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

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INTRODUCTION

- Abdominal pain is commonly reported in patients with Crohn’s disease (CD) and has significant consequences for patient quality of life.
- Pain, bloating, and eretic bowel habits persist in 41% of patients with CD despite apparent remission of inflammation.
- Abdominal pain is severe enough to require pain-specific treatment in many cases.
- Current treatment options for abdominal pain in patients with CD include anticholinergics (eg, atropine sulphate), antispasmodics (eg, selective serotonin-reuptake inhibitors, bicarbonate antacids), and opioids, but these have demonstrated limited efficacy and/or unacceptable adverse event profiles.
- The cannabinoid receptor type 2 (CB2) has the potential to provide analgesia in CD pain without the pitfall of other pain medications.
- CB2 has been shown to be upregulated in the gastrointestinal tract during intestinal inflammation and can modulate visceral sensitivity in animal models.
- Olorinab (APD371) is a full agonist of CB2 and was shown to activate CB2 receptors in primary rat splenocytes, human HCE-2 cells, and primary human B cells.
- Olorinab exhibited 1,000-fold selectivity for CB2 over CB1 and displayed efficacy in several animal models of chronic pain reducing inflammatory bowel disease.
- Olorinab is peripherally restricted, showing low blood-brain barrier penetration in rats, which minimizes potential for addiction.
- Olorinab was generally well tolerated in healthy volunteers in a single oral dose up to 100 mg.

OBJECTIVES

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

METHODS

Study Design

- In an open-label, parallel-group, multicenter 2a phase 2a study, eligible subjects with chronic CD experiencing abdominal pain were randomly assigned 1:1 to receive 25 or 100 mg oral olorinab 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 linear scale between Baseline and Week 8.

RESULTS

- 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 (∆ Week 1 = −3.0; ∆ Week 2 = −3.6). Significant improvement in AAPS was observed from Baseline to Week 4 (P = 0.0043) and Week 8 (P = 0.0009).
- A summary of adverse events is provided in Table 2.
- No clinically significant changes in vital signs (including heart rate and blood pressure) or clinical safety laboratory results were observed.
- No subjects discontinued the study because of AEs.

EFFECTS ON ABDOMINAL PAIN

- The AAPS was significantly improved from Baseline at Weeks 4 and 8 in both treatment groups (Figure 3).
- Clinical response in AAPS (≥50% reduction from Baseline) was observed in 100% (11/11) of the subjects treated with both 25 and 100 mg olorinab.
- A summary of adverse events is provided in Table 2.

CONCLUSIONS

- Olorinab was generally safe and well tolerated in subjects with mild to moderate CD experiencing abdominal pain.
- AAPS were generally mild to moderate and limited in duration.
- The two adverse events (intestinal diarrhoea, acute interstitial pneumonitis) occurred in the same subject (N = 100 mg) and were not considered treatment-related (Table 2).

REFERENCES

1. Olorinab was generally safe and well tolerated in subjects with mild to moderate CD experiencing abdominal pain.
2. Olorinab was generally mild to moderate and limited in duration.
3. The two adverse events (intestinal diarrhoea, acute interstitial pneumonitis) occurred in the same subject (N = 100 mg) and were not considered treatment-related (Table 2).
4. Olorinab was generally well tolerated in healthy volunteers in a single oral dose up to 100 mg.

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