# A Phase 2 randomized, double-blind, placebo-controlled, multi-center study to evaluate the safety and efficacy of the oral, gut-restricted α4β7 integrin peptide antagonist PN-943 in patients with moderate to severe ulcerative colitis: the IDEAL Study

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and the IDEAL Study Group

DDW2022
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# DISCLOSURES

**Bruce Sands** has received consultancy fees from: AbbVie, Abivax, Alimentiv, Amgen, Arena Pharmaceuticals, Artugen Therapeutics, AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Calibr, Celltrion Healthcare, ClostraBio, Entera, Evommune, Galapagos, Genentech, GossamerBio, HMP Acquisition, Index Pharmaceuticals, Innovation Pharmaceuticals, Janssen, Johnson & Johnson, Kaleido, Lilly, Merck, MiroBio, Morphic Therapeutic, MRM Health, Pfizer, Progenity, Prometheus Biosicences, Q32 Bio, Sun Pharma, Takeda, Target RWE, Teva, Theravance Biopharma, TLL Pharmaceutical, Ventyx Biosciences; research funding from Bristol Myers Squibb, Janssen and Pfizer; and stock options from Ventyx Biosciences.

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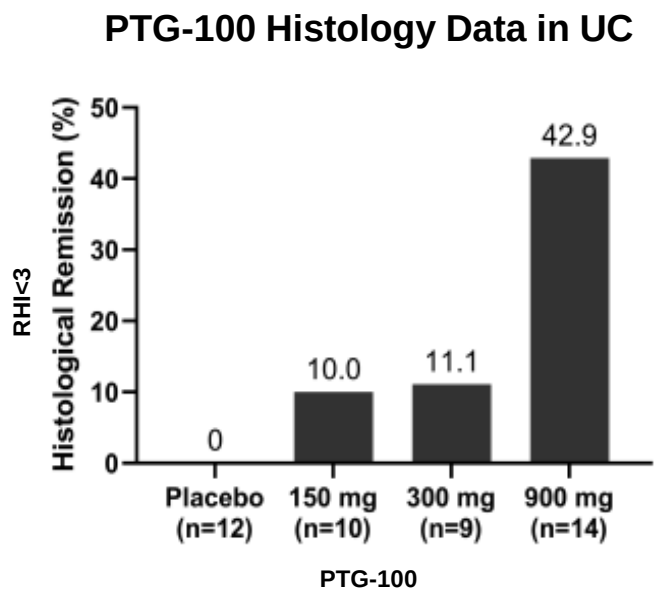
Bruce Sands, Julian Panes, Geert D'Haens, Vipul Jairath, Brian Feagan, Scott Lee, Alessandro Armuzzi, Walter Reinisch, Stefan Schreiber, William Sandborn are consultants for Protagonist Therapeutics, Inc.

Scott Plevy, Suneel Gupta, and CC Hwang are employees of Protagonist Therapeutics, Inc.

# PN-943: An Oral, Gut-Restricted, α4β7-Integrin Peptide Antagonist




**PN-943: Gut-restricted approach clinically validated with first generation compound (PTG-100)**

- IBD Specific α4β7 Target
- T cell homing regulated by α4β7 integrin and MAdCAM-1 interaction

**PN-943 is ~3x more potent in pre-clinical studies & Phase 1 NHV study versus the 1st generation candidate PTG-100 *(DDW, 2019)*[1]**

