PN-881: First-in-class oral peptide targeting the IL-17 pathway

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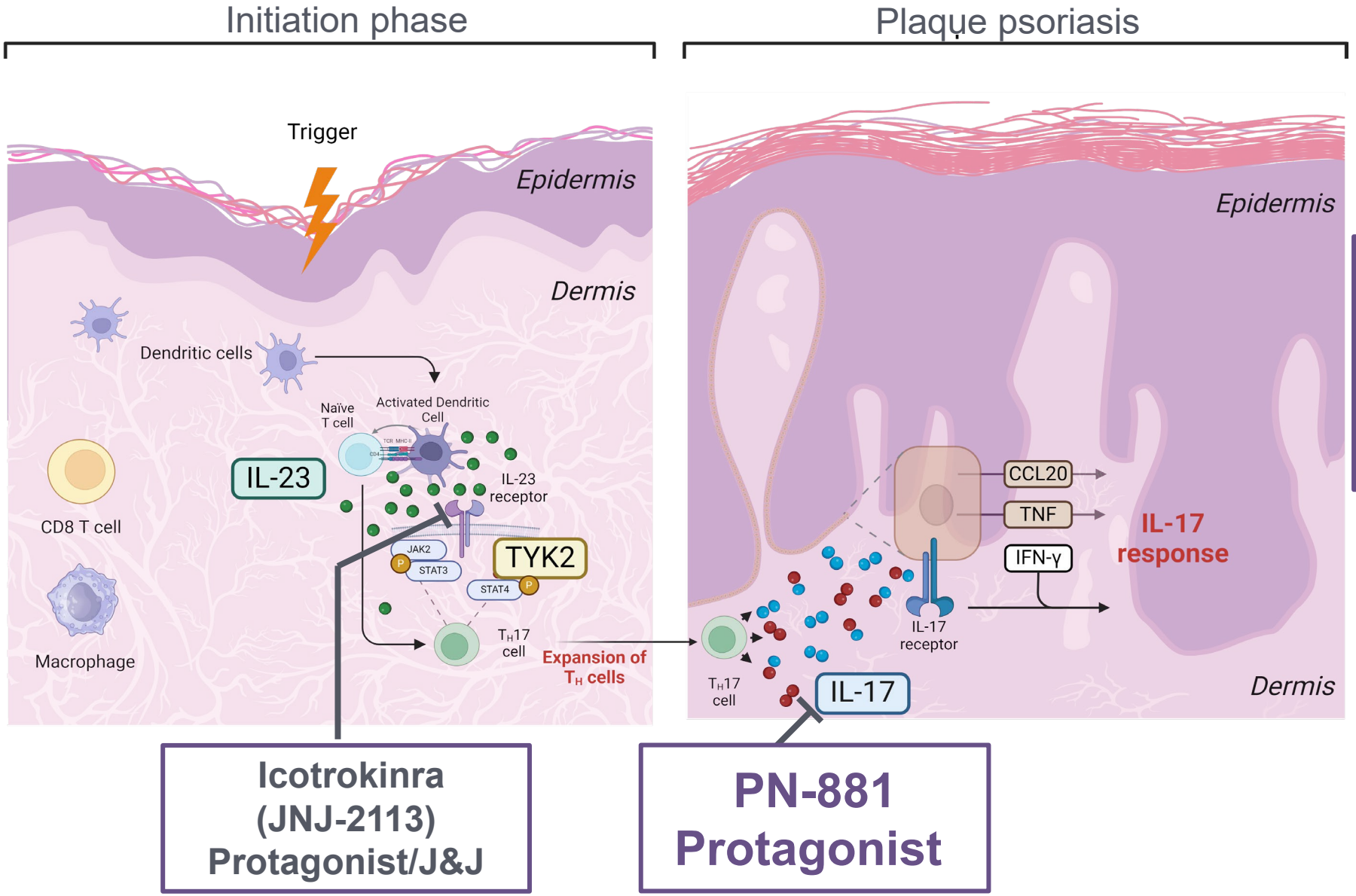
* Poster **ID#0003** session 2 PN-881 Adaptive and Auto-immunity

