



COMPANY OVERVIEW

Dinesh V. Patel, Ph.D.
President & CEO

September 8, 2026

Legal Disclaimer

This presentation and any accompanying oral presentation contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act. All statements other than statements of historical facts contained in this presentation are forward-looking statements, including statements regarding: our potential receipt of milestone and royalty payments from Takeda and J&J; market potential for MIMRYLO™ (rusfertide) and ICOTYDE™ (icotrokinra); actions of the U.S. Food and Drug Administration (“FDA”) and foreign regulatory agencies; timing and results related to our pre-clinical and clinical product candidates (including PN-881, PN-477, PN-458, and PN-8047, among others); and the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates. In some cases, you can identify forward-looking statements by terminology such as “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potentially,” “predict,” “should,” “will,” or the negative of these terms or other similar expressions.

Forward-looking statements are subject to risks and uncertainties, including those discussed in our filings with the Securities and Exchange Commission, including in the “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” sections of our most recently filed periodic reports on Form 10-K and Form 10-Q and subsequent filings and in the documents incorporated by reference therein. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. The information included in these materials is provided as of the date specified on the cover page of this presentation, unless specified elsewhere herein, and is qualified as such. Except as required by applicable law, we undertake no obligation to update any forward-looking statements or other information contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

This presentation includes products under clinical investigation which have not yet been approved for marketing by the FDA. They are currently limited by Federal law to investigational use. No representation is made as to their safety or effectiveness for the purposes for which they are being investigated. All copyrights and trademarks included herein are the property of their respective owners.

ICOTYDE™ and MIMRYLO™ Revenue Engine Drives R&D Pipeline Development

Targeting Combined Addressable Markets >\$100 Billion

Revenue Engine

Commercial & Partnered

ICOTYDE™ (icotrokinra)

Oral IL-23R Antagonist • Partner: J&J

FDA Approved: Mar '26

EMA (CHMP) Positive Opinion: Jul '26

China (NMPA) Approved: Aug '26

Moderate-to-Severe Plaque Psoriasis

6–10% royalties + milestone payments
>\$10B peak potential¹

MIMRYLO™ (rusfertide)

SC Hepcidin Mimetic • Partner: Takeda

FDA Approved: Aug '26

Polycythemia Vera

14–29% royalties + milestone payments
\$1-2B peak sales²

Wholly-Owned Pipeline

Inflammation & Immunology

Oral PN-881 • IL-17A/F

Ph1 completed

Ph2b initiation in psoriasis: Q1 '27

Potential Indications: PsO, PsA, HS, SpA

Oral IL-4Rα Antagonist

Lead optimization

Potential Indications: AD, Asthma

Metabolic

Oral & SC PN-477 • GLP/GIP/GCG

SC Ph1 ongoing; Oral Ph1: 1H '27

Oral PN-458 • GLP/GIP

IND enabling studies

Amylin Mono/Poly-Agonists

Lead optimization

Hematology

Oral PN-8047 • Hepcidin Mimetic

Ph1: Q1 '27

Potential Indication: Polycythemia Vera

Strong Financial Position and Anticipated Future Cash Flows

Supports Aggressive Development of our R&D Portfolio and Potential Capital Return



**CASH,
CASH EQUIVALENTS &
MARKETABLE SECURITIES**

\$849.5M

as of June 30, 2026



**ADDITIONAL PAYMENTS
TRIGGERED UPON MIMRYLO
APPROVAL**

\$275M

\$200M remaining opt-out payment
and \$75M FDA approval milestone



**POTENTIAL FUTURE CASH
INFLOWS FROM
PARTNERSHIPS**

~\$1.5B

Future milestones

+

6-10% royalties on ICOTYDE

+

14-29% royalties on MIMRYLO

Takeda and J&J Partnership Economics

ICOTYDE™ (icotrokinra); Oral IL-23R Antagonist; Partner: J&J

\$387.5M

Payments earned

\$580M

Potential future milestones

6–10%

Tiered worldwide
royalties

>\$10B¹

ICOTYDE peak sales
potential

FDA Approved Mar '26 (Mod to Sev Plaque PsO) · PsA Ph3 · UC Ph3 · CD Ph2/3 · EMA (CHMP) positive opinion: Jul '26 · China (NMPA) Approved Aug '26
7.25% weighted-avg royalty at \$4B; 10% for annual sales ≥\$4B

MIMRYLO™ (rusfertide); SC Hepcidin Mimetic; Partner: Takeda

\$800M

Payments earned

\$875M

Potential future milestones

14–29%²

Tiered worldwide
royalties

\$1–2B³

Takeda-guided
peak sales

FDA Approved Aug '26 (PV) · Ph3 VERIFY PV study met primary + all 4 key secondary endpoints
21% weighted-avg royalty at \$1.5B; 29% for annual sales ≥\$1.5B

~\$1.2B in upfront, milestone, and opt-out payments earned through August 2026

Multiple Programs With Significant Value Creation Over the Next 24 Months

PROGRAM	THERAPEUTIC AREA	STAGE / STATUS	VALUE INFLECTION
ICOTYDE™ Oral IL-23R	I&I	Approved for Mod to Sev Plaque PsO	Launch trajectory Ph2 and Ph3 readouts
MIMRYLO™ Hepcidin mimetic	Hematology	Approved for Erythrocytosis in PV	Launch trajectory
PN-881 Oral IL-17A/F	I&I	Ph1; Ph2b PsO	Ph1 safety/PK completion Ph2b PsO dose finding/PoC
PN-477 Triple agonist; oral + SC	Metabolic	Ph1 SC and Oral	Ph1 SC SAD/Ph1b MAD (13 weeks) PoC Ph1 Oral SAD/MAD (7-day) Ph1b Oral MAD (13 weeks) PoC
PN-458 Dual agonist; oral	Metabolic	Ph1 start planned	Ph1 Oral SAD/MAD
PN-8047 Oral hepcidin	Hematology	Ph1 start planned	Ph1 SAD/MAD PD PoC Ph2 PV study
Discovery IL-4Rα; amylin	Discovery	Candidate selection	Multiple development candidates

... targeting combined addressable markets >\$100bn

Protagonist Therapeutics

Business Overview

- **Commercial Assets**

- ICOTYDE
- MIMRYLO

- **De-risked Strategy and Strengthened Pipeline**

- De-risked targets (e.g., IL-17, IL-4, hepcidin, incretin, glucagon and amylin)
- Validated platform and approach (ICOTYDE, MIMRYLO)

- **Accelerated Path to Clinical Proof of Concept (PoC)**

- Ph1 PoC planned for obesity and oral hepcidin programs
- Well-established clinical PoC pathway in I&I programs

- **Non-Dilutive Funding Model**

- \$849.5M cash (2Q26); additional opt-out, milestones, and royalty payments expected by year-end
- Royalty streams from ICOTYDE (6–10%) and MIMRYLO (14–29%), plus milestone payments
- No expected equity raise in the foreseeable future
- \$300M share buyback announced September 2026



ICOTYDE™ (icotrokinra; JNJ-2113, formerly PN-235): Targeted Oral IL-23 Receptor Antagonist Peptide

Setting a new standard of treatment in moderate to severe plaque psoriasis and other IL-23 mediated diseases

J&J Partnership: 2017 to Present

ICOTYDE™ (icotrokinra): First Oral IL-23R Therapy Targeting >\$80B¹ Market

THE INNOVATION

- **First- and only-in-class targeted ORAL peptide** IL-23R antagonist in late-stage development
- **Four major indications:**
 - Moderate to severe plaque psoriasis (PsO); approved (US)
 - Psoriatic arthritis (PsA); Ph3 ongoing
 - Ulcerative colitis (UC); Ph3 ongoing
 - Crohn's disease (CD); Ph2b/3 ongoing

THE OPPORTUNITY

Ustekinumab >\$11B²

Guselkumab >\$10B³

Risankizumab >\$20B⁴



PsO / IBD patients eligible for advanced therapies but remaining untreated⁶

~50-70% (5M)

