

PN-943

PTG-200

PTG-300

# The Oral $\alpha4\beta7$ Integrin Specific Antagonist PN-10943 is More Effective Than PTG-100 in Multiple Preclinical Studies

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# Outline



- Rationale for Oral Integrin Specific Antagonist for IBD
- Signs of Clinical Efficacy from Phase 2a Trial in UC Patients with First Generation Antagonist PTG-100
- PN-943: More Potent 2<sup>nd</sup> Generation Oral Integrin Antagonist
  - Preclinical and Clinical Comparisons to PTG-100

# Oral PN-943

## An $\alpha 4\beta 7$ Integrin Specific, GI-Restricted, Therapy for IBD

- The  $\alpha 4\beta 7$  integrin is an IBD specific target clinically validated by the approved injectable vedolizumab for Crohn's & UC
- Treatment paradigm is shifting toward oral targeted therapies
  - Protagonist is developing orally stable  $\alpha 4\beta 7$  integrin antagonists for IBD
- PN-943 has potential as first-in-class and first-line therapy
  - Gut-restricted exposure offers additional safety
  - Anchor for combination therapy
  - PN-943 is superior to PTG-100 in both preclinical and early clinical studies
  - PTG-100 demonstrated signs of clinical activity in a Ph2a study in UC patients

# PTG-100: Phase 2a Histologic and Clinical Remission

| Clinical Readout       | Clinical Study | Placebo     | 900 mg       |
|------------------------|----------------|-------------|--------------|
| Clinical Remission*    | Ph 2a UC       | 4.8% (1/21) | 15.8% (3/19) |
| Histologic Remission** | Ph 2a UC       | 0% (0/13)   | 44% (7/16)   |

\*Clinical remission defined as Mayo rectal bleeding score of 0, endoscopic subscore of 0/1, and a stool frequency score of 0/1 with at least a 1-point reduction from baseline

\*\*Histologic remission defined as a Week 12 RHI score of  $\leq 3$  amongst patients who had a score  $> 3$  at baseline

- Dose-related, most efficacious at 900 mg QD dose in UC patients at 12 weeks
  - 11% delta over PBO similar to clinical remission rates for other IBD targeted drugs
- High rate and dose dependent histologic remission
  - 44% at 900 mg dose
- PTG-100 Is Safe and Well-Tolerated

# PN-943: More Effective 2<sup>nd</sup> Generation Oral Integrin Antagonist



- PN-943 superior to PTG-100 by all measures in pre-clinical studies
  - a. In vitro potency
  - b. PD effects of target engagement - blood %RO and circulating T cells
  - c. Efficacy - TNBS induced rat colitis
- PK: Similar oral stability and limited blood exposure
- Different chemical scaffold embedding critical structural features and binding sequences from PTG-100
- Based on preclinical superiority over PTG-100, PN-943 was advanced into clinical development

# PN-943: More Potent Than PTG-100

## Cell Adhesion and Surface Plasmon Resonance Binding Assays



- 5.5-fold more potent in blocking human T cell adhesion assay with similar selectivity

| Integrin | $\alpha 4\beta 7$                 | $\alpha 4\beta 1$               |
|----------|-----------------------------------|---------------------------------|
| Ligand   | MAdCAM-1<br>(IC <sub>50</sub> nM) | VCAM-1<br>(IC <sub>50</sub> nM) |
| PTG-100  | 1.5                               | > 100,000<br>(> 67,000-fold)    |
| PN-943   | 0.27                              | > 12,000<br>(> 44,000-fold)     |

- 2.6-fold longer binding lifetime (i.e. half-life of dissociation) in SPR assay

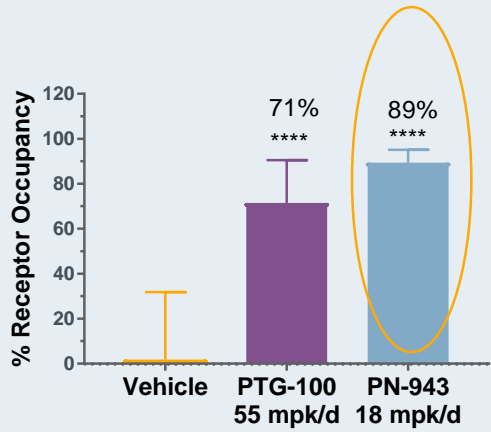
|         | K <sub>a</sub> (on rate) | K <sub>d</sub> (off rate) | Equilibrium constant (K <sub>D</sub> ) | Half life of dissociation |
|---------|--------------------------|---------------------------|--|---------------------------|
| PTG-100 | 1060 s                   | 1.2 e-5 s                 | 11.3 nM                                | 16 h                      |
| PN-943  | 1423 s                   | 4.5 e-6 s                 | 3.5 nM                                 | 42 h                      |