Disclosure statement

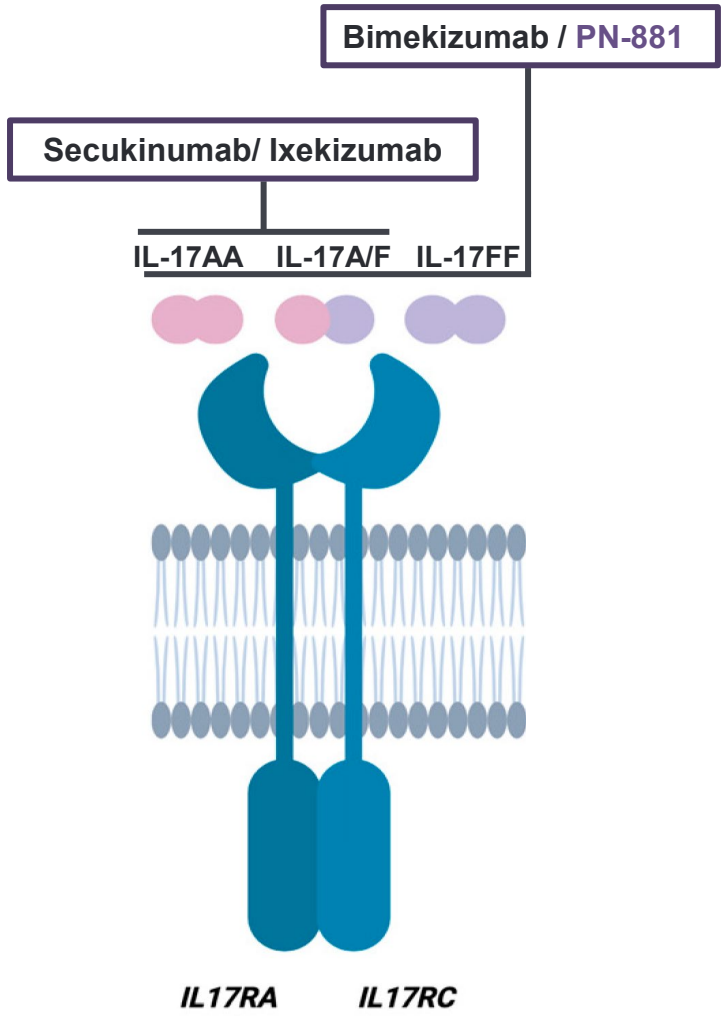
Mariana Manrique, Ph.D. is an employee of Protagonist Therapeutics, Inc. and may have an equity position in the company.

Targeting IL-17 Results in Rapid Onset of Response



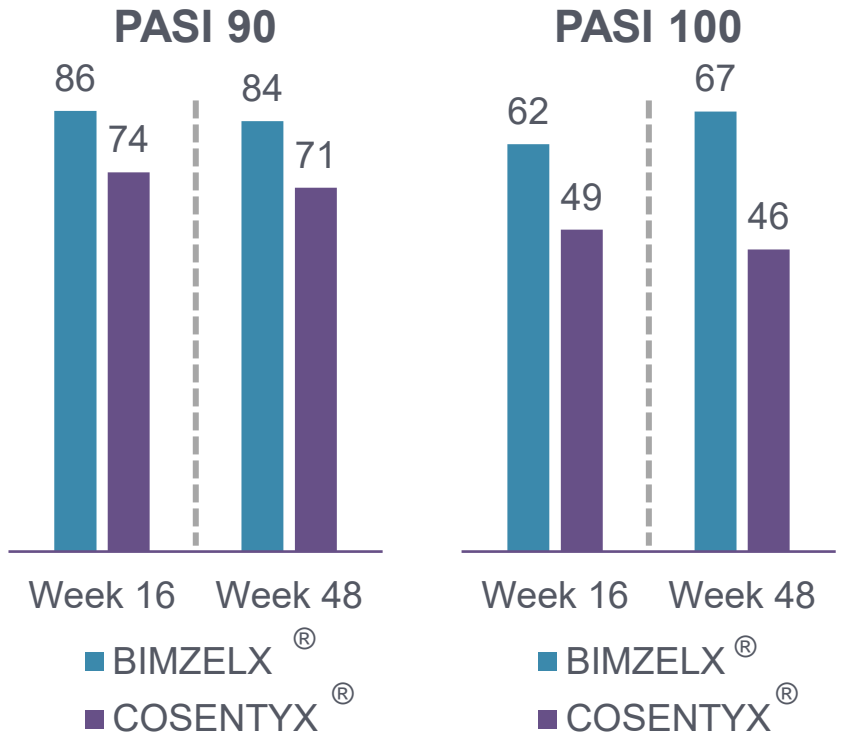
- IL-17 and IL-23 pathways are key mediators of psoriasis pathogenesis
- Proximity of IL-17 to skin pathology may lead to more rapid disease response