>\$10B⁷ blockbuster potential

Established efficacy and proven safety profile in a once-daily pill

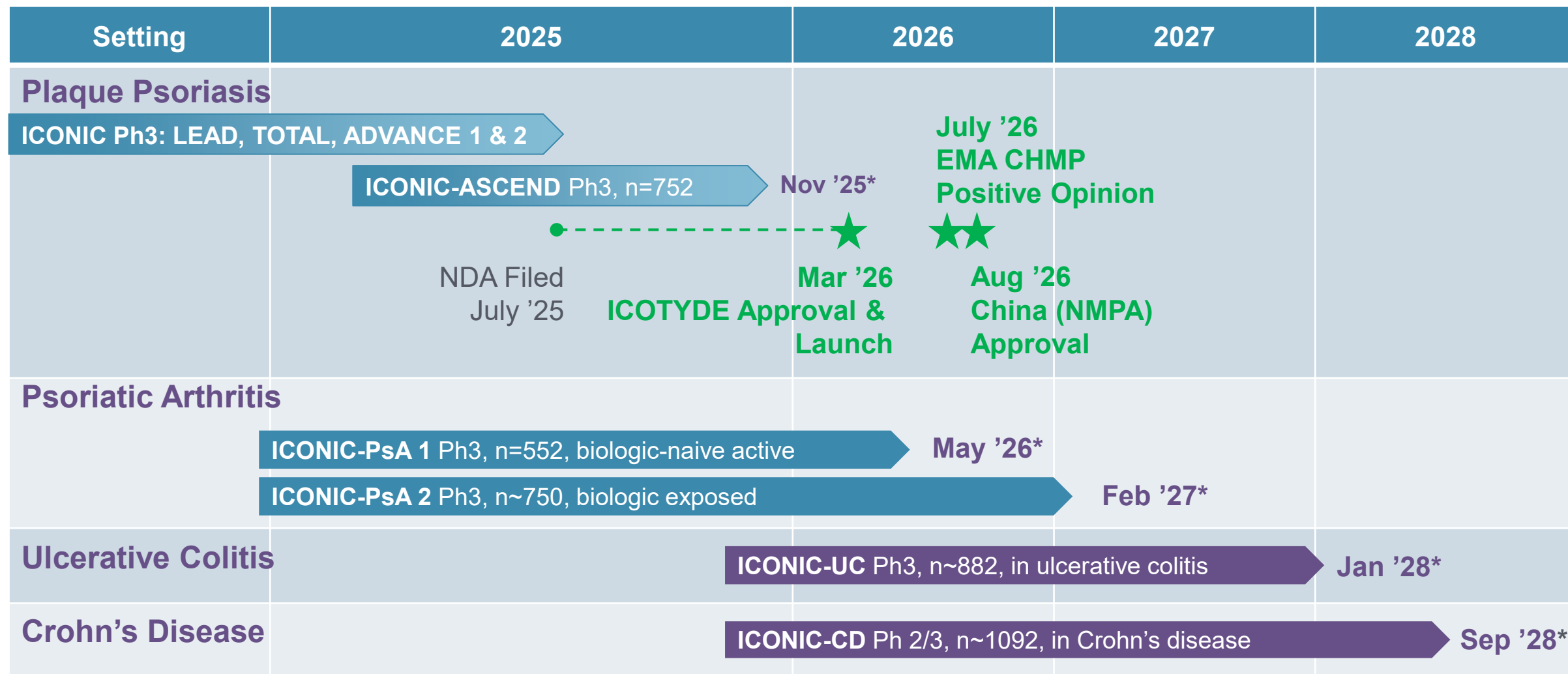
ICOTYDE™ (icotrokinra)

US FDA approval of ICOTYDE™, formerly PN-235

- Johnson & Johnson partnership overview
 - 2017 to present
 - Protagonist completed pre-clinical and first Ph1 study¹
 - J&J responsible for further development and commercialization
- ICOTYDE is the first and only IL-23R targeted oral peptide to
 - clear skin for moderate to severe plaque psoriasis patients, with a
 - favorable safety profile, and the
 - convenience of a once-daily pill
- Approval supported by four phase 3 studies that met all primary endpoints and demonstrated a favorable safety profile in 2,500+ patients

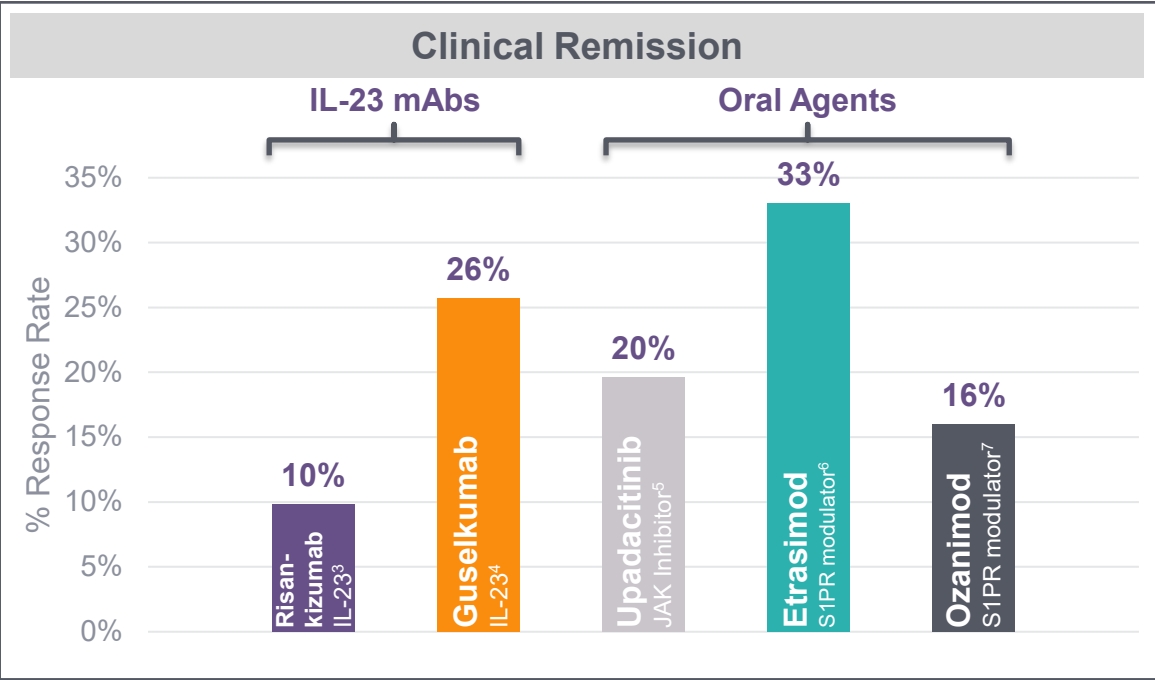
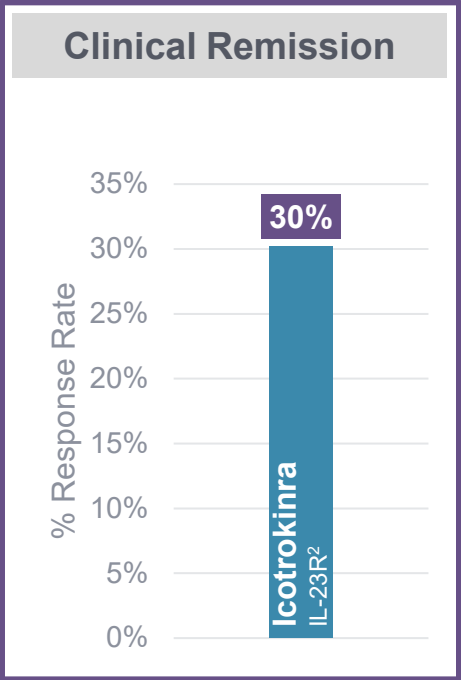
1. Fourie, AM et al. JNJ-77242113, a highly potent, selective peptide targeting the IL-23 receptor, provides robust IL-23 pathway inhibition upon oral dosing in rats and humans. *Sci Rep* 2024(14):17515. <https://doi.org/10.1038/s41598-024-67371-5>.

Icotrokinra Potential Expansion of Multiple Indications in Coming Years



Icotrokinra Cross-Trial Comparison to Phase 2 Benchmarks in UC¹

Clinical Remission



Agent	Endpoint Timeframe	Placebo Remission (%)
Icotrokinra	Wk 12	11.1
Risankizumab	Wk 12	1.7
Guselkumab	Wk 12	9.5
Upadacitinib	Wk 8	0
Etrasimod	Wk 12	8.1
Ozanimod	Wk 8	6

1. Cross trial (not head-to-head) comparisons of unadjusted (ie, non-placebo adjusted) remission data from phase 2 studies.

