Through its full CB_2 agonism, selectivity, and expected low brain penetration, olorinab may provide a novel therapeutic approach for sustained relief of IBD-associated abdominal pain without psychotropic effects and therefore minimal potential for dependence or abuse
- These data support the continued clinical development of olorinab for the treatment of abdominal pain associated with IBD or other gastrointestinal conditions
  - A randomized phase 2a, open-label, 8-week study to assess the tolerability, PK, and efficacy of olorinab (25 or 100 mg TID) in patients with quiescent Crohn's disease experiencing pain has recently been completed (ClinicalTrials.gov, NCT03155945)

REFERENCES

1. Zeitz J et al. *PLoS One*. 2016;11:e0156666.
2. Halpin SJ, Ford AC. *Am J Gastroenterol*. 2012;107:1474-1482.
3. Wright KL et al. *Br J Pharmacol*. 2008;153:263-270.
4. Wright KL et al. *Gastroenterology*. 2005;129:437-453.
5. Kikuchi A et al. *J Pharmacol Sci*. 2008;106:219-224.
6. Iwata Y et al. *Bioorg Med Chem Lett*. 2015;25:236-240.
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.
10. Hughes PA et al. *Gut*. 2009;58:1333-1341.
11. Ness TJ, Gebhart GF. *Brain Res*. 1988;450:153-169.

ACKNOWLEDGMENTS

Medical writing assistance was provided by ApotheCom, San Francisco, CA, and was funded by Arena Pharmaceuticals, Inc.

Poster presented at the 2019 Crohn's & Colitis Congress; February 7-9, 2019; Las Vegas, Nevada.