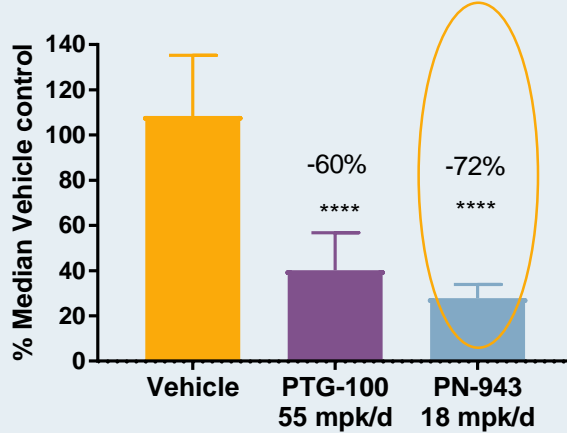
# PN-943: Similar Effects on Target Engagement and Trafficking at 3-Fold Lower Dose

## 15 Day DSS Colitis Mouse Model

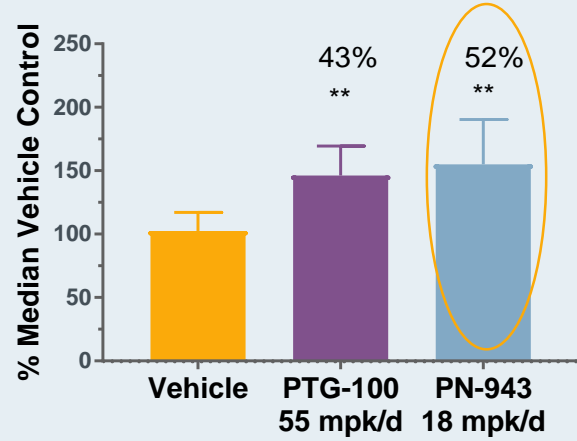
Receptor Occupancy CD4+ Effector Memory T cells



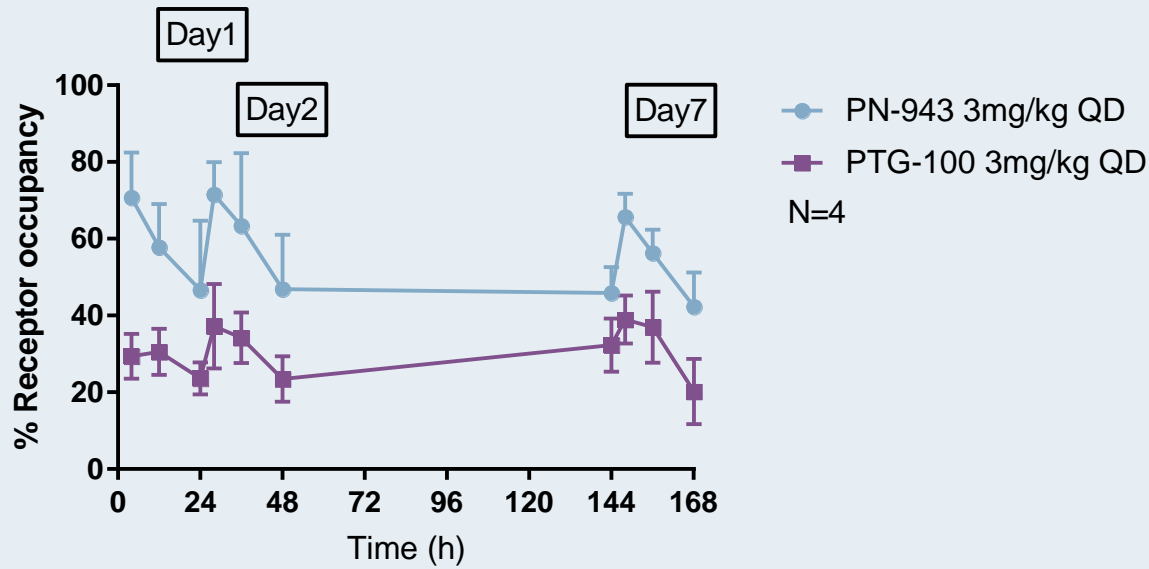
Receptor Expression CD4+ Effector Memory T cells



