The Oral α4β7 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 2nd Generation Oral Integrin Antagonist
  - Preclinical and Clinical Comparisons to PTG-100

Oral PN-943

An α4β7 Integrin Specific, GI-Restricted, Therapy for IBD

- The α4β7 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 α4β7 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 ≤ 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 2nd 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	α4β7	α4β1
Ligand	MAdCAM-1 (IC_{50} nM)	VCAM-1 (IC_{50} nM)
PTG-100	1.5	> 100,000 (> 67,000-fold)
PN-943	0.27	> 12,000 (> 44,000-fold)

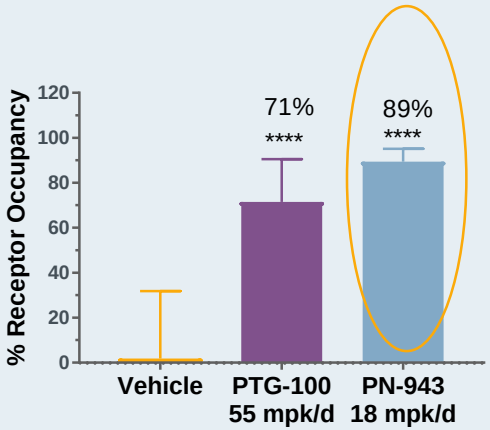
- 2.6-fold longer binding lifetime (i.e. half-life of dissociation) in SPR assay

	K_a (on rate)	K_d (off rate)	Equilibrium constant (K_D)	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

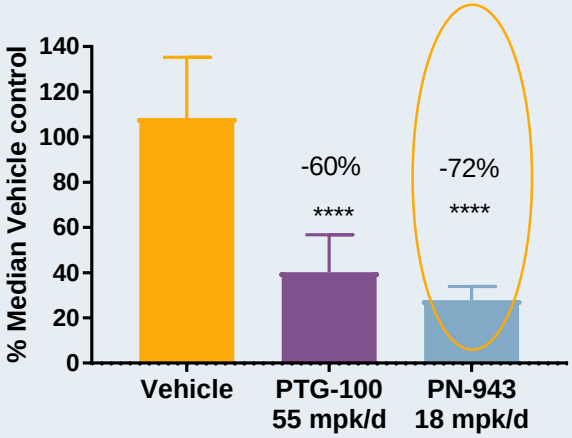
PN-943: Similar Effects on Target Engagement and Trafficking at 3-Fold Lower Dose

15 Day DSS Colitis Mouse Model

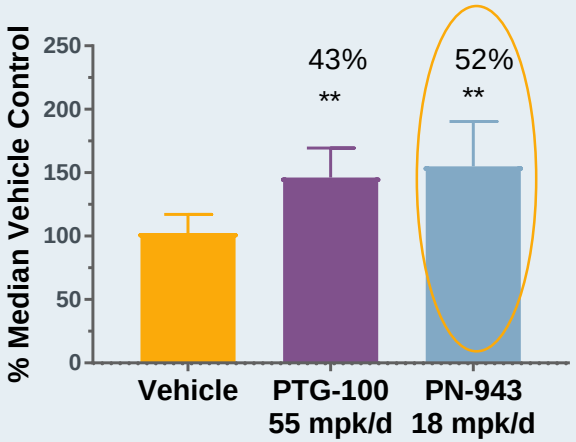
Receptor Occupancy CD4+ Effector Memory T cells



