Abstract 5531

RECEPTOR PROFILE AND EFFICACY OF ETRASIMOD (APD334), AN ORAL, NEXT-GENERATION SPHINGOSINE-1-PHOSPHATE RECEPTOR MODULATOR IN DEVELOPMENT FOR ULCERATIVE COLITIS

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Introduction

Of the 5 sphingosine-1-phosphate (S1P) receptor subtypes, activation of 1, 4 and 5 may be involved with decreasing intestinal inflammation and subtypes 2 and 3 with cardiac, pulmonary and tumor-related side effects. Current S1P modulators lack receptor selectivity and are associated with cardiopulmonary side effects. Etrasimod is a next-generation oral S1P modulator with an optimized S1P receptor activity profile currently in Phase 2 clinical development for treating ulcerative colitis (UC). The objective of these studies was to evaluate the receptor profile of etrasimod and its effects in a UC model in SCID mice.

Aims & Methods

Agonist (S1P1-5) and antagonist (S1P2-3) human S1P receptor β-arrestin recruitment assays were used to determine EC_{50} values for etrasimod. EC_{50} determinations were performed using 10 concentrations and triplicate determinations made at each test concentration. A recombinant human S1P1 receptor agonist cAMP accumulation assay was developed utilizing the same cell line. Additional studies were performed with rodent S1P1 receptors. In vivo, $CD4+CD45RB^{high}$ T cells were isolated from wild type mice and transferred into SCID mice to induce colon inflammation and pathology reminiscent of human UC. Etrasimod (1 and 3 mg/kg) was administered prophylactically from the day of T-cell transfer until Day 32. The relationship between etrasimod plasma concentrations and lymphocyte counts was explored after oral administration in male BALB/c mice.

Results

Using β-arrestin assays, etrasimod demonstrated potent activity at the S1P1 receptor with a mean EC_{50} of 6.10 nM, and partial activity at S1P4 and S1P5 receptors (EC_{50} 147 nM and 63% efficacy for S1P4 receptor vs. S1P and EC_{50} 24.4 nM and 73% efficacy for S1P5 receptor vs. S1P). Etrasimod was inactive at concentrations up to 10 μM in S1P2 or S1P3 assays performed in agonist or antagonist modes. In the S1P1 receptor cAMP accumulation assay, etrasimod was a potent agonist (mean EC_{50} 0.199 nM). Similar potencies were found for non-human S1P1 receptors. Mice that received $CD4+ CD45RB_{high}$ T cells progressively developed symptoms of colitis compared with mice that received unsorted CD4+ T cells. Prophylactic treatment with 3 mg/kg/day etrasimod and 1 mg/kg/day FTY720 significantly inhibited weight loss and colon inflammation versus vehicle-treated controls. Effective lymphocyte-lowering was shown in normal mice at the same doses.

Conclusion

These data demonstrate potent activity of etrasimod at human and non-human S1P1 receptors, with 24X and 4X respective selectivity over human S1P4 and S1P5 and no activity at human S1P2 or S1P3. Etrasimod was also efficacious in an in vivo model of UC in SCID mice. Based on these results, etrasimod may provide systemic and local immune cell modulation in the treatment of UC by selectively targeting S1P receptor subtypes 1, 4 and 5 while avoiding receptors associated with safety issues.

References

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