**PTG-100 showed signals of clinical efficacy in a Phase 2a UC trial *(Gastroenterology*, 2021)*[2]**

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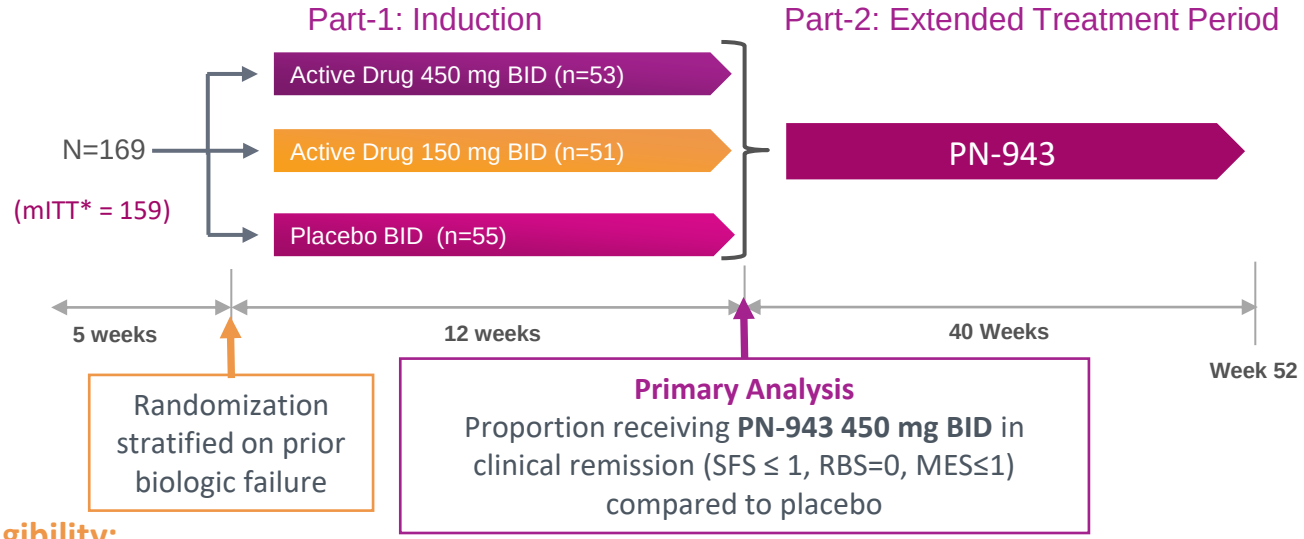
[1]Mattheakis, L., Tang, T., Venkataraman, S., Rao, N., Wang, L., Zhao, L., ... & Liu, D. Y. The oral α4β7 integrin specific antagonist PN-10943 is more effective than PTG-100 in multiple preclinical studies. *Gastroenterology*. 2019;156(Suppl 6):S80-S81.
[2]Sandborn, W. J., Mattheakis, L. C., Modi, N. B., Pugatch, D., Bressler, B., Lee, S., ... & Gupta, S. PTG-100, an oral α4β7 antagonist peptide: preclinical development and phase 1 and 2a studies in ulcerative colitis. *Gastroenterology*. 2021;161(6):1853-1864.

# IDEAL: PN-943 Phase 2 UC Study Design




**Eligibility:**

- Adults with moderate-severe UC: 3-Component Mayo Score 5-9 points
- Failed at least 1 UC medication (5-ASA, steroids, immunomodulators or one biologic)
- Stable dose steroids, prednisone equivalent ≤ 20 mg day
- Stable dose immunomodulators
- One prior biologic exposure (anti-TNF or anti-IL12/23) allowed; prior vedolizumab excluded

*All ITT subjects excluding 10 from Russia and Ukraine who did not complete Week 12 assessments prior to March 3, 2022

# Secondary and Exploratory Analyses



## Secondary

1. Proportion assigned to PN-943 150 mg BID in clinical remission at Week 12 compared to placebo
2. Comparison of PN-943 doses (450 mg BID and 150 mg BID) individually to placebo at week 12:
   - Proportion with **endoscopic improvement** (MES ≤ 1)
   - Proportion with **endoscopic remission** (MES=0)
   - Proportion with **histological improvement (Geboes score <3.1)**
   - Proportion with **histological remission (Geboes score <2.0)**
   - Proportion with **histological remission (RHI ≤ 6)**
   - Proportion with **clinical response** (reduction of Adapted Mayo score ≥2 points and ≥30%, with a reduction in the RBS ≥ 1 or an absolute subscore ≤ 1
   - Mean **change from baseline in Adapted Mayo Score**
   - Mean change from baseline in partial Mayo score at Weeks 2, 4, 8 and 12

## Exploratory

1. Proportion of patients with fecal calprotectin < 150 µg/g at Weeks 12

# Sample Size Assumptions
# IDEAL study



Power Calculation

Assuming a clinical remission rate of approximately **6% from placebo** and **24% from PN-943 450 mg BID**, **50 subjects per treatment group** to detect a difference in the proportion of subjects treated with PN-943 450 mg BID achieving clinical remission compared to subjects treated with placebo at a **one-sided 0.05 level of significance with approximately 80% power**