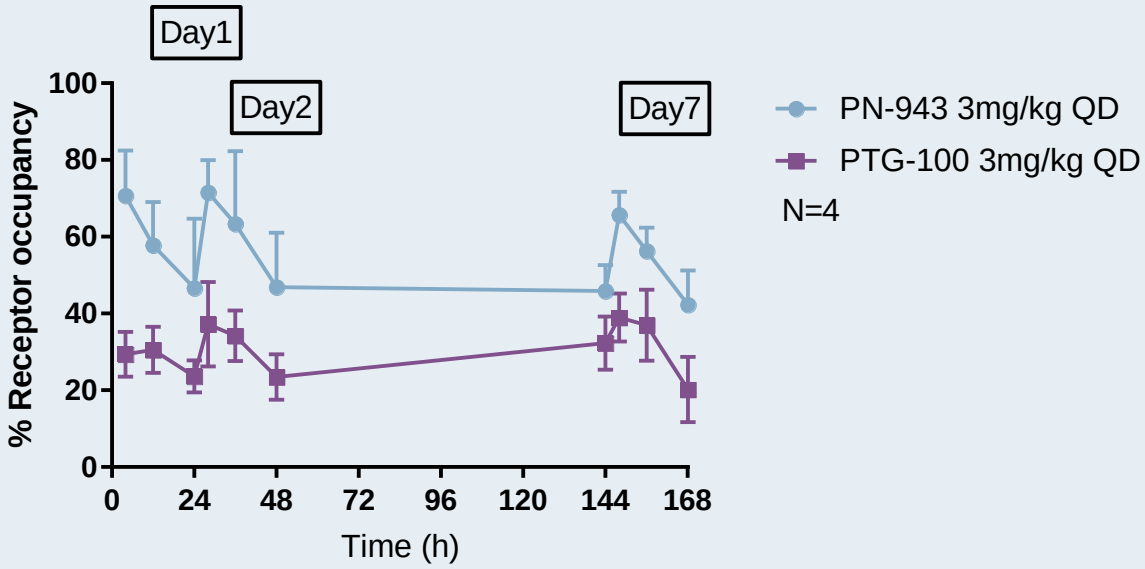
Receptor Expression CD4+ Effector Memory T cells



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_{max} (ng/mL)	AUC_{last} (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

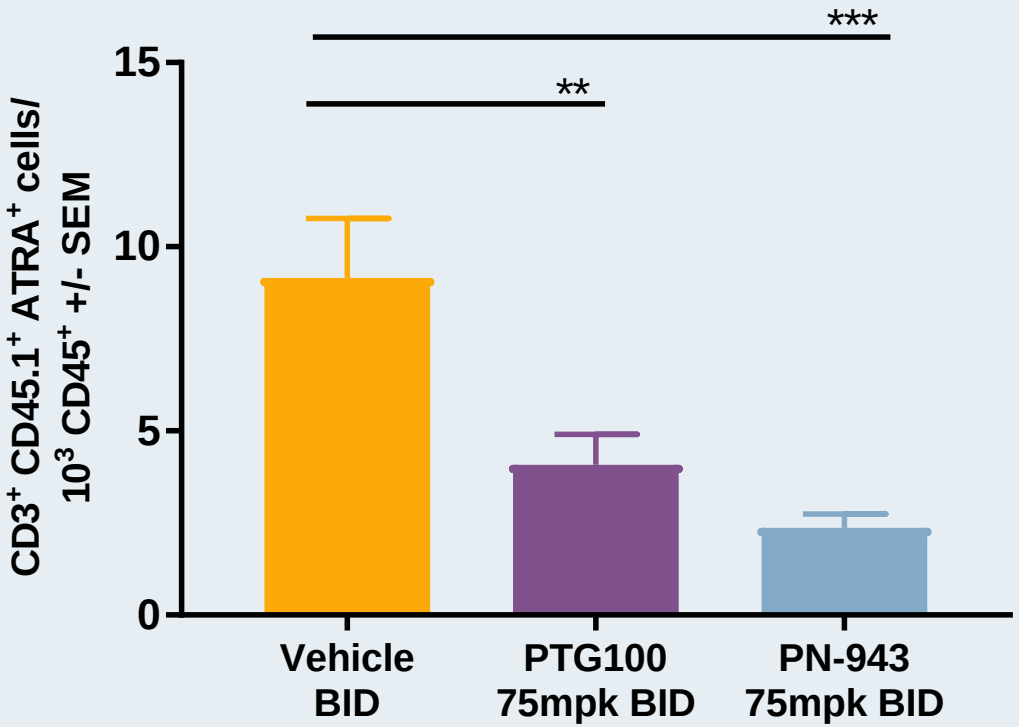
>100-fold Higher Exposure in Gut Tissues Compared to Plasma

