PTG-100, an Oral Gut-Restricted Peptide α4β7 Antagonist, Induces Clinical and Histologic Remission in Patients with Moderate to Severely Active Ulcerative Colitis

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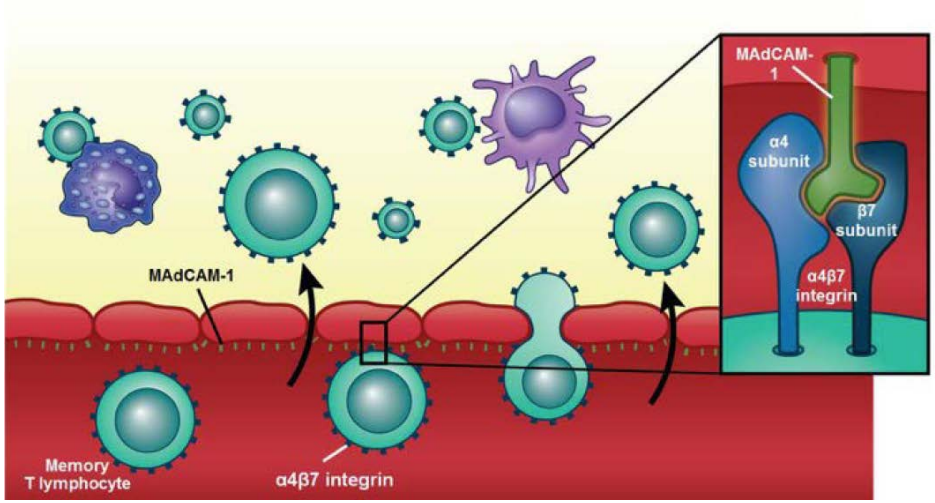
Disclosures

Dr. Sandborn reports consulting fees from Abbvie, Akros Pharma, Allergan, Ambrx Inc., Amgen, Ardelyx, Arena Pharmaceuticals, Atlantic Pharmaceuticals, Avaxia, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Conatus, Cosmo Technologies, Escalier Biosciences, Ferring, Ferring Research Institute, Forward Pharma, Galapagos, Genentech, Gilead Sciences, Immune Pharmaceuticals, Index Pharmaceuticals, Janssen, Kyowa Hakko Kirin Pharma, Lilly, Medimmune, Mesoblast, Miraca Life Sciences, Nivalis Therapeutics, Novartis, Nutrition Science Partners, Oppilan Pharma, Otsuka, Palatin, Paul Hastings, Pfizer, Precision IBD, Progenity, Prometheus Laboratories, Qu Biologics, Regeneron, Ritter Pharmaceuticals, Robarts Clinical Trials (owned by Health Academic Research Trust or HART), Salix, Seattle Genetics, Seres Therapeutics, Shire, Sigmoid Biotechnologies, Takeda, Theradiag, Theravance, Tigenix, Tillotts Pharma, UCB Pharma, Vascular Biogenics, Vivelix; research grants from Atlantic Healthcare Limited, Amgen, Genentech, Gilead Sciences, Abbvie, Janssen, Takeda, Lilly, Celgene/Receptos; payments for lectures/speakers bureau from Abbvie, Janssen, Takeda; and holds stock/stock options in Escalier Biosciences, Oppilan Pharma, Precision IBD, Progenity, Ritter Pharmaceuticals

PTG-100

Oral α4β7-specific, GI-restricted, Targeted Therapy for IBD

- First-in-class potential as a GI-restricted α4β7-specific blocker
  - Small constrained peptide
  - ~2.5 kDa
- α4β7 integrin, a clinically validated IBD target
- Oral, once daily dosing
- Blood-based PD biomarkers reflect local target engagement with effects on trafficking



Briskin M, et al *Am J Pathol.* 1997;151:97-110

Phase 2 PROPEL Study in Ulcerative Colitis

Randomized, double-blind, placebo-controlled adaptive parallel design

- 12 week induction study, QD dosing
- Primary endpoints: Clinical remission, safety and tolerability