# Baseline Demographics and Disease Characteristics

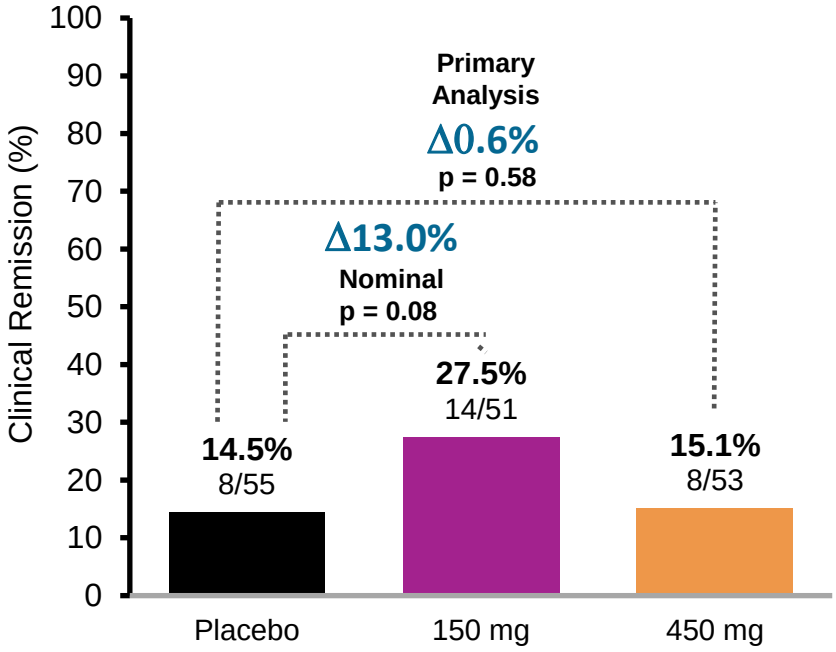
| | Placebo (n=55) | PN-943 150mg (n=51) | PN-943 450mg (n=53) | Total (N=159) |
|---|---|---|---|---|
| **Age years, mean (SD)** | 38 (10.6) | 42 (12.6) | 38 (13.3) | 39 (12.3) |
| **Male sex, n (%)** | 35 (63.6) | 26 (51.0) | 33 (62.3) | 94 (59.1) |
| **Weight (kg), mean (SD)** | 71.7 (17.4) | 74.3 (15.6) | 74.4 (15.2) | 73.5 (16.1) |
| **Disease Extent** | | | | |
| Left Sided Colitis, n (%) | 39 (70.9) | 36 (70.6) | 34 (64.2) | 109 (68.6) |
| **Adapted Mayo Score, mean (SD)** | 6.95 (1.06) | 6.76 (0.99) | 6.81 (1.14) | 6.84 (1.07) |
| **Mayo Endoscopic Subscore=3, n (%)** | 34 (61.8) | 30 (58.8) | 32 (60.4) | 96 (60.4) |
| **Disease Duration (Years), mean (SD)** | 6.4 (5.5) | 5.5 (5.2) | 6.1 (5.4) | 6.0 (5.3) |

# Ulcerative Colitis Medications

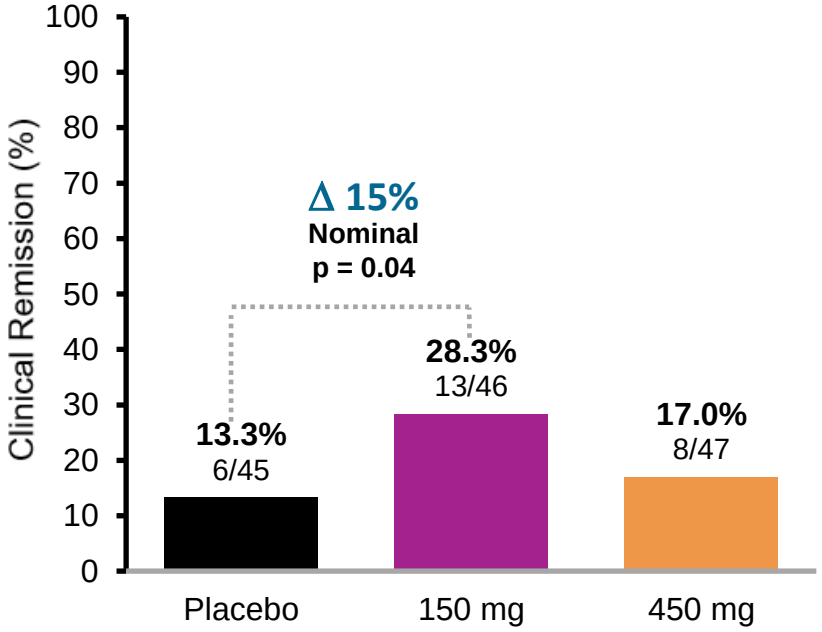
| | Placebo (n=55) | PN-943 150mg (n=51) | PN-943 450mg (n=53) | Total (N=159) |
|---|---|---|---|---|
| **Concomitant 5-ASA, n (%)** | 54 (98.2) | 44 (86.3) | 51 (96.2) | 149 (93.7) |
| **Prior Biologic Exposure*, n (%)** | 11 (20.0) | 7 (13.7) | 6 (11.3) | 24 (15.1) |
| **Prior Biologic Failure**, n (%)** | 10 (18.2) | 5 (9.8) | 6 (11.3) | 21 (13.2) |
| **Concomitant Steroid Use***, n (%)** | 19 (34.5) | 9 (17.6) | 26 (49.1) | 54 (34.0) |
| Mean prednisone dose per group, mean (SD) | 13.6 (5.3) | 17.1 (4.8) | 12.1 (7.5) | 13.5 (6.5) |
| **Concomitant Immunosuppressant Use, n (%)** | 11 (20.0) | 6 (11.8) | 10 (18.9) | 27 (17.0) |

*TNF antagonist or IL-12/23 antagonist
**Biologic stopped for reasons other than nonresponse or loss of efficacy
*** ≤20 mg prednisone equivalent