Tissue	PN-943			
	C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (ng*h/mL)	AUC_{last} Ratio Normalized to Plasma
Plasma	19.0	3	95.4	1
MLN	56.8	1	226.4	2
Peyer's 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

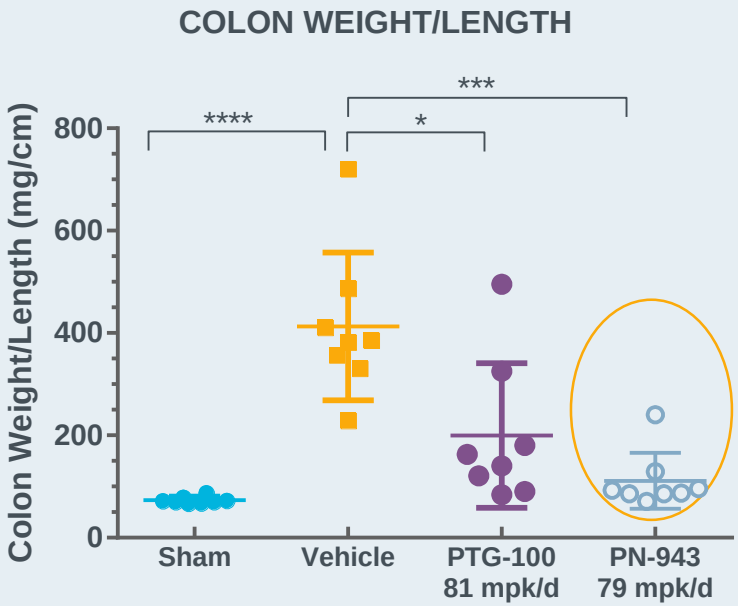
Homing to Ileal Lamina Propria in Healthy Mice

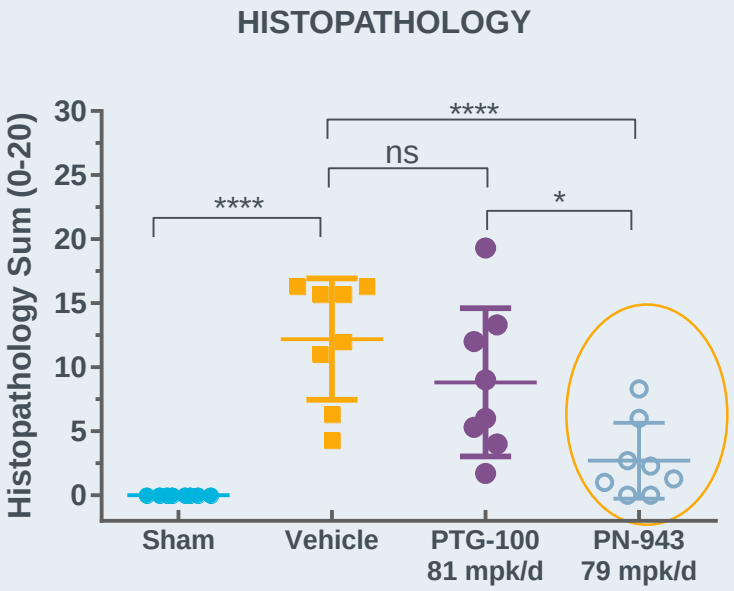


CD3+ cells expressing gut homing receptors CCR9 and α4β7 integrin were labeled with CTFR and injected into recipient mice. Approximately 24 hours after injection, the number of donor cells in the lamina propria of recipient mice were measured by FACS.
p values: ** ≤ 0.01, *** ≤ 0.001

