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, its presence is largely restricted to the GI tract. Thus, PTG-100 can target α4β7 integrin within the GI tissue compartment.

Both in vitro and in vivo pharmacology studies have been conducted to assess the activity, mechanism of action, and toxicity of PTG-100. In a dextran sulphate sodium (DSS)-induced colitis mouse 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 blinded endoscopy.

We have developed peripheral blood pharmacodynamic (PD) markers of receptor occupancy (RO) and receptor expression (RE) using FACS analysis of whole blood from healthy mice and cynos that reflect target engagement in the GI tissue. These analyses have demonstrated that blood RO of <50% is correlated with in vivo efficacy in the 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 homing of α4β7+ memory T cells redistributes these cells to the blood.

In 42-day (GLP) toxicology studies, no adverse toxicological findings were observed at once daily doses up to 90 mg/kg/day and 75 mg/kg/day 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.

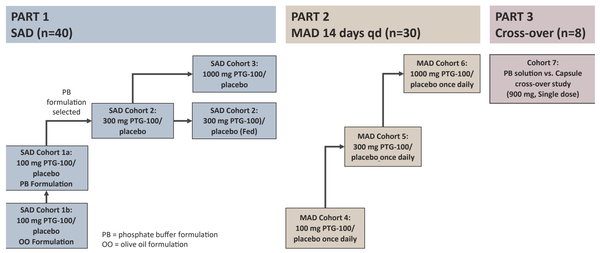
METHODOLOGY

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), PK (blood, urine, feces), PD activity (RO and α4β7 RE on peripheral blood memory T cells). The PD markers, derived from the animal studies, were designed to evaluate PD-based POC in the Phase 1 study.

The study consisted of three parts: 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. 1).

Subjects were closely monitored for adverse events (AEs), physical examination findings, ECGs and safety labs. The safety monitoring committee made the determination of dose escalation based on review of blinded safety data.

Figure 1. Phase 1 study schema



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 (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=13, 20.3%), URTI (n=4, 6.3%) back pain (n=3, 4.9%), fatigue (n=2, 3.1 %). No dose-dependent increase in specific AEs was observed.
- One subject in Cohort 6 (1000 mg PTG-100 PB) 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.

Table 1. Summary of treatment-emergent adverse events for the SAD cohorts

	PTG-100					Placebo			Total
	PB 100mg	OO 100mg	PB Fasted 300mg	PB Fed 300mg	PB 1000mg	PB Fasted	OO	PB Fed	
	Cohort 1a	Cohort 1b	Cohort 2	Cohort 2	Cohort 3				
	(N=8)	(N=8)	(N=8)	(N=8)	(N=8)	(N=6)	(N=2)	(N=2)	(N=40)
All TEAEs	0	2	7	0	2	2	0	1	14
Treatment Related TEAEs	0	0	6	0	0	1	0	1	8
SAEs	0	0	0	0	0	0	0	0	0
AEs Leading to Discontinuation	0	0	0	0	0	0	0	0	0

- Cohort 1 (100 mg) was conducted with PTG-100 or placebo formulated in phosphate buffer (PB) or olive oil (OO). PB was then selected as the formulation for the remainder of the SAD and MAD cohorts.
- Cohort 2 (300 mg) was conducted in a fasted state followed by washout and then the same subjects dosed on a high fat diet.
- All dose cohorts consisted of 8 PTG-100 treated subjects and 2 placebo-treated subjects. Placebo PB fasted subjects were pooled for the analysis.

Table 2. Summary of treatment-emergent adverse events for the MAD cohorts

	PTG-100			Placebo	Total
	PB 100mg	PB 300mg	PB 1000mg	PB Fasted	
	Cohort 4	Cohort 5	Cohort 6	(N=6)	(N=30)
	(N=8)	(N=8)	(N=8)		
All TEAEs	11	8	8	6	33
Treatment Related TEAEs	5	2	1	3	11
SAEs	0	0	0	0	0
AEs Leading to Discontinuation	0	0	1	0	1

- All subjects were fed a standard diet prior to dosing.
- All dose cohorts consisted of 8 PTG-100 treated subjects and 2 placebo-treated subjects.
- Placebo subjects were pooled for this analysis.

Pharmacokinetic Results

- As expected for a GI-restricted drug, PTG-100 plasma levels were extremely low and increased in a dose-dependent manner with both single (Fig. 2a) and multiple dosing (Fig. 2b).
- There was minimal evidence of drug accumulation with multiple dosing.
- Minimal drug was recovered in the urine (Table 3). Approximately 8-16% of intact drug was recovered in the feces (MAD cohorts 5 and 6), confirming that the drug was stable throughout the GI tract.