# Clinical Remission at Week 12 – mITT

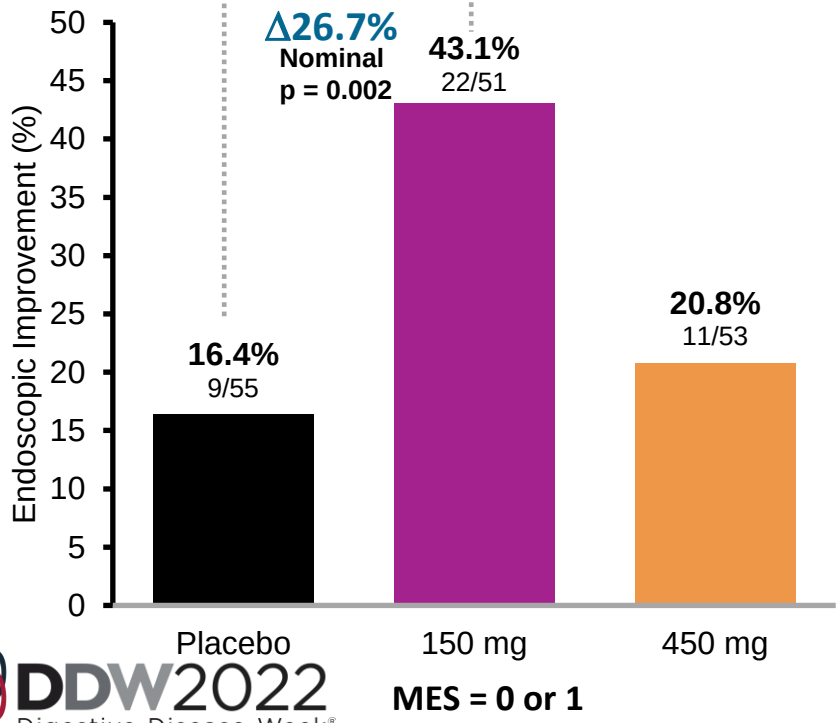


# Clinical Remission at Week 12 – mITT, Biologic Naïve and Biologic-Exposed-Non-Failure Patients*

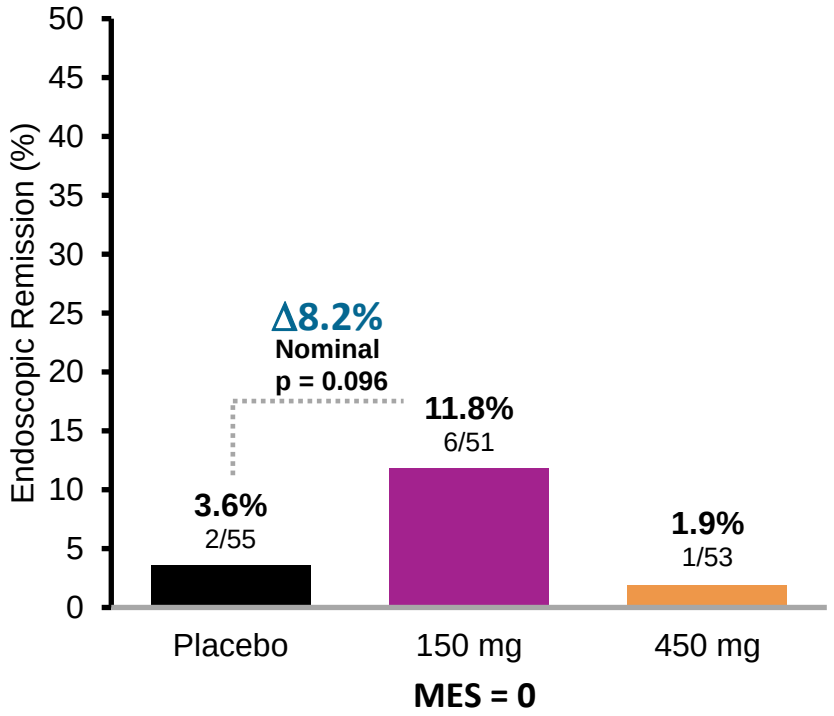



*post-hoc analysis

# Endoscopic Improvement and Remission at Week 12 mITT

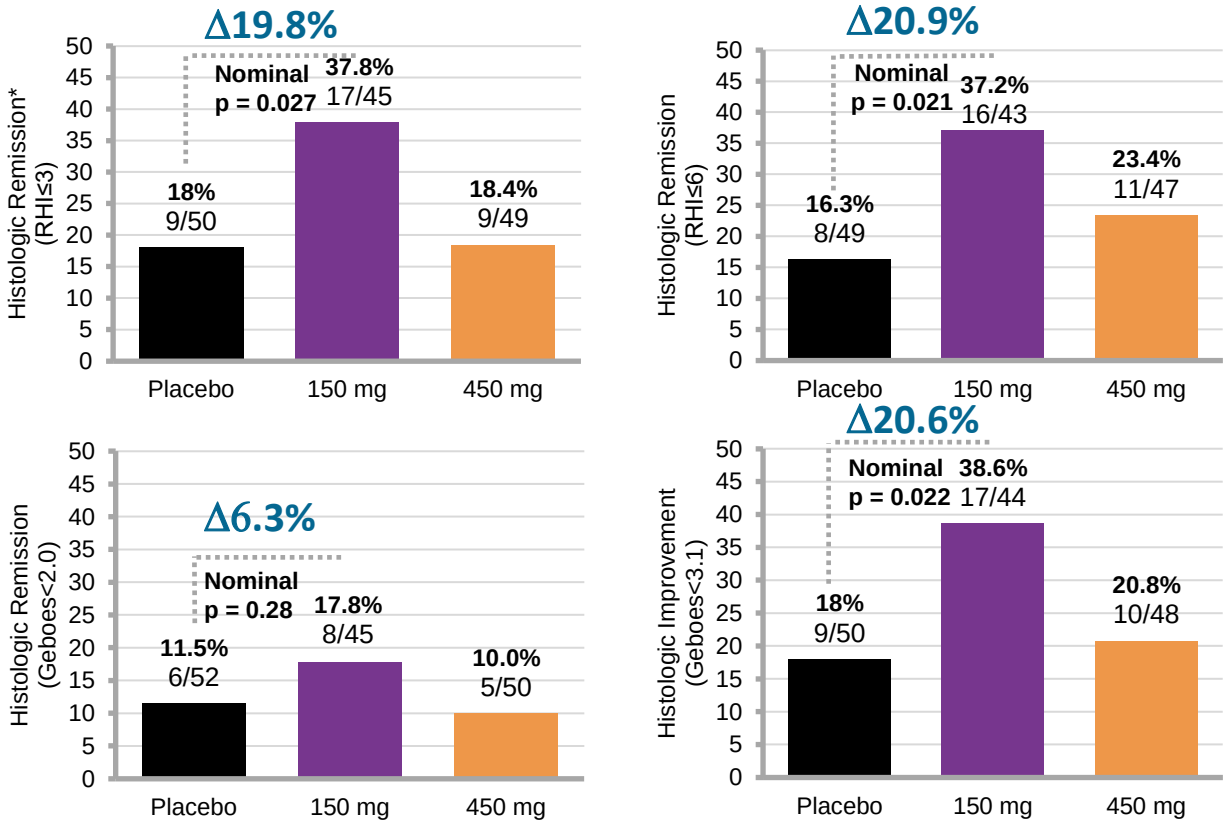



