Establishing the human equivalent dose for PTG-100, an oral peptide antagonist of integrin α4β7
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ABSTRACT

PTG-100, a novel selective oral peptide antagonist of α4β7 integrin, is being developed for the treatment of patients with moderate to severe ulcerative colitis. PTG-100 alters trafficking of gut homing T cells in preclinical animal models, and its potency and selectivity are similar to that of the approved anti-α4β7 antibody vedutizumab. Pharmacokinetic studies in rodent or cynomolgus (cyno) monkeys show that PTG-100 exposure in the blood is <0.1% of dose, but >90% of dose in the small intestine and colon and up to 40% in feces, which indicate PTG-100 is orally stable and largely gut restricted. To help establish the potential efficacious dose range in humans, we developed a receptor occupancy assay to measure occupancy of CD4+ memory α4β7+ T cells in mouse blood and gastrointestinal (G) tissues and in cyno blood. Daily dosing of PTG-100 and other similar antagonists in DSS (dextran sodium sulfate) treated mice showed a significant reduction in disease activity index (DAI), mucosal histopathology, and number of β7+ positive cells in the distal colon lesions. At these efficacious oral doses, α4β7 receptor occupancy in the blood, mesenteric lymph nodes, and Peyer’s Patches ranged from 45-81% at 4 h post dose. Single and multiple oral gavage administration of PTG-100 in healthy cynons showed that despite low systemic exposure, occupancy of blood αβ7 by PTG-100 is dose proportional, time-dependent, and influenced by the small intestine and fasted state of the animal. Allometric scaling from the mouse to human based on whole body surface area suggests that a similar level of blood receptor occupancy is associated with the cyno equivalent dose. The data suggests that 100% receptor occupancy over 24 h in the blood or gut in the mouse DSS model is not required for efficacy by an oral gut-restricted α4β7 antagonist. Together, these studies point to blood receptor occupancy and possibly receptor expression as useful clinical surrogates for the local effects of PTG-100 in the intestine.

RESULTS

Table 1. PTG-100 is selective for human circulating α4β7+ memory T cells.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>MAbα4/β7</th>
<th>VSCAN-4</th>
<th>KAM-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50 [nM]</td>
<td>1.3</td>
<td>&gt;100,000</td>
<td>&gt;100,000</td>
</tr>
</tbody>
</table>

Table 2. PTG-100 exposure is largely gut-restricted (Fp<0.5). 30mg/kg PO administration in healthy C57BL/6 mouse.

<table>
<thead>
<tr>
<th>Dose [mg/kg]</th>
<th>AUC [µg/mL/h]</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
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<tr>
<td>18</td>
<td>88</td>
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<td>53</td>
<td>30</td>
</tr>
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<td>160</td>
<td>79</td>
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PHARMACOKINETIC STUDIES

PTG-100 reduces number of β7+ cells in the lamina propria of the distal colon comparable to α4β7. 15 day chronic DSS colitis study.

15 day chronic DSS colitis study. BALB/c mice were treated continuously with 3% DSS. PTG-100 total daily dose was a combination of oral gavage BID plus drug in the drinking water. At 4 h post last dose, whole blood, MLN and PP were collected for α4β7 receptor occupancy of memory CD4+ T cells measured by FACS. Distal colon sections were fixed and processed for β7+ cell IHC staining using the anti-β7 antibody M293. Data is presented as means ± SD. n=10 mice per group. Statistical significance relative to vehicle control assessed by one-way ANOVA, *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns, not significant.

PTG-100 increases circulating numbers of α4β7+ but not α4β7- CD4+ effector memory T cells in blood.

Figure 4. PTG-100 receptor occupancy of CD4+ α4β7+ memory T cells in whole blood correlates to mesenteric lymph node (MLN) and Peyer’s Patches (PP).

Figure 5. PTG-100 reduces number of β7+ cells in the lamina propria of the distal colon comparable to α4β7. 15 day chronic DSS colitis study.

Figure 6. Specific downregulation of α4β7 expression on CD4+ effector memory T cells in blood.

PHARMACODYNAMICS IN DSS COLITIS MICE

PTG-100 treatment decreases disease activity index (DAI) compared to vehicle control.

CONCLUSIONS

- PTG-100 is the first oral antagonist selective for α4β7 integrin, an IBD target clinically validated by the approval of vedutizumab.
- JR data show that PTG-100 exposure is gut restricted. Exposure in the small intestine, colon and Peyer’s Patches is 150 to 480 fold higher compared to plasma based on AUC.
- PTG-100 reduces Disease Activity Index and ββ7 cell number in the colon lamina propria in the mouse DSS colitis model comparable to α4β7 mAb.
- Target engagement by PTG-100 is accompanied by specific downregulation of α4β7 expression and increase in circulating effector memory T cells in the blood of colitis mice which indicate pharmacological activity of PTG-100.
- High exposure in gut tissues and loss of α4β7 expression may explain PTG-100’s significant pharmacological activity at less than 100% blood receptor occupancy.
- PTG-100 exhibits dose dependent target engagement in cynomolgus monkeys.
- Human equivalent doses established by allometric scaling based on blood target engagement and pharmacological activity observed in colitis mice and healthy monkeys.

PTG-100 is currently being investigated in a Phase 1 clinical trial in normal healthy volunteers.

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