Circulating Cell Numbers CD4+ Effector Memory T cells



# PN-943: Higher %RO At Similar Plasma Exposure With Equivalent Dose in Cynomolgus Monkey



| Day # | Compounds | C <sub>max</sub> (ng/mL) | AUC <sub>last</sub> (ng*h/mL) |
|-------|-----------|--------------------------|-------------------------------|
| Day 1 | PTG-100   | 12.1                     | 50.5                          |
|       | PN-943    | 12.7                     | 72.0                          |
| Day 2 | PTG-100   | 17.5                     | 60.1                          |
|       | PN-943    | 7.64                     | 53.2                          |
| Day 7 | PTG-100   | 6.71                     | 29.5                          |
|       | PN-943    | 8.34                     | 49.5                          |

Despite similar PK properties, PN-943 has higher levels of target engagement (%RO)



# PN-943 Exposure in Mouse is Gut-Restricted

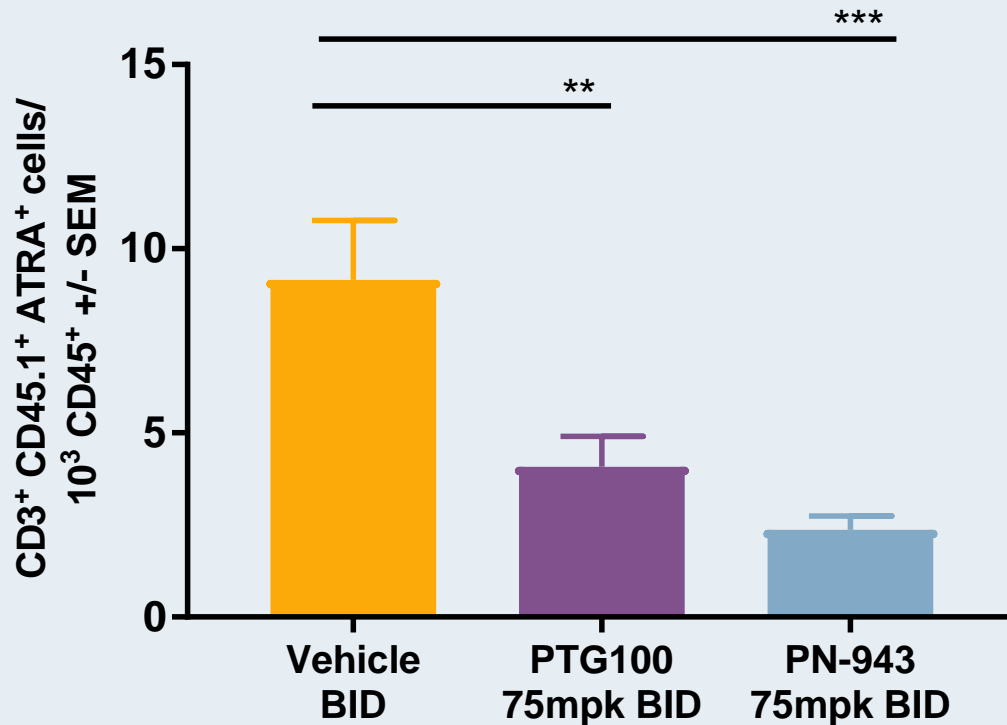
## >100-fold Higher Exposure in Gut Tissues Compared to Plasma



| Tissue             | PN-943               |                  |                           |   |
|--------------------|----------------------|------------------|---------------------------|---|
|                    | $C_{max}$<br>(ng/mL) | $T_{max}$<br>(h) | $AUC_{last}$<br>(ng*h/mL) | $AUC_{last}$ Ratio<br>Normalized to<br>Plasma |
| Plasma             | 19.0                 | 3                | 95.4                      | 1   |
| MLN                | 56.8                 | 1                | 226.4                     | 2   |
| Peyer's<br>Patches | 6792.5               | 1                | 37901.3                   | 397   |
| Small Intestine    | 13287.5              | 1                | 48635.0                   | 510   |
| Colon              | 5582.5               | 6                | 15675.0                   | 164   |

30 mg/kg PO QD. C57BL/6 female. Samples collected at 1, 3, and 6 h post-dose.  
Oral bioavailability (%F) < 1%