**MES = 0 or 1**




**MES = 0**

# Histologic Remission and Improvement[1] at Week 12 - mITT

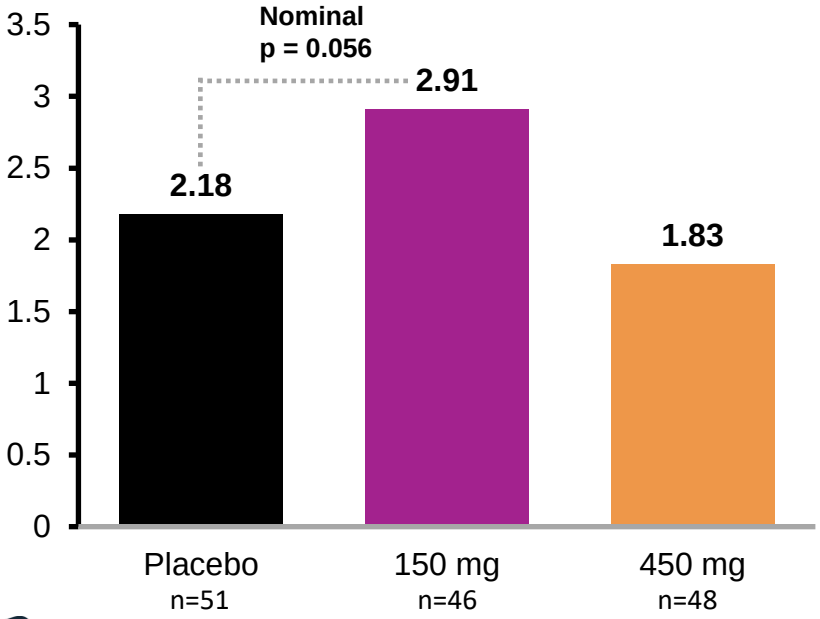



*post-hoc analysis

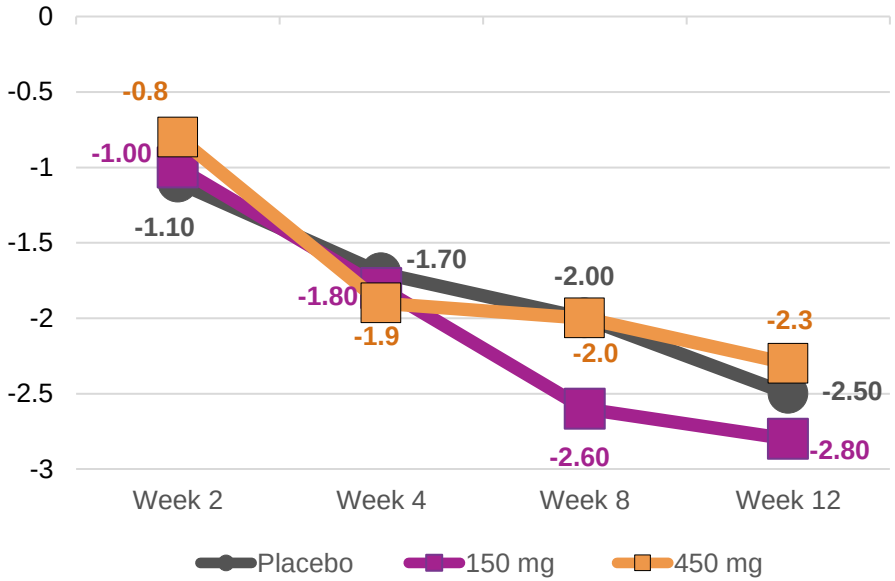
[1]patients who already met the outcome at baseline were excluded

# Changes in Adapted and Partial Mayo Scores - mITT

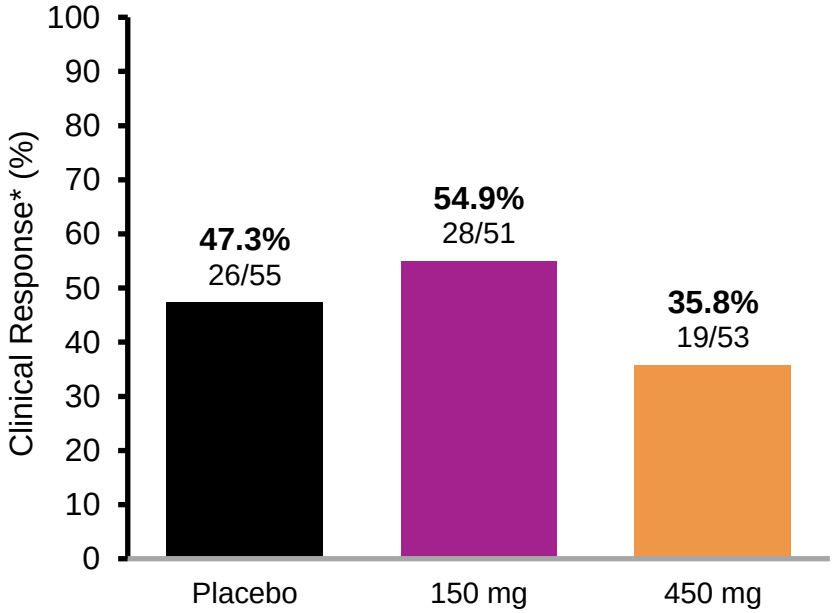