2. Icotrokinra (JNJ-2113) highest dose (in mg; PO qd) with clinical remission at Wk 12 (ie, Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy). Clinical remission (placebo): 11.1%. Protagonist Therapeutics, Inc. "Protagonist Reports Positive Top Line Results from Phase 2b Study of Icotrokinra Showing Potential to Transform the Treatment Paradigm for Patients with Ulcerative Colitis." News release. 10 March 2025.

3. Risankizumab 1200 mg IV (approved dose; phase 2 data) clinical remission per Adapted Mayo score at Wk 12 (ie, stool frequency subscore ≤1, and not greater than baseline, rectal bleeding subscore =0, and endoscopic subscore ≤1 without the evidence of friability). Clinical remission score (placebo): 1.7%. Louis E, et al., *JAMA*. 2024;332:881-97.

4. Guselkumab 200 mg IV (approved dose; phase 2 data) clinical remission at Wk 12 (ie, Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on endoscopy). Clinical remission (placebo): 9.5%. Peyrin-Biroulet L, et al., *Gastroenterology*. 2023;165:1443-57.

5. Upadacitinib 45 mg PO QD (approved dose; phase 2 data) with clinical remission at Wk 8 (ie, adapted Mayo score; defined as stool frequency subscore of 1, rectal bleeding subscore of 0, and endoscopic subscore of 1). Clinical remission (placebo): 0%. Sandborn WJ, et al., *Gastroenterology*. 2020;158:2139-49.

6. Etrasimod 2 mg PO QD (approved dose; phase 2 data) with clinical remission at Wk 12 (ie, Mayo Clinic endoscopic subscore ≤1 [with absence of friability], rectal bleeding score ≤1, and stool frequency score ≤1, with a frequency decrease of ≥1 point from baseline). Clinical remission (placebo): 8.1%. Sandborn WJ, et al., *Gastroenterology*. 2020;158:550-61.

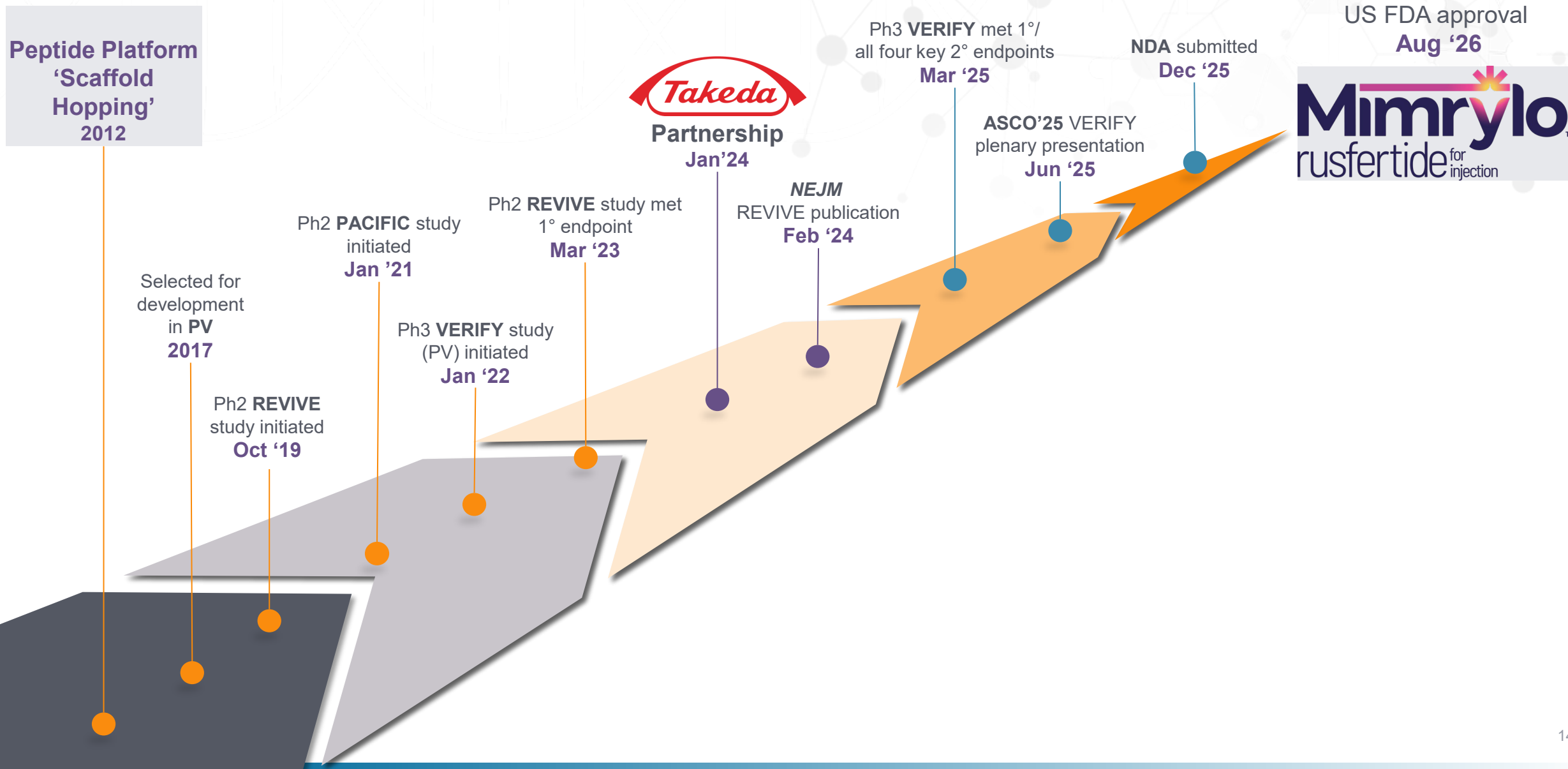
7. Ozanimod 1 mg PO QD (approved dose; phase 2 data) with clinical remission at Wk 8 (ie, Mayo Clinic score ≤2, with no subscore >1). Clinical remission (placebo): 6%. Sandborn WJ, et al., *New Engl J Med*. 2016;374:1754-62.

**MIMRYLO™ (Rusfertide):
Treatment For
Erythrocytosis in Adults
With Polycythemia Vera (PV)**



MIMRYLO™ (Rusfertide, PTG-300): A Hepcidin Mimetic

Journey from 'Concept to Commercial'



Now FDA Approved: MIMRYLO™

First and Only Hepcidin Mimetic



Indication

- Indicated for treatment of erythrocytosis in adults with polycythemia vera (PV)

