achieving clinical response, clinical remission, and mucosal healing were observed at doses ≥75mg qd. The safety profile of peficitinib through wk8 was generally consistent with the known profile of JAK inhibitors.

DOP077
Immunomodulatory effects of etrasimod (APD334), an oral, potent, next-generation, selective S1P receptor modulator

S.D. Lee*[1], R. Christopher[2], L. Trokan[2], C. Lassen[2], J. Adams[2], M. Chiorean[3]
[1]*University of Washington Medical Center, Seattle, United States;* [2]*Arena Pharmaceuticals, Inc., San Diego, United States;* [3]*Virginia Mason, Digestive Disease Institute, Seattle, United States*

Background: Etrasimod is an oral potent, next-generation S1P modulator with an optimized S1P receptor activity profile that is currently in Phase 2 clinical development for ulcerative colitis.
Methods: Two randomised, double-blind studies evaluated safety, tolerability and pharmacodynamic (PD) responses of etrasimod, administered orally as single dose (dose-escalation design; 8 subjects/cohort) or repeat once daily (QD) dosing for 21 days (multiple ascending-dose design; 12 subjects/cohort), in healthy adults. PD parameters, including complete blood count (CBC) with differential, platelet count and lymphocyte immunophenotyping, were determined from peripheral blood sampling. Single-dose study assessments were Day –1, pre-dose (Day 1) and pre-specified times post-dose on Day 1, and up until Day 7 (Exit). Multiple-dose study assessments were screening, pre-dose (Day 1) and 4–8 hours post-dose on Days 1, 3, 5, 7, 9, 15, 21, 23 (Exit), and Day 28 (follow-up), with peripheral blood lymphocyte immunophenotyping performed on Days 1 and 21 (2mg cohort only).
Results: In the single-dose study, etrasimod 3mg and 5mg induced a decline in absolute number of B cells, Natural Killer cells, and T cells (absolute and subsets): lower doses (0.1, 0.35 or 1mg) had little or no effect. In the multiple-dose study, lymphocyte lowering was dose-dependent, plateauing at 2mg: median reductions in lymphocyte counts were ~67% with etrasimod 2 and 3mg, returning to baseline within 7 days of discontinuation. Reductions from baseline in T cells (as a % of white blood cell count [WBC] and lymphocytes) were greater with etrasimod (2mg) than placebo. The primary effect of etrasimod was seen in the Thelper and Tnaïve subpopulations, with a lesser extent in Tcentral memory cells (consistent with an expected retention of CCR7+ cells in secondary lymphoid tissue) [1]. Tsuppressor and Teffector memory cells were generally spared. Decreases in neutrophils were not consistently dose responsive: change from baseline in minimal neutrophil count (placebo subtracted) was $0.04–0.65 \times 10^3$/UL.
Conclusions: Etrasimod modulates lymphocyte subpopulations believed to be involved in IBD pathogenesis. These findings support further evaluation of this S1P modulator in clinical studies.
References:
[1] Gergely P, et al. Br J Pharmacol 2012;167:1035–47.

DOP078
Pharmacology and safety of etrasimod (APD334), an oral, potent, next-generation, selective S1P receptor modulator

T. Kühbacher*[1], R. Christopher[2], L. Trokan[2], C. Lassen[2], J. Adams[2], L. Peyrin-Biroulet[3]
[1]*Asklepios Westklinikum Hamburg and Christian Albrechts University, Department of Internal Medicine/Gastroenterology, Kiel, Germany;* [2]*Arena Pharmaceuticals, Inc., San Diego, United States;* [3]*Nancy University Hospital and Lorraine University, Department of Gastroenterology, Nancy, France*

Background: Etrasimod is an oral, potent, next-generation S1P modulator in clinical development for ulcerative colitis.
Methods: *In vitro*, etrasimod potency and selectivity was assessed at mouse, rat, dog and human S1P receptors in intracellular β-arrestin recruitment and cAMP accumulation assays using S1P receptor-expressing cells. *In vivo*, etrasimod (1 and 3 mg/kg, until Day 32) was evaluated in a CD4+CD45RBhigh T cell adoptive transfer model in SCID mice. Chronic toxicology studies of etrasimod once daily (QD) were conducted in rats (≤250mg/kg/day for 26 weeks) and dogs (≤15mg/kg/day for 39 weeks). In healthy adults, two randomised, double-blind studies evaluated safety, tolerability and pharmacology of single or repeat etrasimod QD dosing.
Results: Etrasimod is a potent, full agonist at human S1P1 receptors with a mean EC50 value of 6.10nM. It was selective for S1P1, with 24 fold and 4 fold selectivity versus human S1P4 and S1P5, respectively, and no activity at S1P2 and S1P3 (>1000 fold selectivity). Similar results were found in all species tested. In the T-cell adoptive transfer model, etrasimod (3 mg/kg/day) significantly inhibited weight loss and colon inflammation versus vehicle-treated controls. Chronic administration to rats was well tolerated at ≤150mg/kg/day, but 250mg/kg/day showed significant adverse effects, including mortality. Chronic administration to dogs at ≤15mg/kg/day was well tolerated. The no-observed-adverse-effect level (NOAEL) was therefore 150mg/kg/day for rats and 15mg/kg/day for dogs. Based on these study data, human safety margin for a clinically relevant dose of 2mg etrasimod were 1,068-fold and 402-fold for rats and dogs, respectively. In healthy adults, single doses of etrasimod 0.1–3mg were well tolerated; 4 events (3 subjects) of first/second degree atrioventricular block, with/without bradycardia, were reported in the 5 mg cohort. No other clinically significant safety issues were reported. Etrasimod exposure was dose proportional from 0.1–5mg, with a consistent mean terminal t1/2 (30.7–37.4 hours), and no quantifiable levels in urine analysis. With multiple QD dosing for 21 days, no safety concerns were reported and etrasimod was well tolerated at all doses (0.7–3.0mg). Etrasimod plasma exposure accumulation after 21 days was >2-fold versus single dose administration across all doses: C_{max}: 2.12–2.72; $AUC_{0–24}$: 2.33–3.03. Etrasimod produced a dose-dependent, sustained decrease in total lymphocyte count, with the maximal effect at the 2mg dose.
Conclusions: The combined preclinical/clinical safety and pharmacology profile of etrasimod provides rationale for further evaluation of this selective S1P modulator in clinical studies.

DOP079
The role of intestinal transplant in patients with complicated inflammatory bowel disease: the Cambridge experience

S.P. Yeap*[1], L.M. Sharkey[1], J.M. Woodward[1], D.C. Massey[1], S.J. Middleton[1], N.K. Russell[2], A.J. Butler[2]
[1]*Addenbrooke's Hospital, Gastroenterology, Cambridge, United Kingdom;* [2]*Addenbrooke's Hospital, Transplant Surgery, Cambridge, United Kingdom*

Background: A number of patients with inflammatory bowel disease (IBD), despite best medical and surgical interventions, fail to thrive necessitating parenteral nutrition (PN) and in rare cases considera-