Improvement in adapted Mayo score at week 12




Change from baseline in partial Mayo score

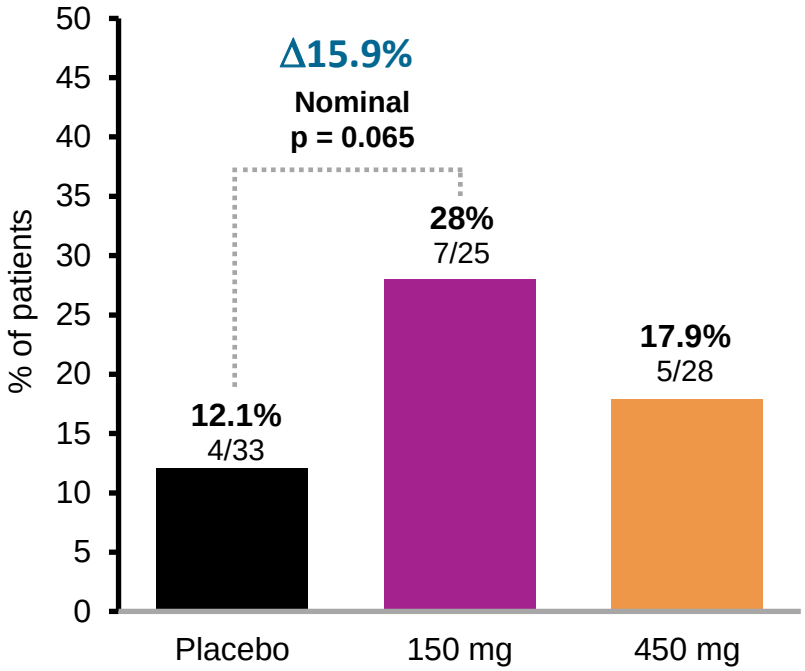


# Clinical Response at Week 12 - mITT




*Proportion of patients with clinical response defined as a reduction of Adapted Mayo score ≥ 2 points and ≥30%, with a reduction in the RBS ≥ 1 or an absolute subscore ≤1