Polycythemia Vera

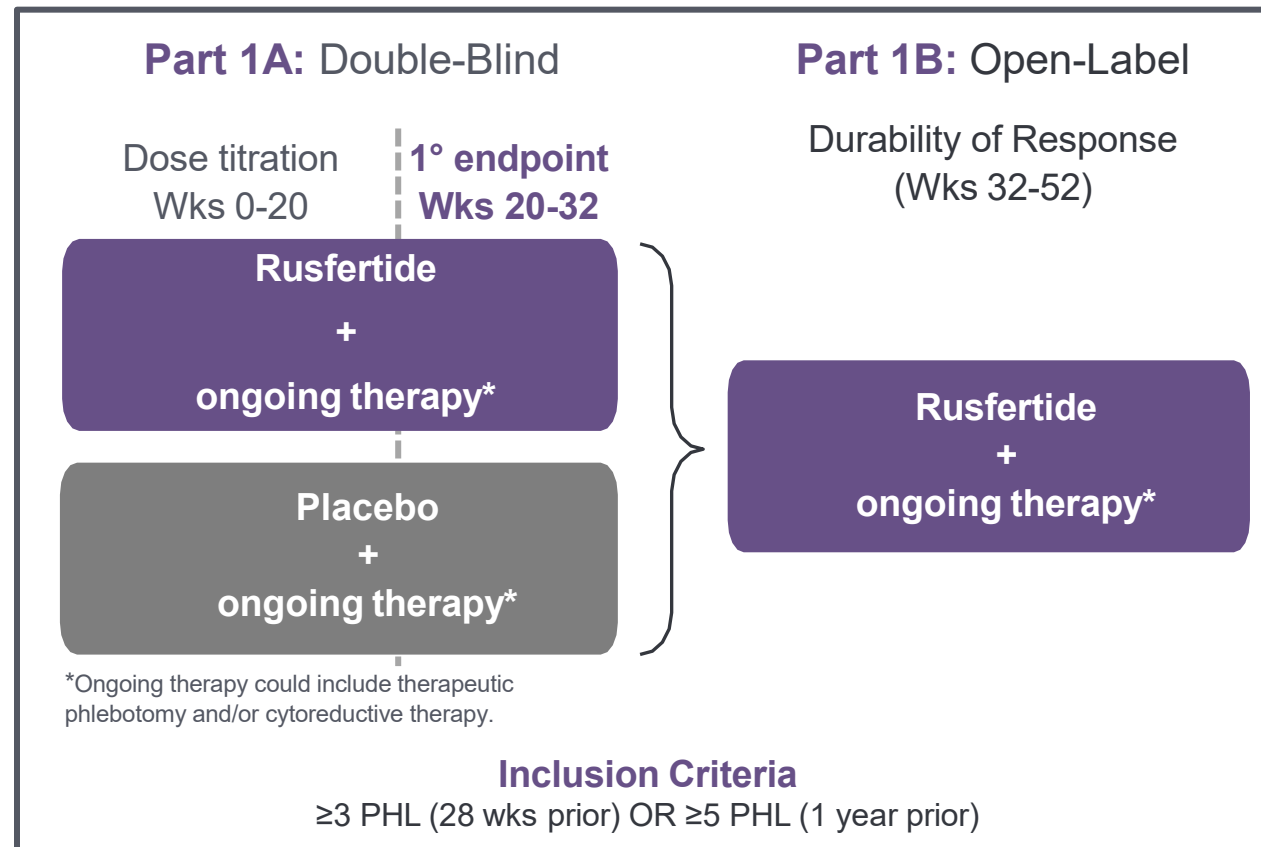
- Blood cancer characterized by excessive production of red blood cells¹
 - Elevated hematocrit (Hct)²
 - Primary treatment goal: maintain Hct <45%^{3,4}

MIMRYLO™: Highlights of Prescribing Information ([Link](#))¹

- **Efficacy:** 76.9% of patients achieved response between Weeks 20-32
 - MIMRYLO maintains hematocrit control and reduces phlebotomy burden
- **Patient reported outcomes (PRO):** MIMRYLO improves fatigue in adults with PV
 - Improvement in fatigue measured by the PROMIS Fatigue Short Form 8a
- **Safety:** no black box warning
 - **Carcinogenicity:** Rusfertide was not carcinogenic in a 6-month transgenic mouse study at subcutaneous doses up to 25 mg/kg/week or in a 2-year rat carcinogenicity study at doses up to 3 mg/kg/week.
 - **Warnings and Precautions:** New or worsening thrombocytosis, injection-site reactions, and embryo-fetal toxicity.
 - **Adverse reactions:** The most common (>15%) adverse reactions were injection site reactions (56%) and anemia (16%).
 - **Discontinuations:** Adverse reactions which resulted in permanent discontinuation of MIMRYLO included injection site reactions in 2 (0.7%) patients, thrombocytosis in 2 (0.7%) patients, and anemia in 1 (0.4%) patient.

Ongoing Phase 3 VERIFY Study: PV^{1,2}

Sustained Hct Control With Fewer PHLs vs. Placebo; Addresses Major Unmet Need in PV



- **Primary endpoint: Wks 20-32**

1. Response: rusfertide vs placebo ($p < 0.0001$) ✓

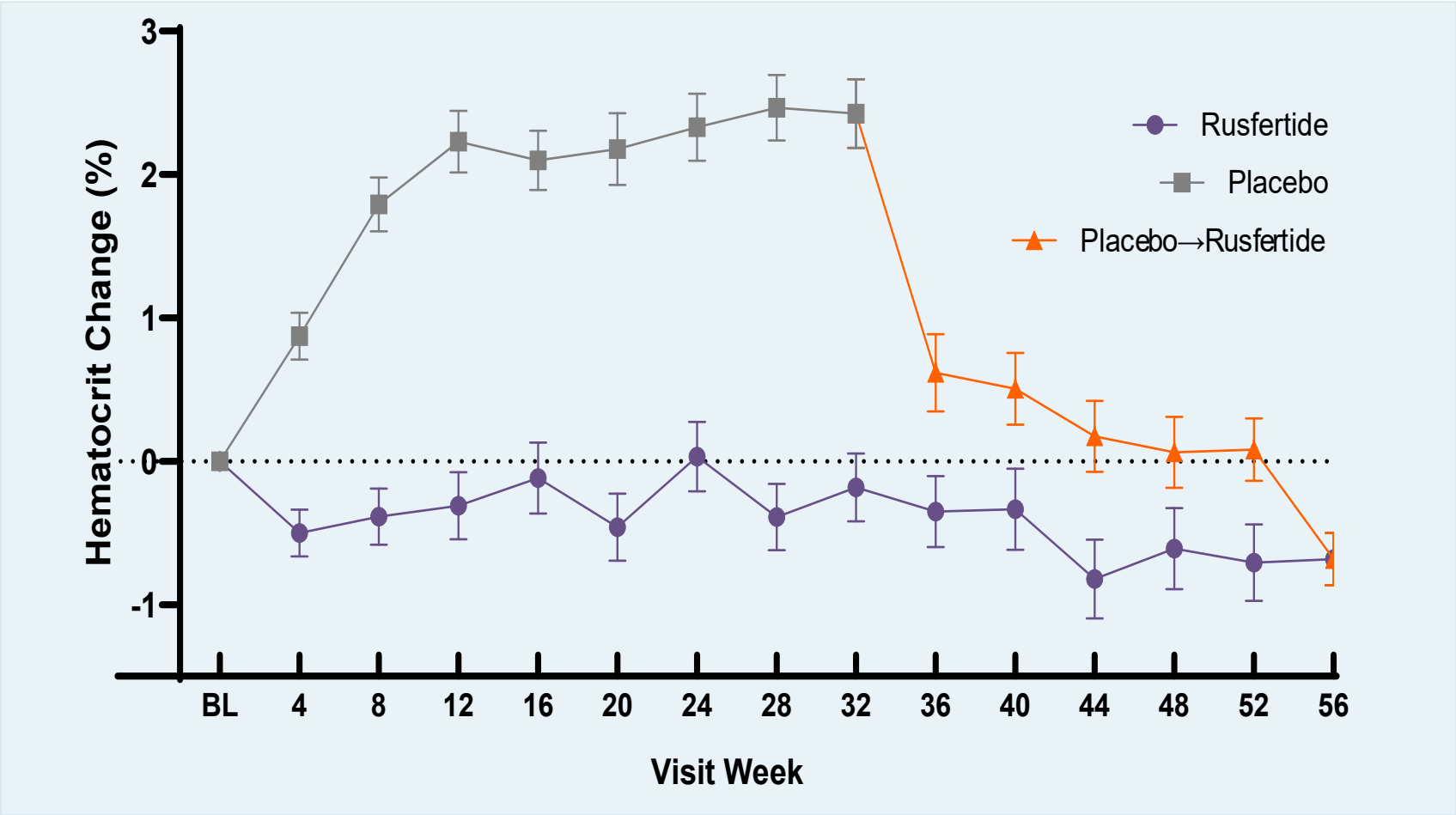
- **Key 2° endpoints: Wks 0-32**

1. Average number of PHLs ($p < 0.0001$) ✓
2. Proportion of patients with Hct $< 45\%$ ($p < 0.0001$) ✓
3. **PROMIS Fatigue SF-8a Score** ✓
4. MFSAF Total Symptom Score ✓

VERIFY featured in Plenary Presentation at ASCO'25

Rusfertide Phase 3 VERIFY Study Results: PV^{1,2}

Durable, Sustained Hct Control With Fewer PHLs vs. Placebo, Addressing Major Unmet Need in PV^{1,2}



VERIFY featured in Plenary Presentation at ASCO'25

Polycythemia Vera (PV)

Significant Unmet Medical Need

1. Hct Control

- **Maintaining Hct<45% is critical**, as per NCCN guidelines
- **~4 times higher risk of death from uncontrolled Hct¹**