# PN-943: More Effective in Blocking Donor T Cell Homing Homing to Ileal Lamina Propria in Healthy Mice



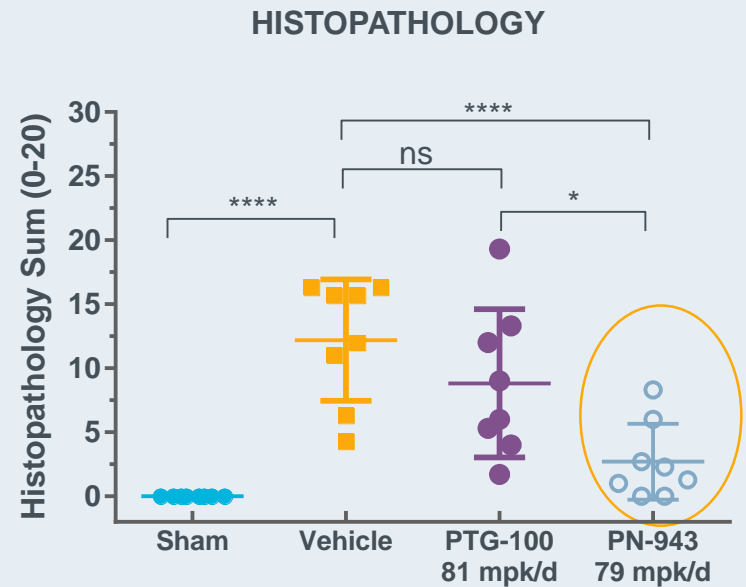
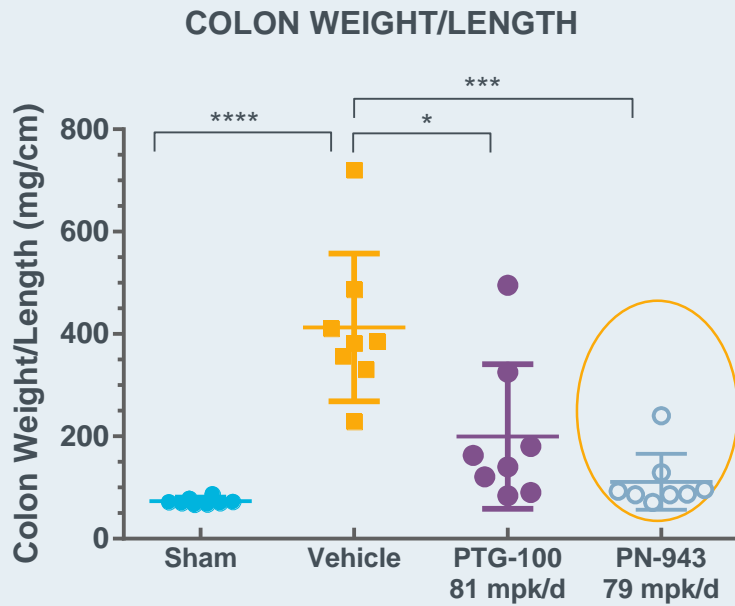
CD3<sup>+</sup> cells expressing gut homing receptors CCR9 and  $\alpha 4\beta 7$  integrin were labeled with CTFR and injected into recipient mice. Approximately 24 hours after injection, the number of donor cells in the lamina propria of recipient mice were measured by FACS.

p values: \*\*  $\leq 0.01$ , \*\*\*  $\leq 0.001$

# PN-943: Significantly More Efficacious than PTG-100 in Preserving Colon Integrity



## 9 Day TNBS Colitis Rat Study

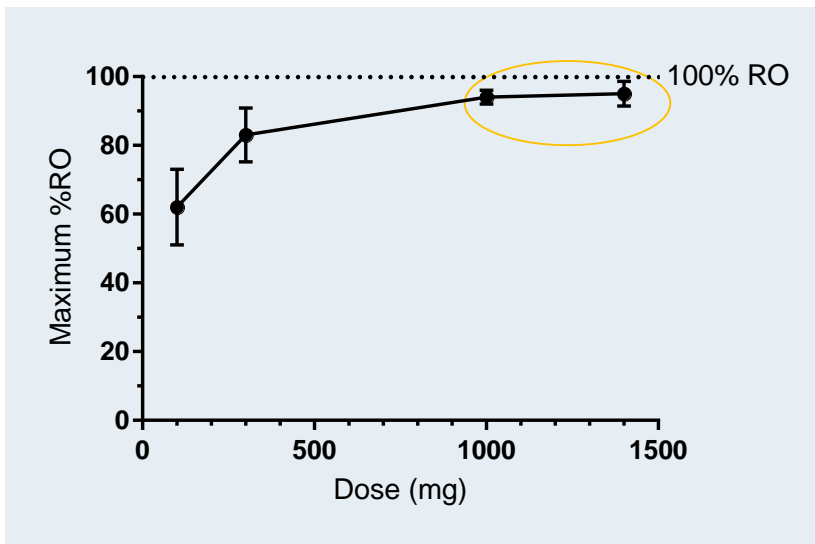


# PN-943: Dose Related and Saturable Increase in Receptor Occupancy in Ph1 NHV Study



## Single ascending dose study (SAD)

| Dose (mg)     | PN-943 %RO (max)* | PN-943 %RO (AUC <sub>0-24h</sub> ) |
|---------------|-------------------|------------------------------------|
| 100 mg (n=8)  | 62 ± 11.0         | 933 ± 299                          |
| 300 mg (n=8)  | 83 ± 7.9          | 1542 ± 158                         |
| 1000 mg (n=8) | 94 ± 2.0          | 1944 ± 84                          |
| 1400 mg (n=8) | 95 ± 3.6          | 2064 ± 164                         |