Figure2a. Single Ascending Dose

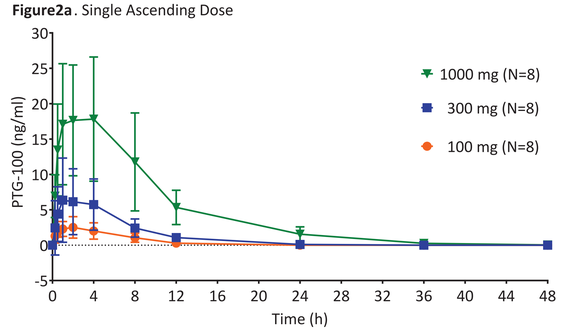


Figure 2b. Multiple Ascending Dose

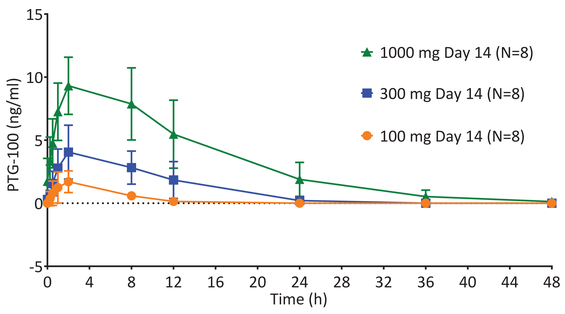


Table 3. PTG-100 excretion in the urine and feces

Cohort	Dose (mg)	% of Dose Excreted in Urine	% of Dose Excreted in Feces
5	300	0.07%	7.6%
6	1000	0.07%	15.8%

Pharmacodynamic Results

- Similar to observations in the healthy and colitis mice studies, PTG-100 blood RO on CD4+ memory α4β7+ T cells increased in a dose-dependent manner in both SAD and MAD (Figure 3a) cohorts in Study PTG-100-01. Based on the data in the mouse colitis studies, the blood RO is a correlate of target engagement in the GI tissue. These levels persisted to 24 hours with once daily dosing, indicating that a sustained level of target engagement was achieved with once daily dosing over 14 days.
- Consistent with the mouse models, α4β7 RE on CD4+ memory T cells (e.g. receptor down-regulation) was reduced following single and multiple (Figure 3b) dosing. The maximal effect was achieved at the 300 mg dose level, suggesting a potentially saturating dose in healthy human subjects.
- At 12 and 24 hours following the last dose of PTG-100, blood RO and RE levels at the 300 mg dose level exceeded threshold levels in the healthy mice at a comparable dose level based on whole body surface area allometric scaling (i.e. approx. 50 mg/kg) (Table 4). Since inhibition of cell trafficking and improvements in disease activity were observed in colitis mice at a similar dose level, the data suggest a potentially efficacious dose of approximately 300 mg in humans.

Figure 3a. ↑α4β7 Receptor Occupancy (%RO)

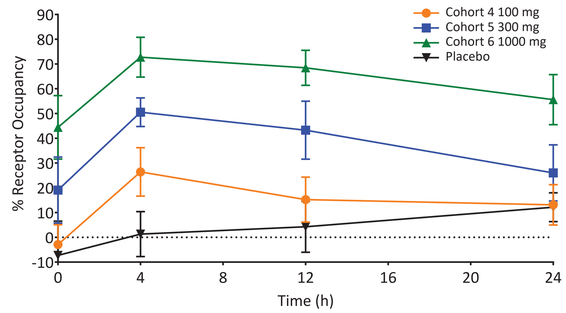


Figure 3b. ↓ α4β7 Receptor Expression (%RE)

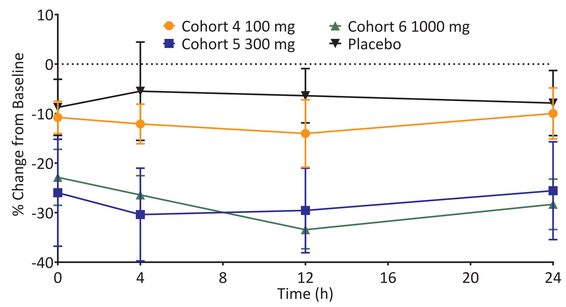


Table 4. Translating Pre-clinical to Clinical PD Readout (RO and RE)

Species and Dose	%RO @12h	%RO @24h	%RE @12h	%RE @24h
Healthy Mice 50 mg/kg	38%	8%	27%	14%
Healthy Humans 300 mg	43%	26%	29%	26%
Healthy Humans 1,000 mg	70%	56%	32%	28%

SUMMARY

- In this Phase 1 FIH study in NHVs, PTG-100 was well-tolerated; there were no SAEs or dose-limiting toxicities reported.
- Both single and multiple dosing was escalated to 1000 mg, the highest dose tested in the trial.
- As expected for a GI-restricted drug, blood levels of PTG-100 were extremely low with minimal drug accumulation with multiple dosing.
- Similar to observations in healthy and colitis mice studies, PTG-100 blood RO on CD4+ memory α4β7+ T cells increased in a dose-dependent manner in the SAD and MAD cohorts. RO levels persisted to 24 hours in the absence of detectable plasma drug levels, indicating sustained target engagement with QD dosing over 14 days. The blood RO is a correlate of target engagement in the GI tissue.
- Consistent with observations in the mouse models, α4β7 RE on CD4+ memory T cells was reduced following single and multiple dosing with a potentially saturating dose of 300 mg in human subjects.
- Both blood RO and RE levels at the 300 mg dose level exceeded threshold levels in the healthy mice at a comparable dose level (i.e. approx. 50 mg/kg/day). Since inhibition of cell trafficking and improvement in disease activity was observed over a dose range of 6-55 mg/kg/day in the colitis mice, the data suggest a potentially efficacious dose of approximately 300 mg in humans.

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 pharmacologic activity in peripheral blood CD4+ 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.
- A Phase 2 study in patients with ulcerative colitis is currently planned.

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