2. Patients

- Up to **78% of patients have uncontrolled Hct $\geq 45\%$ ²**
- **Thrombotic events (34-41%)³⁻⁵**
- **Burdensome symptoms**
 - Fatigue within last 12 months (73%)⁶
 - Full days in bed (23%)⁶
 - Iron deficiency (anemia)⁷

3. Therapy

- **Current standard of care (SOC)**
 - Phlebotomy, hydroxyurea (HU), interferon, Jakafi
 - Inadequate
- **No RBC-specific pharmaceutical option available**

Hypothesis: MIMRYLO™, a hepcidin mimetic, could provide a erythrocytosis-specific treatment for PV

1. Marchioli R, et al. *N Engl J Med*. 2013;368:22-33.

2. Verstovsek S, et al. *Ann Hematol*. 2023;102(3):571-581.

3. Kaifia A, et al. *J Hematol Oncol*. 2016;9:18.

4. Griesshammer M, et al. *Ann Hematol*. 2019;98(5):1071-1082.

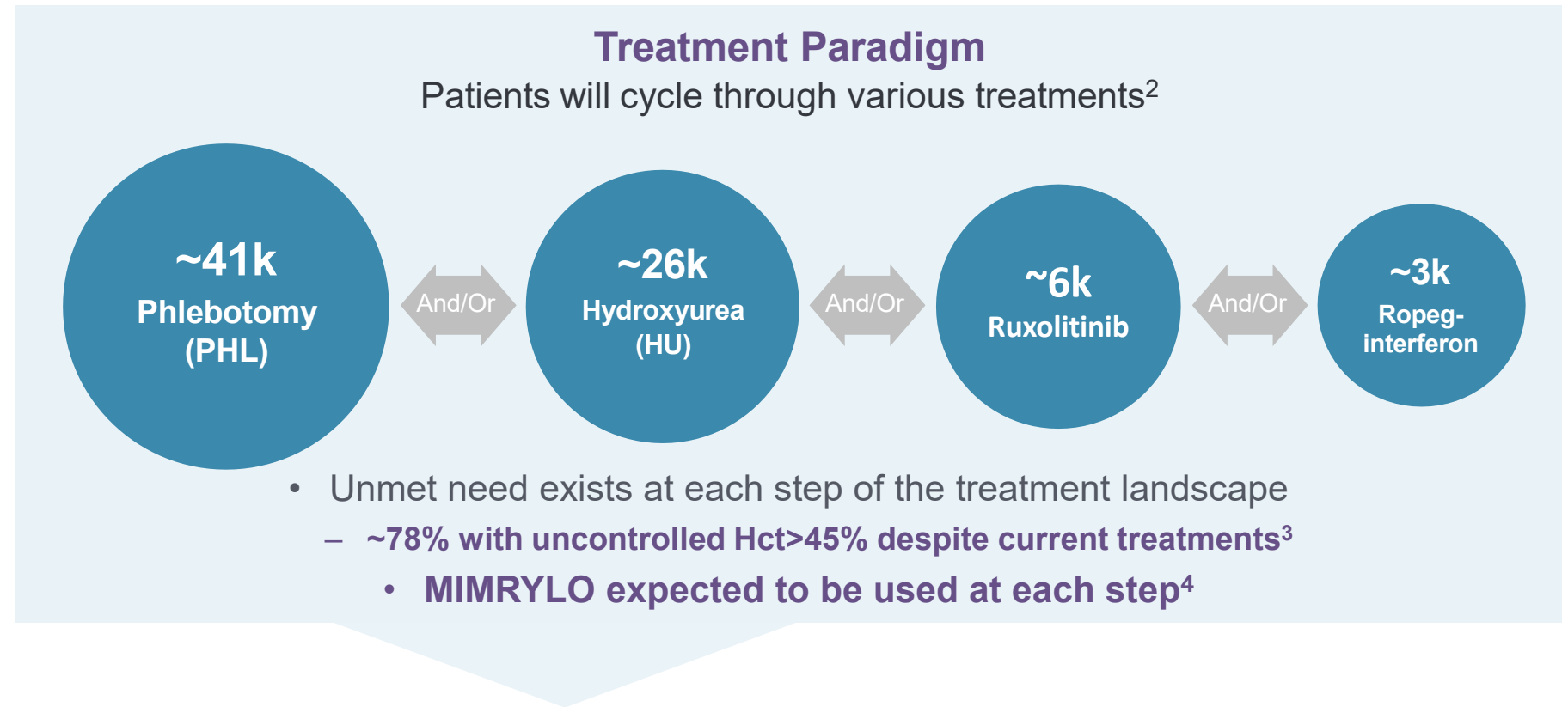
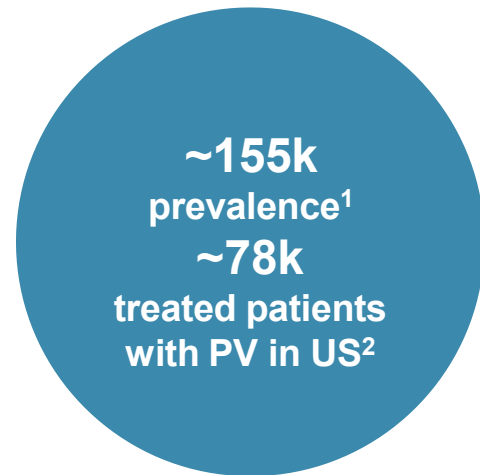
5. Polycythemia vera: the natural history of 1213 patients followed for 20 years. Gruppo Italiano Studio Policitemia. *Ann Intern Med* 1995;123(9):656-64.

6. Mesa R, et al. *BMC Cancer* 2016;16:167.

7. Ginzburg et al. *Leukemia* 2018;32:2105-2116.

MIMRYLO™: Erythrocytosis-Specific Treatment Option for Adults With PV

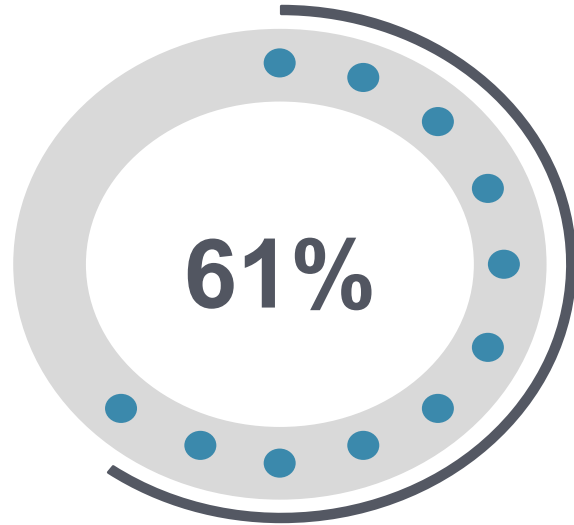
Peak Revenue Potential of \$1-2 Billion⁴



MIMRYLO maintains hematocrit control, reduces phlebotomy burden and improves fatigue

Most Patients With Polycythemia Vera Experience Suboptimal Hct Control

Frequent Phlebotomies, High-Dose Hydroxyurea and/or Post-Treatment TEs Are Common



Regimens among patients with PV who received burdensome treatment and/or experienced a TE (N=27,116)¹