# Improvement in Fecal Calprotectin[1] - mITT
## < 150 mcg/g at week 12




[1]26% missing samples at baseline or week 12; 19% excluded because baseline FCP <150 mcg/g

# Key Safety Findings Through Week 12 - ITT

| | Placebo | PN-943 150 mg | PN-943 450 mg |
|---|---|---|---|
| **Number of Patients** | 57 | 55 | 57 |
| **Patients with ≥1, n (%)** | | | |
| Adverse events (AEs) | 22 (38.6) | 21 (38.2) | 30 (52.6) |
| Serious AEs | 2 (3.5) | 2 (3.6) | 2 (3.5)* |
| AEs leading to study discontinuation | 1 (1.8) | 2 (3.6) | 2 (3.5)* |
| Infections | 2 (3.5) | 7 (12.7) | 12 (21.1) |
| Serious infections | 0 (0) | 0 (0) | 1 (1.8)* |

*CMV colitis identified on screening colonic biopsies post-randomization in 1 patient

# Conclusions

## IDEAL study

- No treatment effect for primary endpoint (clinical remission at week 12, PN-943 450 mg BID vs placebo)
- Clinical remission in 27.5% of PN-943 150 mg BID group vs 14.5% in placebo (Δ 13%, nominal p = 0.08) for mITT analysis
  - Δ in Biologic-Non-Failure population 15% (nominal p = 0.04)
- Concordance with efficacy across multiple key secondary endpoints including histologic remission/improvement, and endoscopic remission at the 150 mg BID dose
- No significant safety signals detected
- 40-week extended treatment period (Part 2) ongoing
- The IDEAL study supports further development of PN-943 in UC registrational trials

# Thank you

Acknowledgements: We thank the patients, families, and study site collaborators who made the IDEAL study possible. This study was funded by Protagonist Therapeutics, Inc.

# Backup Slides

# IDEAL Study: Key Secondary and Exploratory Endpoints

## Secondary:

1. Proportion of patients achieving clinical remission who received PN-943 150 mg BID at Week 12 compared to Placebo
2. Comparison of PN-943 doses (450 mg BID and 150 mg BID) individually to placebo:
   - Proportion of patients with endoscopic improvement at Week 12 (defined as MES ≤ 1)
   - Proportion of patients with endoscopic remission (defined as MES=0) at Week 12
   - Proportion of patients with histological improvement (Geboes score <3.1) at Week 12
   - Proportion of patients with histological remission defined as Geboes score <2.0 and RHI ≤ 6 at Week 12
   - Proportion of patients with clinical response define as a reduction of Adapted Mayo score ≥ 2 points and ≥30%, with a reduction in the RBS ≥ 1 or an absolute subscore ≤ 1
   - Mean change from baseline in Adapted Mayo Score at Week 12
   - Mean change from baseline in partial Mayo score at Weeks 2, 4, 8 and 12

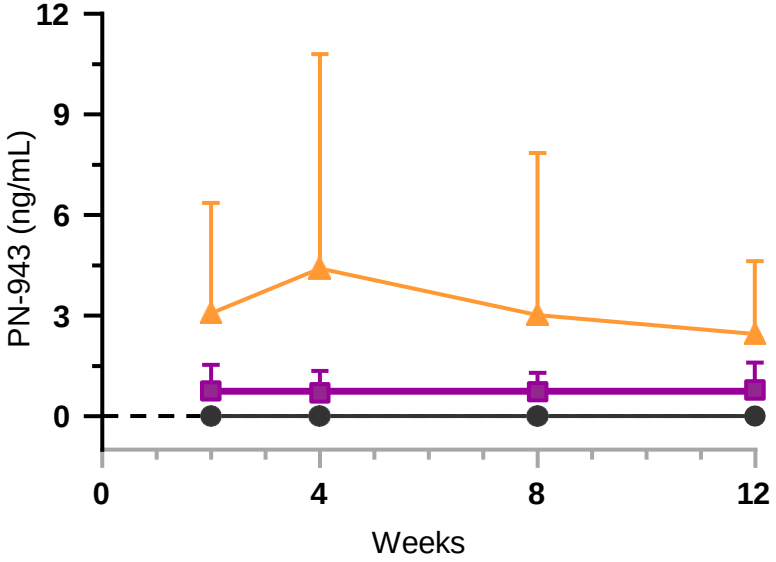
## Exploratory:

