Preclinical Safety Assessment of Etrasimod (APD334), An Oral Sphingosine-1-Phosphate Receptor (S1P) Modulator with a Favorable Profile

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Background

- Sphingosine-1-phosphate (S1P) is a membrane-derived lysophospholipid signaling molecule – implicated in a vast array of physiological and pathological processes, primarily via activation of S1P1–S1P5 receptors.

Methods

- Potency of etrasimod at human and non-human (mouse, rat, dog, monkey) S1P receptors was assessed in radioligand binding assays using S1P1 receptor-expressing cells (HepG2 cells).

Results

- Etrasimod showed high potency at human and non-human S1P1 receptors, with IC50 values ranging from 0.00001 to 0.0005 µM.

Table 1. Similar EC50 values and efficacies were found in all species tested: mean EC50 values were 3.65–3.07 nM and efficacy was >80% for S1P1 receptors in the 3-min assay.

Human safety margin estimates: based on steady-state systemic exposures from the chronic toxicology studies in rats and dogs.

Clinical toxicology findings

- Consistent with the pharmacological effect of etrasimod on lymphocyte trafficking, moderate-to-marked, partially reversible, decreases in circulating lymphocytes were found at all dose levels, with the exception of lymphopenia in the lymph nodes and spleen in dogs, and increased thyroxine levels in rat and dog studies.

Table 2. Etrasimod was generally well tolerated in rats, with expected and typical pharmacological effects with 210 mg/kg/day, and in dogs with doses 215 mg/kg/day.

Table 3. Administration of etrasimod at 235 mg/kg had no effects on respiratory frequency, tidal volume or minute volume, or on gross behavioral or neurological state in rats.

Figure 1. Safety margin relationships for etrasimod: comparing preclinical safety in rats and dogs with the human pharmacodynamic profile.

Table 4. Acute administration of etrasimod at 10 and 20 mg/kg had no effect on any CV parameter or body temperature in dogs.

Table 5. Acute administration of etrasimod at 100 mg/kg/day had no effect on any CV parameter or body temperature in dogs.

Table 6. Etrasimod had a wide safety margin based on exposure date from the chronic toxicity studies in rats and dogs.

Conclusions

- Etrasimod, a potent, full agonist at the S1P1 receptor across a range of species, with selectivity at S1P1 versus other S1P receptors, is a potential therapeutic for IBD.

Author Disclosures


Acknowledgments

- Authors disclose potential conflicts of interest and funding sources. No other disclosures.

References


Table 7. Summary of adverse drug reactions in beagle dogs.

Table 8. Summary of adverse drug reactions in beagle dogs.

Table 9. Summary of adverse drug reactions in beagle dogs.

Table 10. Summary of adverse drug reactions in beagle dogs.

Table 11. Summary of adverse drug reactions in beagle dogs.

Table 12. Summary of adverse drug reactions in beagle dogs.

Table 13. Summary of adverse drug reactions in beagle dogs.

Table 14. Summary of adverse drug reactions in beagle dogs.

Table 15. Summary of adverse drug reactions in beagle dogs.