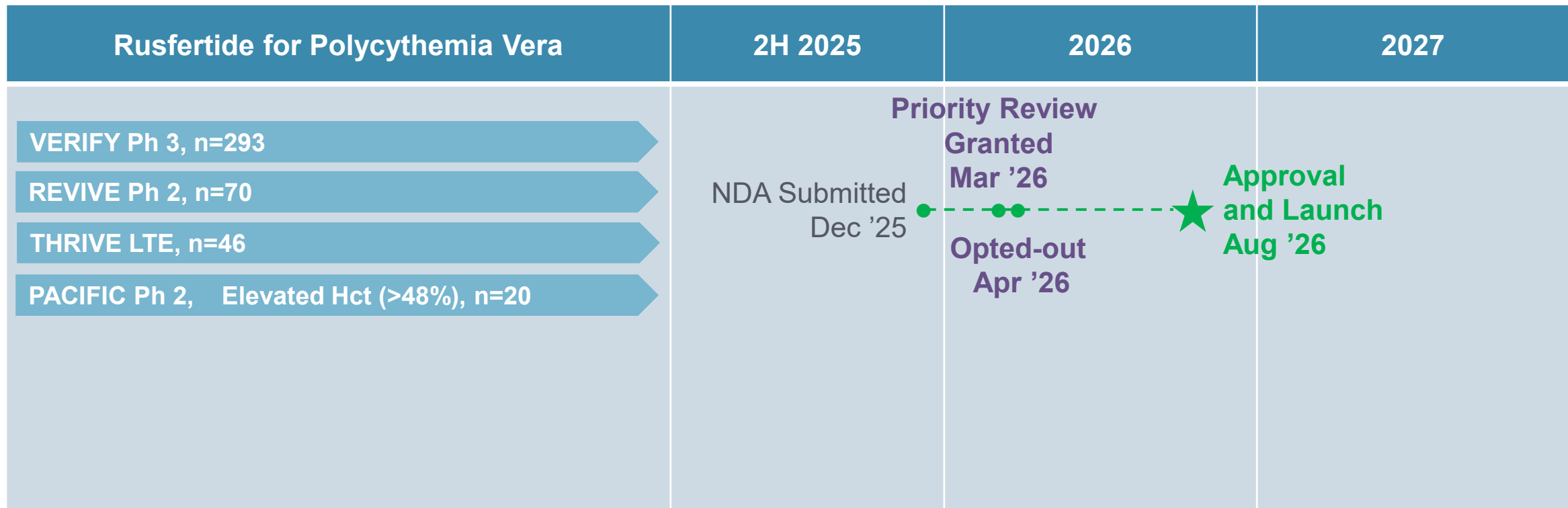
- 54%**  **Frequent phlebotomies (PHLs)**
Patients receiving ≥ 3 PHLs in 6 months
- 28%**  **High-dose hydroxyurea (HU)**
Patients receiving $\geq 1,000$ mg HU per day
- 8%**  **Combination of PHL and HU**
Patients receiving a combination of frequent phlebotomies and high-dose HU

Komodo Health claims database (data from January 2016 to December 2022); includes patients who were ≥ 18 years old and had at least two clinical diagnoses of PV that were at least 6 months apart.

1. Kuykendall A, et al. *Expert Rev Hematol*. 2025;18(11):979-86.

Rusfertide for PV: NDA Filing, Approval and Commercialization Launch Timelines

MIMRYLO™ (rusfertide) Approved on 28 August 2026



Rusfertide has **Orphan Drug** designation, **Fast Track** status, and **Breakthrough Therapy** designation

FDA approval and commercial launch beginning in Aug 2026

R&D Pipeline

I&I, Hematology, Obesity

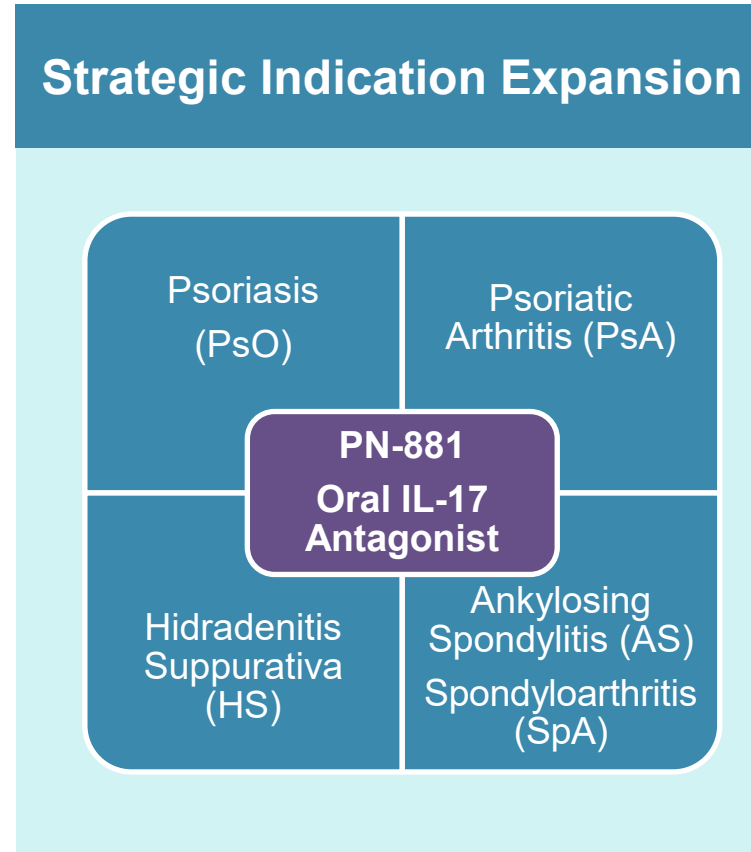
PN-881: A Potential Best-in-Class Oral
IL-17A and IL-17F Antagonist

Clinically and commercially validated target
for multiple inflammatory conditions

Targeting a \$55B+ Market Opportunity with Differentiated ORAL IL-17 Inhibition

PN-881: A Potential Best-in-Class Oral IL-17A and IL-17F Antagonist

IL-17: Large & Expanding Market Opportunity	
\$12B	CURRENT IL-17 SALES ¹
28%	ANNUAL MARKET GROWTH ²
~2.5M	PATIENTS ELIGIBLE BUT UNTREATED ³
>\$55B	LONG-TERM MARKET OPPORTUNITY ⁴



PN-881: Differentiated Target Product Profile

PN-881 Blocks All Three IL-17 Dimers

IL-17AA IL-17AF IL-17FF

- **Oral Peptide**
- **Triple specificity⁵** matching Bimzelx profile
- Potential **best-in-class profile**

PN-881: A wholly-owned ORAL IL-17A and F antagonist in Clinical Studies

1. 2025 Company reported revenues (Novartis, Eli Lilly, UCB)

2. Historical CAGR based on FY2023-2025 actual reported revenues (Novartis, Eli Lilly, UCB)

3. Clarivate (PsO, PsA, AxSpA) and DelveInsight (HS), 2025 diagnosed and treated prevalence in G7 markets. Untreated patients calculated as moderate-to-severe diagnosed population minus drug-treated population