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

9 Day TNBS Colitis Rat Study

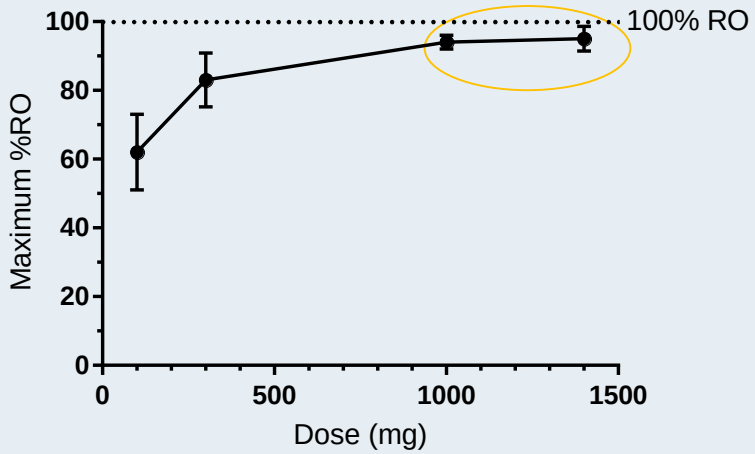




PN-943: Dose Related and Saturable Increase in Receptor Occupancy in Ph1 NHV Study

Single ascending dose study (SAD)

Dose (mg)	PN-943 %RO (max)*	PN-943 %RO ($AUC_{0\text{-}24h}$)
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

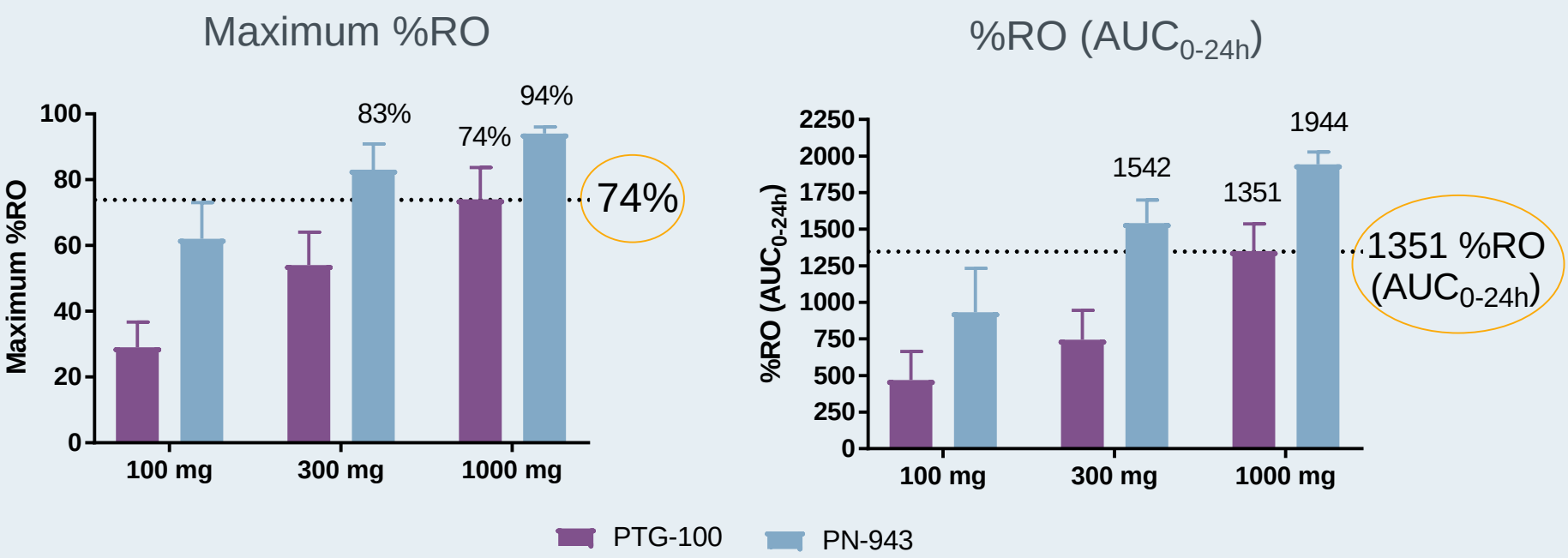


*%RO in peripheral blood for CD4+ memory α4β7+ T cells
Data shown is mean ± standard deviation

- ✓ 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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