IL-17 Receptor Activated by Three Dimeric Forms of IL-17: IL-17AA, AF, and FF[1]



BE RADIANT Clinical Trial:

Blockade of IL-17A and F Yields Greater Efficacy in Psoriasis[1]



[1]Reich et al., N Engl J Med 2021;385:142-52. DOI: 10.1056/NEJMoa2102383

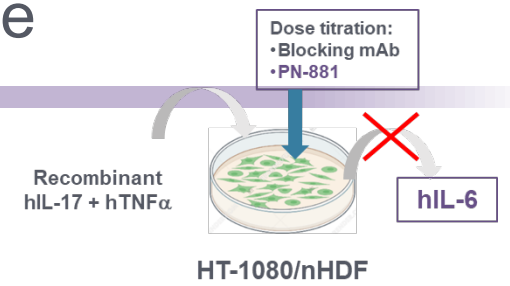
- Oral **PN-881** was designed to inhibited IL-17AA, AF and FF to achieve maximal clinical benefit

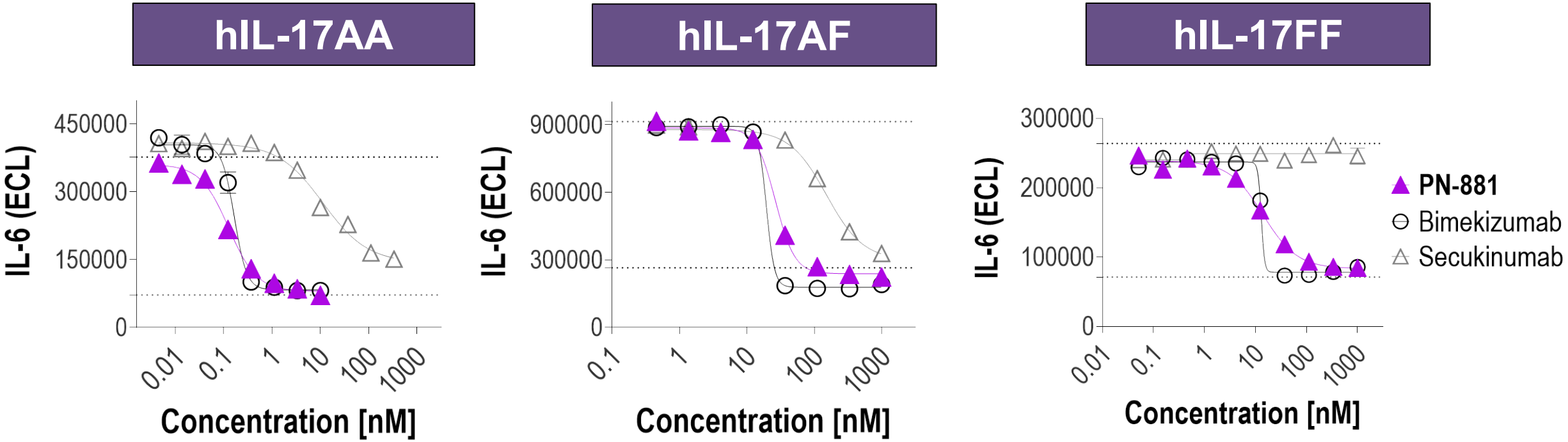
Criteria for nomination of Oral PN-881 Development Candidate