4. 2032 projected market size for PsO, PsA, axSpA, and HS; Evaluate Pharma

5. Reich et al., *N Engl J Med* 2021;385:142-52.

Criteria for Nomination of Oral PN-881 Development Candidate¹

Oral PN-881 Achieved all Defined Criteria for Development Candidate Nomination

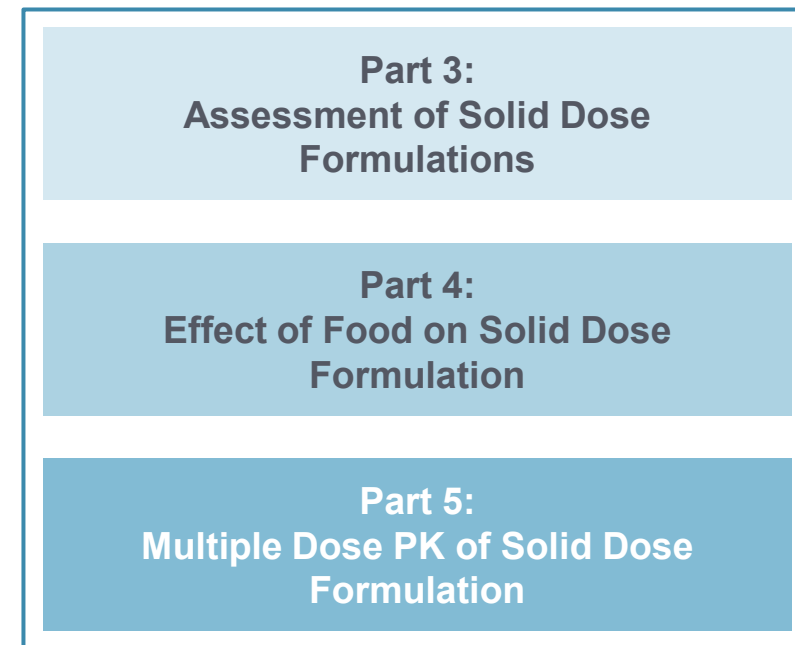
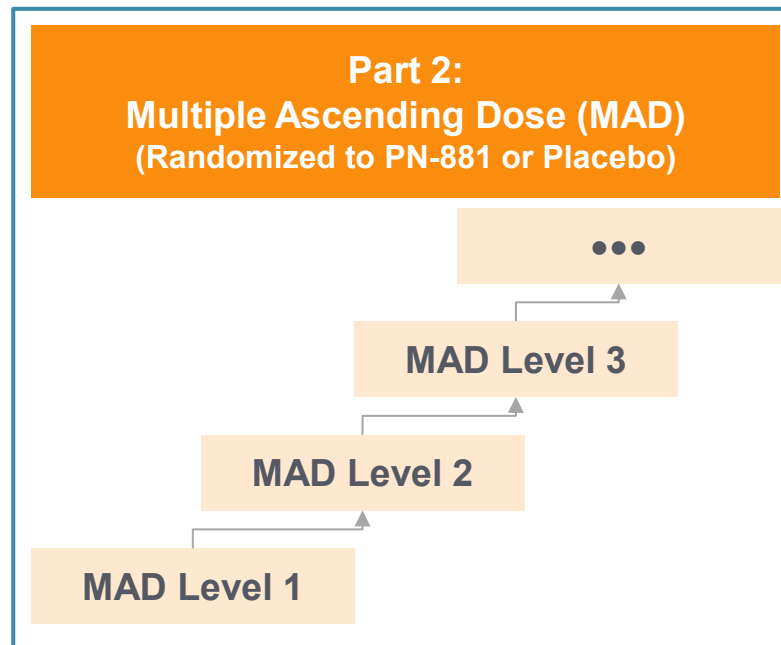
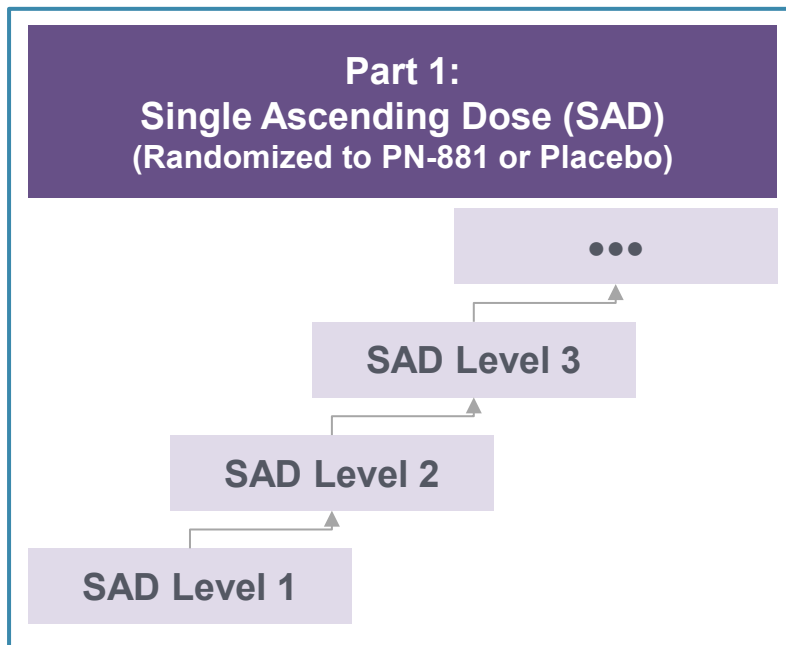
Attribute	Criteria
Potency	✓ Sub-nM potency vs. IL-17 AA ✓ Blocks all dimeric forms of IL-17: AA, AF, FF
Stability	✓ Stable in simulated gastric and intestinal fluids ✓ Stable in serum with $t_{1/2}$ >24 hr ✓ Metabolic stability ✓ Thermostability
PK	✓ Oral exposure and half-life in rodent and higher species sufficient for oral daily dosing
PD model	✓ Mouse hIL-17 challenge, CXCL1 model
Efficacy Model	✓ Rat IL-23-induced skin inflammation model

PN-881 Achieved Desired Pharmacology in Preclinical Models

- High systemic exposures after oral administration to mice, rats, dogs, and cynomolgus monkeys
 - >100 ng/mL in cynomolgus monkeys with oral dose of 2.5 mg/kg
- Blockade of IL-17 in in vivo mouse models after oral administration
 - PN-881 inhibits CXCL1 production in serum and skin in mice challenged with supra-physiologic doses of human IL-17
 - PN-881 shows efficacy at doses as low as 1 mg/kg BID in inhibiting ear inflammation (erythema and thickness) in rats challenged with repeated IL-23 injections
- Suitable tissue distribution into the skin in preclinical models
 - Ratio of skin-to-plasma concentrations comparable to or better than monoclonal antibodies

PN-881: Comprehensive Phase 1 Study in Healthy Volunteers (N~142)

Phase 1 Study Completed



- **Primary endpoint:**

- Incidence and severity of treatment-emergent adverse events (pre-dose to 7 days after last dose)

- **Secondary endpoint:**

- Pharmacokinetics

PN-881 Potently Inhibits Both IL-17A and IL-17F Isoforms

	Neonatal Human Dermal Fibroblast					
	IL-17AA ¹		IL-17FF ¹		IL-17AA+IL-17FF ²	
	IC ₅₀ (nM)	IC ₉₀ (nM)	IC ₅₀ (nM)	IC ₉₀ (nM)	IC ₅₀ (nM)	IC ₉₀ (nM)
Oral Peptide, PN-881	0.0026	0.031	0.015	0.124	0.013	0.098
Injectable mAb, Bimzelx [®] (Bimekizumab)	0.0007	0.003	0.014	0.037	0.015	0.071

mAb, monoclonal antibody; PsO, psoriasis.

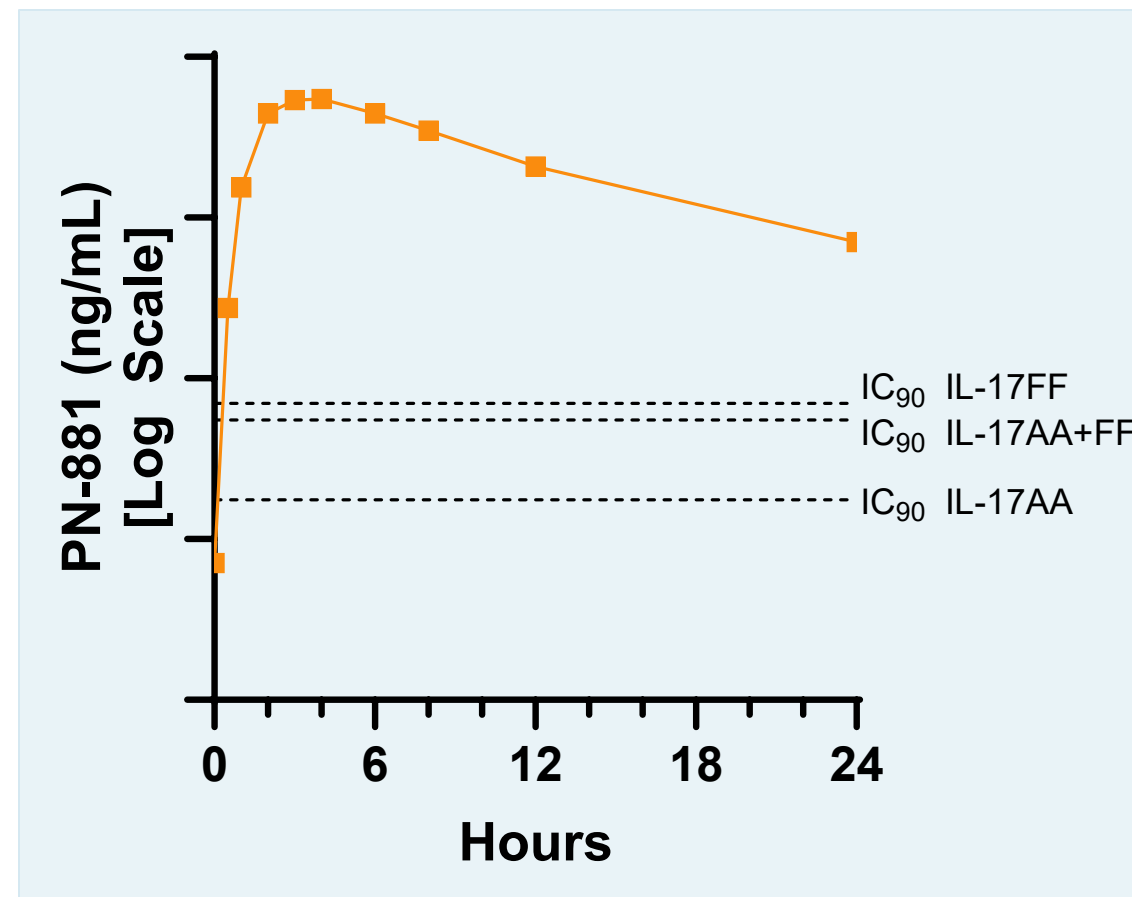
¹IC₅₀/IC₉₀ values reflect drug potency for inhibiting IL-17 signaling at IL-17 levels relevant for PsO patients, i.e., IL-17A = 0.1 ng/mL; IL-17F concentration = 1 ng/mL

²IL-17A and IL-17F were used in vitro in a PsO-relevant ratio of 1:30, i.e., 0.1 ng/mL IL-17A + 3 ng/mL IL-17F, to demonstrate the inhibitory potential of PN-881 compared to bimekizumab.