PROPEL STUDY

Moderate to severe UC
N~260, ~100 sites

Enrollment Criteria:

- Mayo Score 6-12
- Central read endoscopic score ≥ 2
- Biologics-naïve or TNFα-experienced (≤ 50%)

Interim Analysis
n = 65

- Placebo
- 150 mg QD
- 300 mg QD
- 900 mg QD

Interim Analysis

Adhering to the most current and stringent definition of clinical remission

Criteria	Stool Frequency	Rectal Bleeding	Endo-scopy	Total Score
Score	0-1*	0	0-1	0-2

* change of one or more from baseline

Interim futility analysis based on 1° end point of clinical remission

Baseline Demographics

Interim Analysis Dataset (n = 65)

Demographic	Placebo	150 mg	300 mg	900 mg
Age (mean)	42.4	45.2	43.7	40.9
Gender (% M)	57	72	46	35
BMI (kg/m^2)	23.4	25.7	24.4	24.4
Duration of UC (years)	7.5	5.1	6.9	5.6
Baseline Total Mayo Score	8	8.1	8.9	8.3
% TNF-experienced	29.4	37.5	31.3	43.8

- Patients were balanced across all treatment arms

Interim Analysis

Futile Outcome Driven by Unusually High Placebo Rates

- Interim outcome (n=65) declared futile by DMC and trial was discontinued
- No safety concerns were noted
- Unusually high placebo effect was observed: 4/17 (23.5%)
  - Historic average for similar trials is ~ ≤6%
- A comprehensive data review was undertaken
  - Operational misconduct and trial design issues were ruled out
  - Issues with central endoscopy reading were identified
    - All 4 PBO clinical remitters were scored by a single reader
    - Friability incorrectly scored by reader
- An independent blinded re-read of endoscopy videos was conducted by Robarts Clinical Trials

Re-analysis Based on Endoscopy Re-Reads

Interim dataset summary (n = 65)

- **Original Reads**
- **High Placebo Rate**

	Remission	Endoscopic Response
150 mg	1/16 (6%)	1/16 (6%)
300 mg	2/16 (13%)	2/16 (13%)
900 mg	**3/16 (19%)**	**4/16 (25%)**
PBO	4/17 (24%)	4/17 (24%)

- **Re-read**
- **Normal Placebo Rate**

	Remission	Endoscopic Response
150 mg	1/16 (6%)	1/16 (6%)
300 mg	2/16 (13%)	2/16 (13%)
900 mg	**3/16 (19%)**	**3/16 (19%)**
PBO	1/17 (6%)	1/17 (6%)

- 1/17 (5.9%) placebo rate of remission; this indicated non-futile outcome
- Efficacy observed in PTG-100 higher dose arms

Re-analysis Based on Endoscopy Re-Reads

Full Dataset Summary (n = 83)

Blinded endoscopy re-reads on complete data set (n=83)

Criteria	Placebo	150 mg	300 mg	900 mg
# Patients	21	22	21	19
Clinical Remission	1 (4.8%)	2 (9.1%)	2 (9.5%)	3 (15.8%)
Endoscopic Response	1 (4.8%)	2 (9.1%)	3 (14.3%)	3 (15.8%)

- Placebo remission rate in line with historical norms (1/21, 4.8%)
- Efficacy observed in PTG-100 higher dose arms
  - 900 mg arm showed 11% delta over PBO

PTG-100 is Safe and Well-Tolerated

Full Analysis Set (n=98)

	PBO (n=21)	150 mg (n=22)	300 mg (n=25)	900 mg (n=20)
Subjects with at least one AE	10 (48%)	6 (27%)	10 (40%)	12 (60%)
Subjects with SAEs	1 (4.8%)	2 (9.1%)	1 (4%)	1 (5%)
Discontinuations (n=25/arm)	3 (14%)	3 (14%)	4 (16%)	2 (10%)
AEs leading to d/c	1 (4.8%)	2 (9.1%)	0 (0%)	1 (5%)
Deaths	1 (4.8%)	0 (0%)	0 (0%)	0 (0%)