Attribute	Criteria
Potency	• **Sub-nM potency *vs.* IL-17 AA** • **Blocks all dimeric forms of IL-17: AA, AF, FF**
Stability	• Stable in simulated gastric and intestinal fluids • Stable in serum with $t_{1/2}$ >24 hr • Metabolic stability • Thermostability
PD model	• **Mouse hIL-17 challenge, CXCL1 model**
Efficacy Model	• **Rat IL-23-induced skin inflammation model**

Oral PN-881 achieved all the criteria for a development candidate nomination

PN-881 Potently Inhibits IL-17-induced responses in HT-1080 cell line





- **PN-881** has similar blocking curves as **Bimekizumab** while **Secukinumab**'s curves for IL-17AA and IL-17AF are shifted to the right
- **Secukinumab** does not block IL-17FF

PN-881 Potently Inhibits IL-17AA and IL-17FF

Similar potency as Bimekizumab and ~70-fold more potent than Secukinumab

HT-1080 IC_{50} (nM)				
		IL-17 AA	IL-17 AF	IL-17 FF
PN-881	**oral**	**0.13**	**27**	**14**

nHDF IC_{50} (nM)		
IL-17 AA	IL-17 AF	IL-17 FF
0.15	**29**	**15**

		IL-17 AA	IL-17 AF	IL-17 FF
Bimekizumab	**SC**	0.17	19.5	13
Secukinumab	**SC**	11	151	Inactive

IL-17 AA	IL-17 AF	IL-17 FF
0.12	18	14
10	175	Inactive

- **PN-881** has sub-nM IL-17AA blocking potency (IC_{50}) similar to **Bimekizumab** and 70 times more potent than **Secukinumab**
- **PN-881** inhibited IL-17 AF and FF with similar potency than **Bimekizumab**

Oral PN-881 Neutralizes Human IL-17 in Mouse IL-17 Challenge PD Model

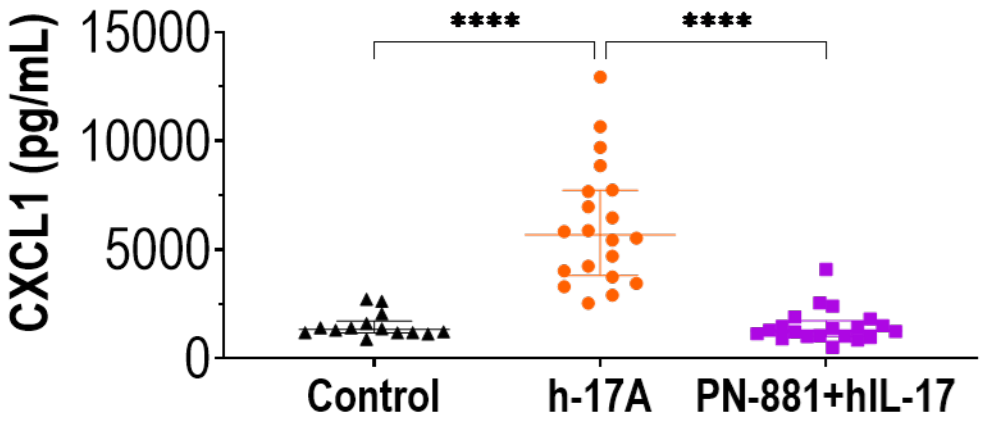
PN-881 significantly reduces serum and skin CXCL1 levels after oral administration