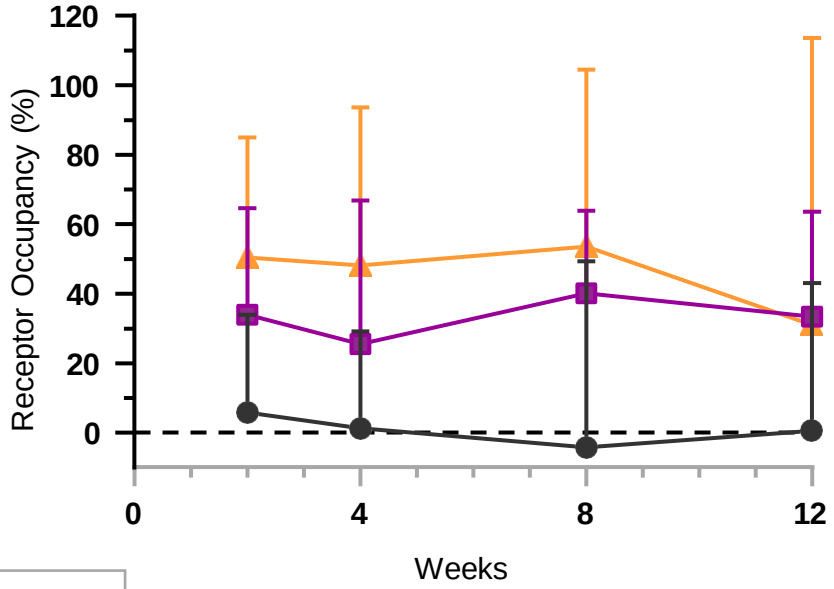
1. Proportion of patients with fecal calprotectin < 150 µg/g at Weeks 12

# Enrollment by Country

| Country | Patients Screened n (%) | Patients Randomized n (%) |
|---|---|---|
| Poland | 163 (48.2) | 97 (57.4) |
| Russia | 45 (13.3) | 24 (14.2) |
| United States | 60 (17.8) | 13 (7.7) |
| Georgia | 20 (5.9) | 10 (5.9) |
| Ukraine | 15 (4.4) | 9 (5.3) |
| Italy | 11 (3.3) | 5 (3.0) |
| Korea, Republic of | 5 (1.5) | 5 (3.0) |
| Hungary | 3 (0.9) | 2 (1.2) |
| Canada | 10 (3.0) | 1 (0.6) |
| Austria | 2 (0.6) | 1 (0.6) |
| Serbia | 2 (0.6) | 1 (0.6) |
| Germany | 1 (0.3) | 1 (0.6) |
| Bulgaria | 1 (0.3) | 0 |
| | | |
| Total (n) | 338 | 169 |

# PN-943 Plasma Trough Concentrations and Peripheral Blood T cell α4β7 Receptor Occupancy




Placebo
150 mg BID
450 mg BID

# Infections And Infestations by treatment

| System Organ Class<br>Preferred Term | Placebo<br>(N=57)<br>n(%) | PN-943 150mg<br>(N=55)<br>n(%) | PN-943 450mg<br>(N=57)<br>n(%) | Total<br>N=(169)<br>n(%) |
|---|---|---|---|---|
| Total Number of TEAEs | 48 | 47 | 55 | 150 |
| Number Of Subjects With At Least One TEAE | 22 (38.6) | 21 (38.2) | 30 (52.6) | 73 (43.2) |
| Infections And Infestations | 2 ( 3.5) | 7 (12.7) | 12 (21.1) | 21 (12.4) |
| Covid-19 | 1 ( 1.8) | 2 ( 3.6) | 3 ( 5.3) | 6 ( 3.6) |
| Nasopharyngitis | 0 | 1 ( 1.8) | 3 ( 5.3) | 4 ( 2.4) |
| Upper Respiratory Tract Infection | 1 ( 1.8) | 1 ( 1.8) | 1 ( 1.8) | 3 ( 1.8) |
| Urinary Tract Infection | 0 | 0 | 2 ( 3.5) | 2 ( 1.2) |
| Cervicitis | 0 | 0 | 1 ( 1.8) | 1 ( 0.6) |
| Conjunctivitis | 0 | 1 ( 1.8) | 0 | 1 ( 0.6) |
| Cytomegalovirus Infection | 0 | 0 | 1 ( 1.8) | 1 ( 0.6) |
| Fungal Skin Infection | 0 | 1 ( 1.8) | 0 | 1 ( 0.6) |
| Hordeolum | 0 | 0 | 1 ( 1.8) | 1 ( 0.6) |
| Respiratory Tract Infection | 0 | 0 | 1 ( 1.8) | 1 ( 0.6) |
| Respiratory Tract Infection Viral | 0 | 0 | 1 ( 1.8) | 1 ( 0.6) |
| Rhinitis | 0 | 1 ( 1.8) | 0 | 1 ( 0.6) |