- All SAEs and AEs leading to discontinuation were due to worsening of UC
- Cause of death in placebo patient:
  - Mesenteric ischemia due to complications of UC surgery

Histopathology Analysis

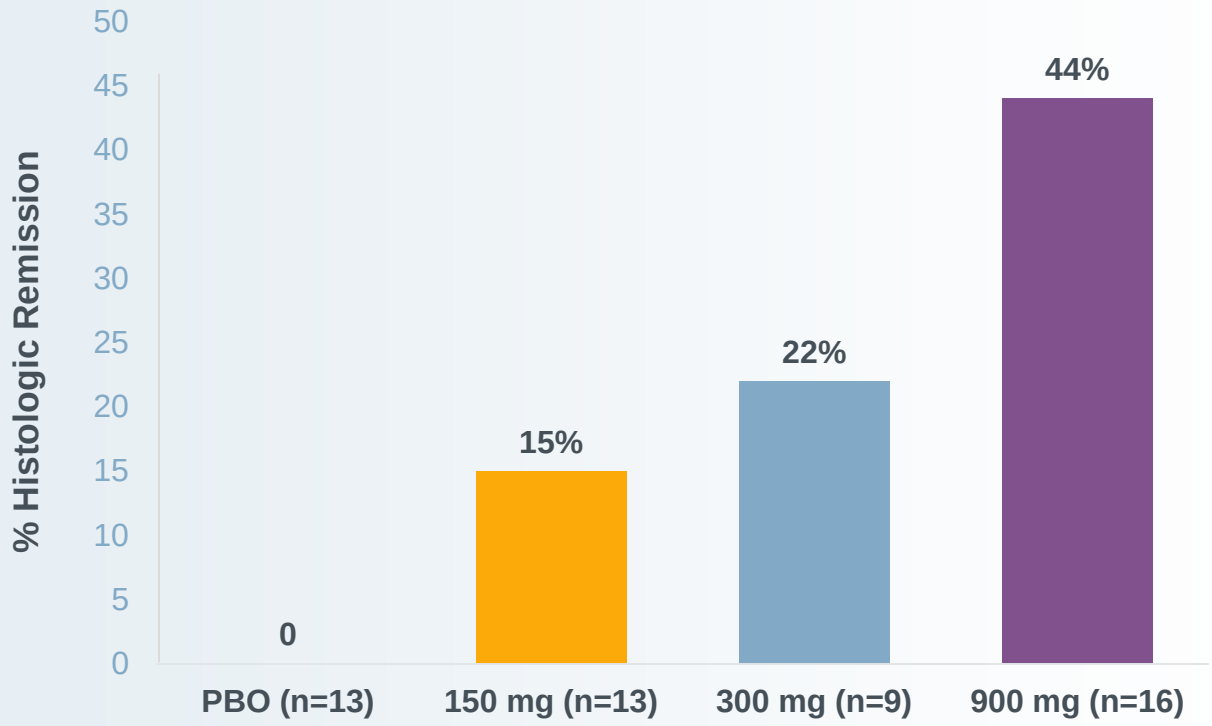
Robarts Histopathology Index (RHI)

- Four components
  - Chronic Inflammatory Infiltrate
  - Lamina Propria Neutrophils
  - Epithelial Neutrophils
  - Erosions/Ulcerations
- Included patients with disease activity at baseline (RHI > 3)
- Histologic remission defined as an RHI score ≤3 with no neutrophils, erosions, or ulcerations