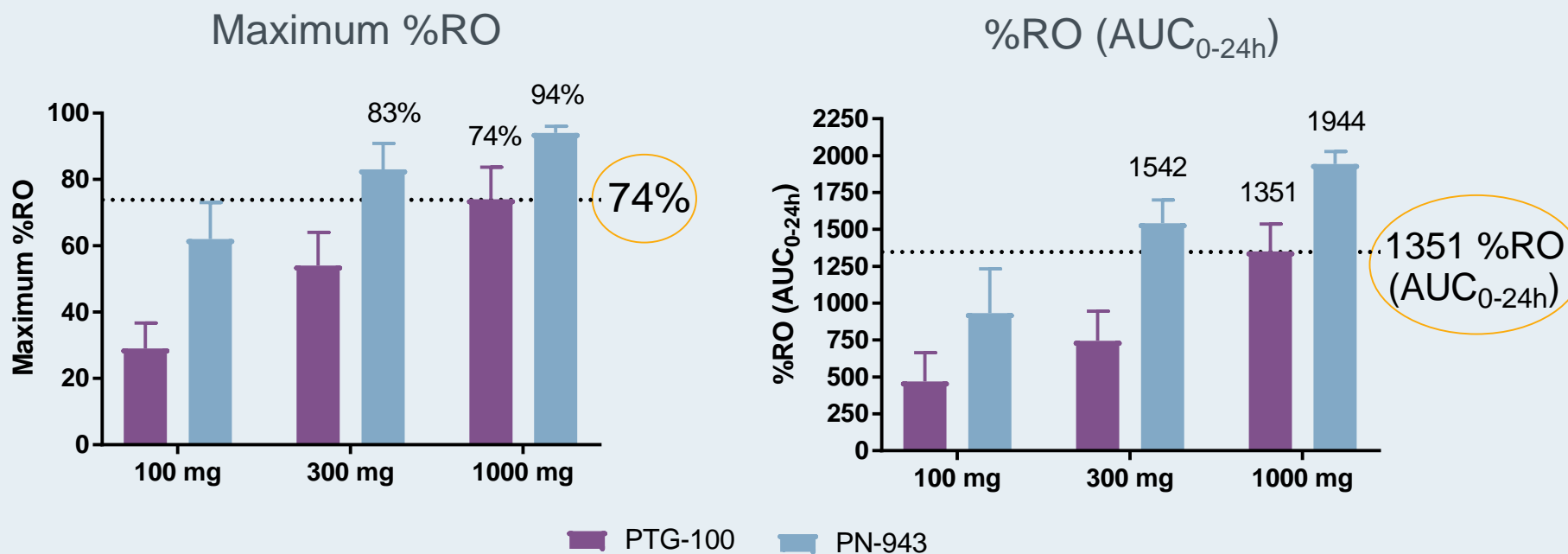


\*%RO in peripheral blood for CD4+ memory  $\alpha 4\beta 7+$  T cells  
Data shown is mean  $\pm$  standard deviation

- ✓ Saturable %RO at 1000 mg (> 90%)
- ✓ Dose dependent increase in %RO
- ✓ PN-943 was safe and well tolerated with gut restricted exposure

# PN-943: Superior Target Engagement in Phase 1 NHV

Higher %RO in NHV Confirm Higher Potency Compared to PTG-100 Observed in Preclinical Studies



PTG-100 at 900 mg dose achieved 16% clinical remission and 44% histologic remission in a Phase 2a study in UC patients

# Conclusions



- PTG-100: Established signs of clinical efficacy in Ph2a UC trial
- PN-943 is superior to PTG-100 in multiple preclinical studies
  - ~5-fold more potent in *in vitro* binding and adhesion studies
  - Superior target engagement and effects on T cell trafficking in mice and cynos
  - Greater preservation of colon integrity in a rat TNBS colitis model
- A Ph1 NHV SAD study confirmed higher potency of PN-943
  - Consistent with preclinical studies showing PN-943 has higher levels of target engagement compared to PTG-100
- Ph1 NHV MAD data available 2H 2019 followed by Ph2 IND submission

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