SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF THE NOVEL ORAL PEPTIDE THERAPEUTIC
PTG-100 (α4β7 INTEGRIN ANTAGONIST) IN NORMAL HEALTHY VOLUNTEERS

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INTRODUCTION
Protagonist Therapeutics, Inc. is developing PTG-100, an orally stable peptide therapeutic, for the treatment of patients with moderate to severely active ulcerative colitis (UC). PTG-100 potently and selectively inhibits α4β7 integrin on leukocytes, the same target as the FDA-approved antibody product vedolizumab (Entyvio®). PTG-100 does not bind α4β1 integrin.
PTG-100 is designed to be stable against GI mechanisms of peptide degradation. When administered orally in mice, PTG-100 has high exposure in the colon, small intestine, Peyer's patches, and in the mesenteric lymph nodes with <1% systemic bioavailability; therefore, exposure in mice is largely restricted to the GI tract. Thus, PTG-100 can target α4β7 integrin within the GI tract of the host.
Both in vitro and in vivo pharmacology studies have been conducted to assess the activity on cell adhesion, and toxicity of PTG-100. In a depletion substitute (DDS)-reduced colitis mice model, PTG-100 oral administration induced a dose-dependent reduction in α4β7+ memory T cell homing to inflamed gut tissue and a significant improvement in mucosal damage as assessed by 3-MA endpoints.
We have developed peripheral blood pharmacodynamics (PD) markers of receptor occupancy (RO) and receptor expression (RE) using FACS analysis of whole blood from healthy mice and cynomolgus that reflect target engagement in the GI tissue. These analyses have demonstrated that blood RO of <50% is correlated with in vivo efficacy in mouse colitis studies. Levels of circulating α4β7+ memory T cells were increased when normalized to total CD4 cells following PTG-100 dosing, confirming that blocking homeing of α4β7+ memory T cells reduces these to baseline.
In 3-D GLP toxicity studies, no adverse toxicological findings were observed at once daily doses up to 50 mg/kg/day and 75 mg/kg in both rats and monkeys, respectively. We conducted a randomized, double-blind, placebo-controlled Phase 1 first-in-human (FIH) study to evaluate safety/ tolerability, PK and PD in 78 normal healthy volunteers at a single site in Australia.

METHODLOGY
The primary objective of the study was to determine the safety/tolerability of single and multiple dose administration of PTG-100 in normal healthy volunteers. The secondary objectives were to assess the maximally tolerated dose (MTD), PTG blood, urine, feces, PD activity, RO and RE; and PD biomarker levels of CD4+ and CD8+ T cells markers, derived from the animal studies, were designed to evaluate PD-based POC in the Phase 1 study.
The study consisted of three part: a single ascending dose, multiple ascending dose (once daily dosing for 14 days up to a maximum dose of 1000 mg) using a liquid phosphate buffer formulation and a single dose crossover to establish the relative bioavailability of a capsule formulation compared to the liquid formulation (Fig. 2a). Subjects were closely monitored for adverse events (AEs), physical examination and vital signs, bioavailability of a capsule formulation compared to the liquid formulation (Fig. 1).

RESULTS
Safety Results
PTG-100 was administered to 64 normal healthy volunteers up to a maximum dose of 1000 mg QD for 14 days. Fourteen subjects received placebo. PTG-100 was well-tolerated; see Tables 1 and 2. There were no SAEs or dose-limiting toxicities observed. All AEs were mild to moderate severity.
The most common AEs reported by subjects receiving PTG-100 were headache (n=5, 20%), URI (n=6, 24%), fatigue (n=5, 21%), nausea (n=3, 13%). No dose-dependent increase in specific AEs was observed.
One subject (in Cohort 6 (1000 mg) PTG-100) withdrew from the study due to a toothache (not related to the study drug).
There were no clinically significant abnormalities or trends in clinical labs, ECGs or vital signs.

INTRODUCTION
• Findings, ECGs and safety labs. The safety monitoring committee made the review and meta-analysis including Continuing Medical Education questions. Am J Gastroenterol 107(2):S77-77.

CONCLUSIONS
• Overall, PTG-100 was well-tolerated following single and multiple dose administration in normal healthy volunteers up to a maximum dose of 1000 mg.
• The PK and PD data indicate that oral administration of PTG-100 results in extremely low plasma levels with evidence of sustained target engagement and saturation of pharmacodynamic activity in peripheral blood α4β7+ memory T cells in a dose- and time-dependent manner.
• The Phase 1 data supports estimation of a human equivalent dose and further development of PTG-100 in patients with ulcerative colitis.

REFERENCES
• Overall, UC. Ulcerative Colitis. Lancet 2012; 380: 1606–19