Female
C57BL/6

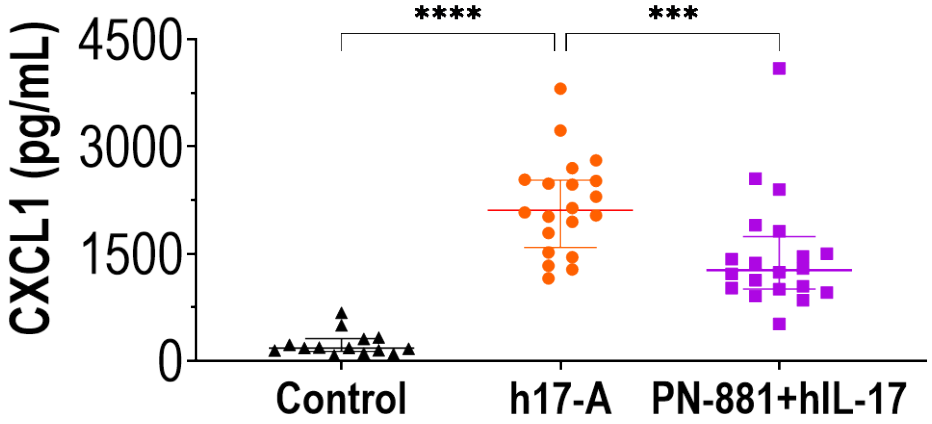
Treatment Groups:
a) Vehicle control
b) IL-17 alone
c) PN-881 (PO, QD)

1 hr → rhIL-17AA (SC 2µg/Mouse) or vehicle administered → 2 hr → Serum or skin collected → **CXCL1 (ELISA)**

Skin



Serum

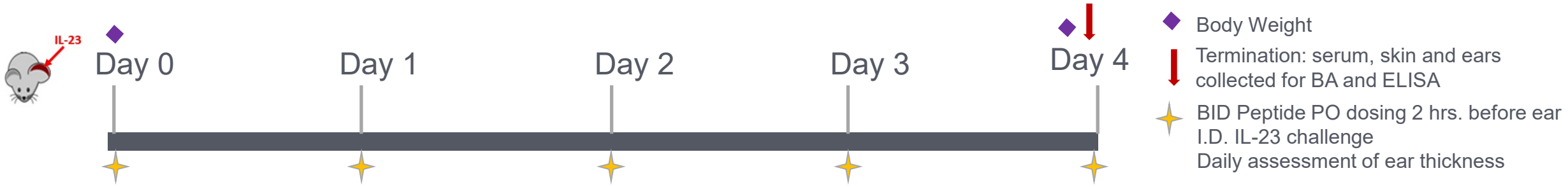


- Human IL-17 s.c. challenge induced systemic and skin production of CXCL1
- Oral administration of **PN-881** significantly reduced CXCL1 responses in serum and skin

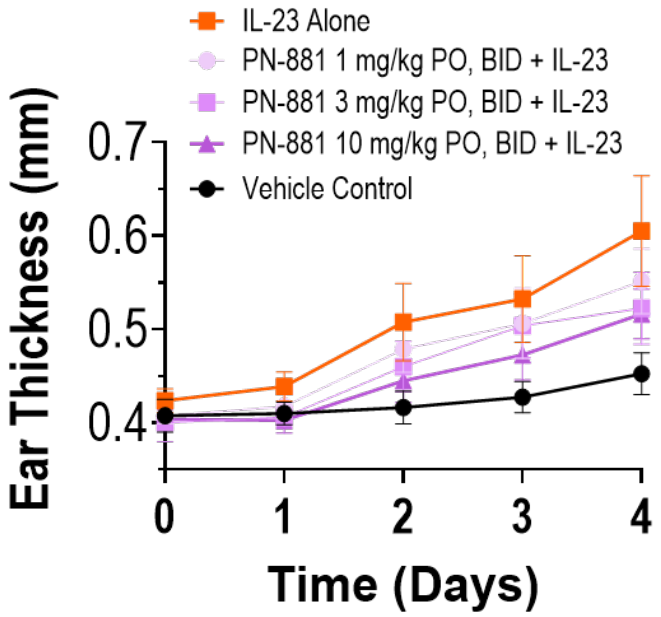
***p<0.001, ****p<0.0001 dop plot depict median and interquartile ranges,