Mosli MH, Feagan BG, Zou G, *et al Gut* 2017;**66:**50-58

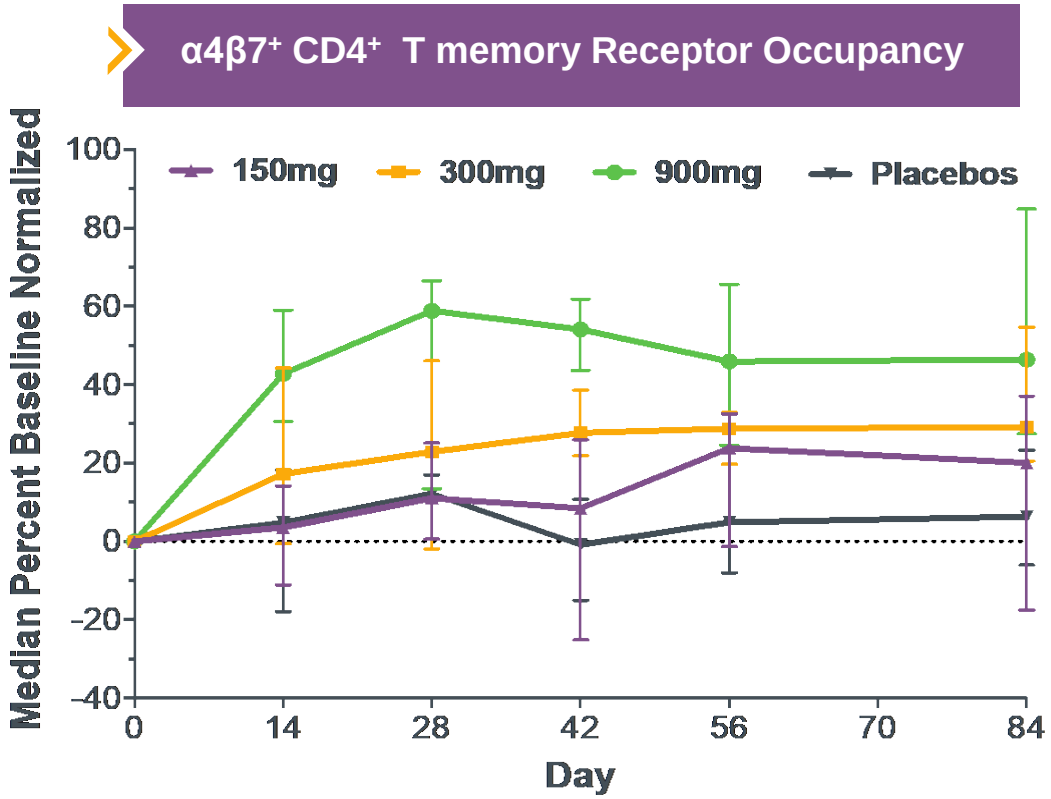
Dose-dependent Increase in Rates of Histologic Remission

Defined as an RHI score ≤ 3 at Week 12



PTG-100 Does Not Require 100% Target Engagement in Blood for Clinical Efficacy

PROPEL STUDY



- The above data is consistent with previous pre-clinical colitis and Phase 1 PD results
- Receptor occupancy in blood and in the GI tissue are correlated in preclinical studies (data not shown)

PTG-100 Phase 2 PROPEL Study

Conclusions

1. Initial erroneous central read endoscopy scores led to a futile outcome. Re-analysis based on endoscopy re-reads indicated a non-futile outcome and clinical efficacy in higher dose arms
2. These data must be interpreted with caution given that the re-read was post hoc, the sample size is relatively small, and changes in the outcome of a small number of patients led to different conclusions
3. PTG-100 is safe and well-tolerated, and the totality of the data which include clinical, endoscopic, histologic, and biomarker data are consistent with both a biological and clinical response and demonstrated dose response
4. Validation of GI-restricted approach with oral α4β7-integrin specific antagonist for potential treatment of UC.
   Current data warrants further clinical development of PTG-100.

Thanks to the patients, families and investigators for their participation in the PROPEL study.