

OP212 PRECLINICAL AND CLINICAL EFFICACY OF OLORINAB, A PERIPHERALLY RESTRICTED, HIGHLY SELECTIVE FULL AGONIST OF THE CANNABINOID RECEPTOR 2 FOR THE MANAGEMENT OF VISCERAL PAIN IN INFLAMMATORY BOWEL DISEASE

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Introduction: Abdominal pain is common in patients with inflammatory bowel diseases (IBDs), including Crohn's disease (CD), and available treatments often fail to relieve this pain. Cannabinoid receptors can modulate visceral pain; however, clinical development of non-selective agonists is limited by unwanted psychoactive effects. Olorinab is a highly selective full agonist of the cannabinoid receptor 2 (CB₂) and showed low bloodbrain barrier penetration in rodents. Reported here, preclinical evaluation assessed whether olorinab reduced visceral hypersensitivity in a rat model of IBD (colitis), and a randomized, open-label, multi-centre, Phase 2a study evaluated olorinab in patients with quiescent CD experiencing abdominal pain.

Aims & Methods: In preclinical study, colitis was induced using 12 mg 2,4,6-trinitrobenzene sulfonic acid (TNBS) in 35% ethanol in rats, applied rectally. Vehicle or olorinab (3 or 30 mg/kg) was given twice daily for 5 days in control or colitis rats beginning 1 day after TNBS. Visceral mechano-sensitivity was measured *in vivo* as visceromotor responses (VMR) to colorectal distension (CRD; distension pressures 0-80 mm Hg). Colonic nociceptor firing was measured *ex vivo*. In the Phase 2a study, subjects aged 18-66 years with quiescent CD (simple endoscopic score-CD < 10 or faecal calprotectin < 500 µg/g) experiencing abdominal pain, defined as weekly average abdominal pain score (AAPS) ≥4 on a scale of 0 (no pain) to 10 (worst possible), were randomly assigned 1:1 to 25 or 100 mg oral olorinab 3 times a day (TIO) for up to 8 weeks. Primary objectives were safety and tolerability. Efficacy endpoints included change in AAPS from baseline week (BL) to weeks 4 and 8, change in AAPS from pre-dose to 1.5 hours post-dose, and proportion of clinical responders (≥30% reduction in weekly AAPS from BL).

Results: Visceral hypersensitivity was observed in vehicle-treated colitis rats with higher VMR to CRD vs healthy controls ($P < 0.05$ at 20 mm Hg; $P < 0.01$ at 40-80 mm Hg). Colitis rats treated with olorinab had lower VMR to CRD vs their vehicle-treated counterparts ($P < 0.001$, $N=9$ /group). Control rats treated with olorinab did not show altered VMR to CRD ($P > 0.05$, $N=8-11$ /group). Olorinab reduced colonic nociceptor hypersensitivity in a concentration-dependent manner via CB₂. In the Phase 2a study ($N=14$), AAPS significantly improved at weeks 4 and 8 from BL. Change in AAPS from BL to the time of peak concentration 115 (1.5 hours post-dose) during week 8 was -4.6 on an 11-point scale ($N=11$; $P < 0.001$). The proportion of clinical responders was 85% (11/13) at week 4 and 100% (11/11) at week 8 among evaluable subjects. Adverse events (AEs) occurred in 4/6 (67%) and 6/8 (75%) subjects who received 25 mg and 100 mg TID, respectively, and were generally mild to moderate with limited duration. AEs in ~2 subjects included drug hypersensitivity, pain in extremity, and hypomagnesaemia; 2 serious AEs (pneumonia, worsening interstitial pneumonia) occurred in 1 subject and were not considered treatment related. There were no discontinuations due to AEs, and no clinically significant changes in vital signs or laboratory results were observed.

Conclusion: Olorinab, a highly selective full agonist of CB₂, showed preclinical efficacy in reducing visceral hypersensitivity in a rat model of IBD. Olorinab-treated subjects with quiescent CD experiencing abdominal pain had an improvement in AAPS without psychoactive effects in Phase 2a. These preclinical and clinical results support further clinical development of olorinab for the treatment of abdominal pain.

Disclosure: B.Y. has received grant support from Merck and advisory board honoraria for Arena; S.M.B. is a consultant to Arena Pharmaceuticals; B.L., J.A., B.E., and K.S. are employees and shareholders of Arena Pharmaceuticals; P.D.R.H. has received grants from NIH, CCF, AbbVie, Janssen, Takeda, Genentech, and Pfizer and advisory board honoraria for Lycera, and Arena Pharmaceuticals.