Oral PN-881 in the Rat IL-23-induced Skin Inflammation Efficacy Model

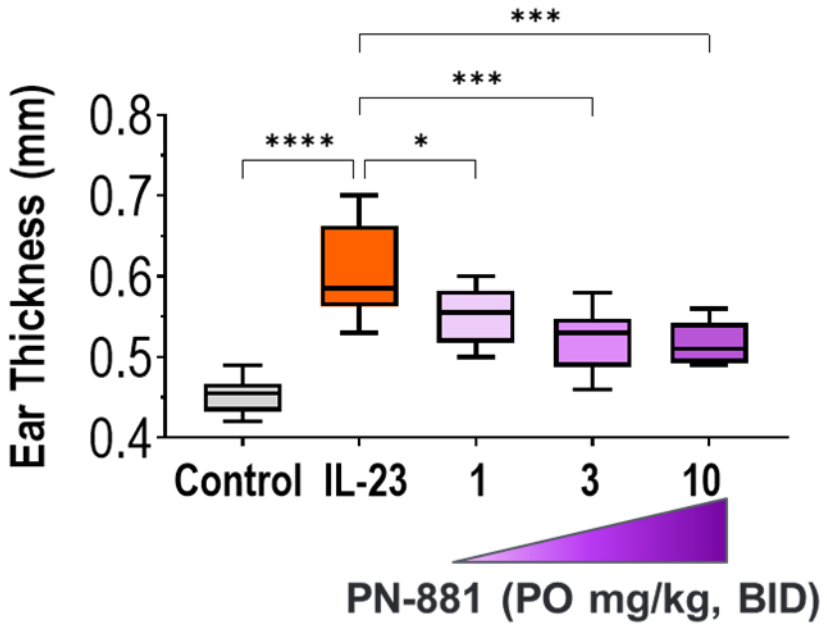
PN-881 significantly reduces IL-23-induced ear thickness after oral administration



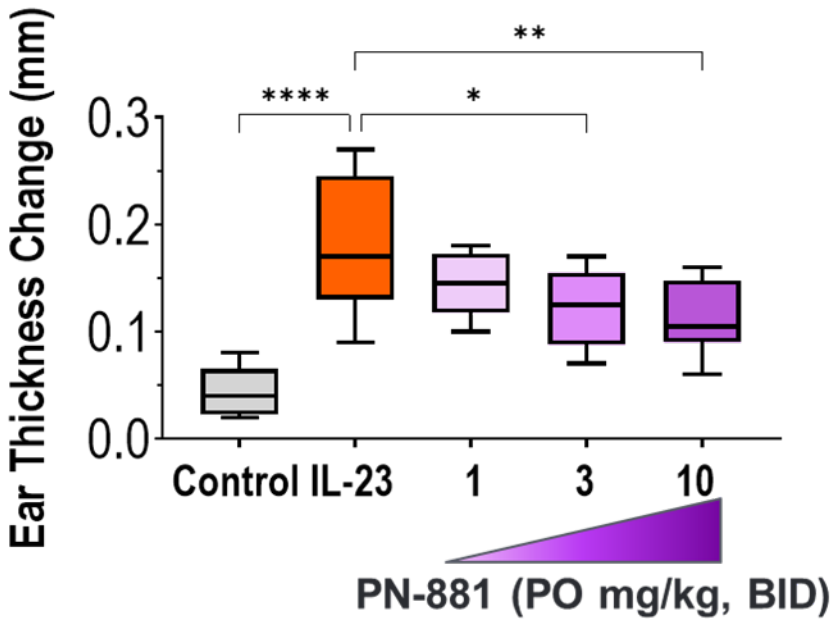
Ear Thickness Over Time



Ear Thickness (Day 4)



Ear Thickness Change



*p<0.05, **p<0.01, ***p <0.001, ****p <0.0001. Data points depict mean ± standard deviation, Boxes depict median and interquartile ranges; bars depict min. and max.

Summary

PN-881 has the potential to be the first-in-class oral peptide targeting all three IL-17 isoforms, the main driver of skin inflammation

- **Oral PN-881** exhibited comparable **potency values (IC_{50})** to Bimekizumab and superior (70-fold) to Secukinumab
- Metabolically stable in several matrices across several species
- Demonstrated PD-based target engagement after PO dosing
- Demonstrated target engagement in 5-day efficacy study after PO dosing

- **Anticipate Phase I initiation Q4 2025**

Thank You!

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