A Peptide Antagonist of Integrin α4β7

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Pharmacokinetics and Pharmacodynamics Following Oral Administration of PTG-100, a Peptide Antagonist of Integrin α4β7

IntrOduction

The α4β7 integrin is a clinically validated target in inflammatory bowel disease (IBD) as reflected by the FDA-approval of the humanized monoclonal antibody vedolizumab (Entyvio®) for the treatment of moderate-to-severe ulcerative colitis (UC) and Crohn's disease. PTG-100 and vedolizumab both bind to α4β7 on circulating memory effector T cells in the blood and block their homing to intestinal tissues that express the ligand Mac-1 integrin. PTG-100 is a novel oral α4β7 antagonist peptide that has minimal systemic absorption and is therefore largely restricted to the gut tissues. A Phase 1 study in normal healthy volunteers has now been completed (see Abstract #3358). The aim of these studies was to characterize the pharmacokinetic (PK) properties and pharmacodynamic (PD) activities of PTG-100 in mice and cynomolgus monkeys and to establish a potentially efficacious dose range in UC patients.

Methodology

We conducted PK and PD studies in mice and cynomolgus monkeys. Peptide concentrations were measured by mass spectrometry. PD responses in whole blood were measured by α4β7 memory T cell receptor occupancy, surface expression, and cell numbers using Fluorescence Activated Cell Sorting (FACS). Cell trafficking in blood and gut lymphoid tissues were measured by FACS or immunohistochemistry (IHC).

Pharmacokinetics – Mice

Oral dosing of PTG-100 in normal mice results in high exposure in the small intestine, colon, Peyer’s Patches (PP), and mesenteric lymph node (MLN) with minimal exposure in the blood. These results indicate that PTG-100 has low systemic absorption and the peptide is stable in the GI tract of non-human primates.

Pharmacodynamics – T Cell Trafficking

Daily dosing with PTG-100 in murine DSS colitis models showed a dose-dependent reduction in CD4+CD45RBlow β7+ cells in the Peyer’s Patches, and concomitant increase in the blood as measured by FACS. There was also a strong reduction of β7+ cell infiltration into lamina propria lesions of the distal colon as measured by IHC.

Pharmacodynamics – Target Engagement

PTG-100 receptor occupancy results in downregulation of α4β7 integrin expression and increases in circulating effector memory T cells in blood.

Summary and Conclusions

PTG-100 is a novel oral α4β7-selective antagonist being developed for the treatment of patients with ulcerative colitis. It is largely gut restricted in mice and cynomolgus monkeys. Mouse blood PD responses indicate that PTG-100 binds to α4β7 integrin and causes a reduction in integrin expression resulting in the inhibition of memory T cell trafficking to gut lymphoid tissues. Allometric scaling was used to estimate the human effective dose range based on data in the mouse and cynomolgus monkey (data not shown).

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