PN-881: Phase 1 Study

Pharmacokinetic Results Support a Comprehensive Phase 2b Study in Plaque Psoriasis

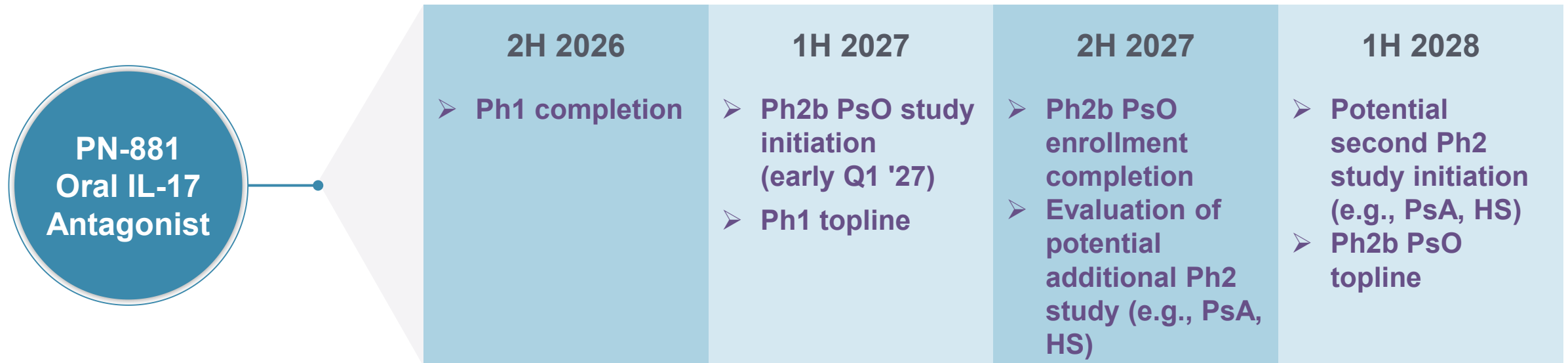
- Achieved 24-hour C_{trough} levels significantly higher than prospectively targeted IC_{90} (IL-17AA, IL-17FF, IL-17AA+FF) values with once-daily oral dosing
- Drug accumulation results in higher drug levels at steady state (data not shown)
- Generally well tolerated; no serious adverse events
- Phase 1 data to be presented at a future medical meeting
- Phase 2b dose range-finding study in plaque psoriasis to be initiated in early Q1 2027



PN-881 Plasma Concentrations Several Fold Higher Than IC_{90} Values For Both Isoforms (AA & FF) and IL-17AA+FF

PN-881: Successful Ph1 Lays a Strong Foundation for Comprehensive Ph2b Program

Clinical Development Plans in Psoriasis and Other Potential Indications



PN-8047: An Oral Hepcidin Functional Mimetic

Working towards a Hepcidin pathway
based ORAL option in polycythemia vera

PN-8047: Oral Hepcidin Functional Mimetic

Leveraging Our Expertise in the Hepcidin Pathway



- Rusfertide established hepcidin mimetics as a therapeutic option for polycythemia vera

- Clinical validation of hepcidin biology



- **PN-8047:** Builds on Protagonist's knowledge base of hepcidin pathway

- **Novel oral small molecule**; selected from extensive head-to-head comparison of different modalities
- Potentially maximizes the total addressable global market for hepcidin mimetics
- Provides a therapeutic option that may reduce treatment barriers



- Wholly-owned asset

PN-8047: An Oral Hepcidin Functional Mimetic for Targeting Polycythemia Vera

PN-8047 has similar potency as rusfertide and is superior to hepcidin

	Human-FPN Potency EC ₅₀ (nM)
Hepcidin	13.7
Rusfertide	2.5
PN-8047	4.3

Table shows average values for effective concentration for 50% signal (EC₅₀) in nano-molar (nM)

Human-FPN assay measured functional response of increases in transferrin-receptor1 due to increase in intracellular iron concentrations after ferroportin internalization

Cyno-FPN assay measured reduction in NanoLuc® Luciferase signal, downstream of ferroportin internalization

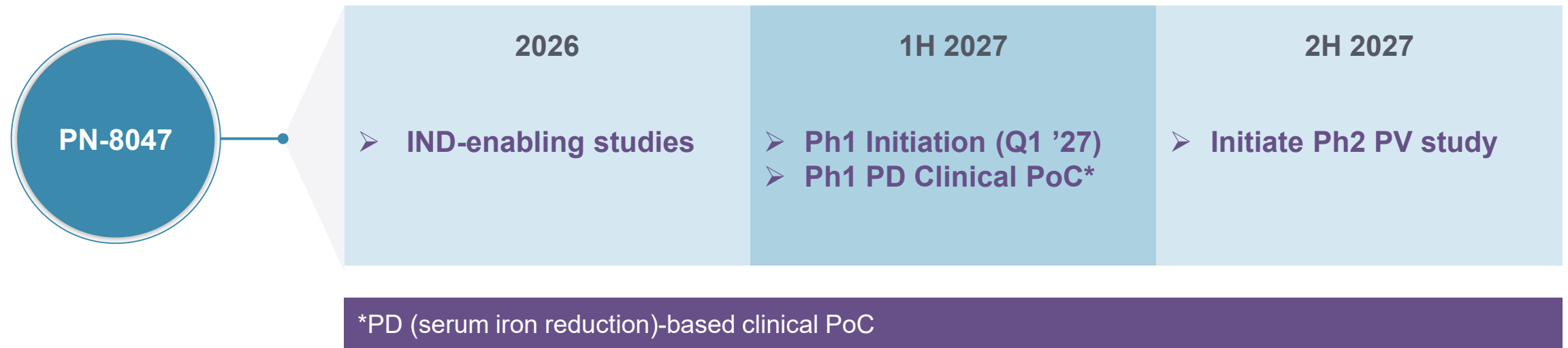
FPN, Ferroportin; Cyno, Cynomolgus Monkey

PN-8047: Novel Potent Oral Small Molecule With Excellent PK, PD, and Efficacy Properties

Attributes	Summary of PN-8047 Properties
Potency	✓ Nanomolar potency in the T47D-TfR1 functional assay ✓ Similar potency as Rusfertide
in vitro ADME	✓ Metabolically stable in liver microsomal incubations ✓ Good permeability for oral dose
PK	✓ Oral exposure and $T_{1/2}$ in rodents, cyno, and dog sufficient for oral daily dosing
PD Model	✓ Iron reduction after single and repeat oral dosing to dog and monkey to support once-daily oral dosing ✓ Sustained iron reduction for 16 hr
Efficacy Model	✓ Efficacy in the erythropoietin (EPO)-induced mouse model for erythrocytosis ✓ Reduction of hemoglobin and hematocrit after repeat oral dosing to cynos
DDI	✓ No DDI risk potential
Safety	✓ No major off-target activities ✓ Tolerated in 7-day rat MTD

Phase 1 initiation in Q1 '27
PD-based clinical PoC achievable in phase 1

PN-8047: Oral Hepcidin Functional Mimetic Development Timelines



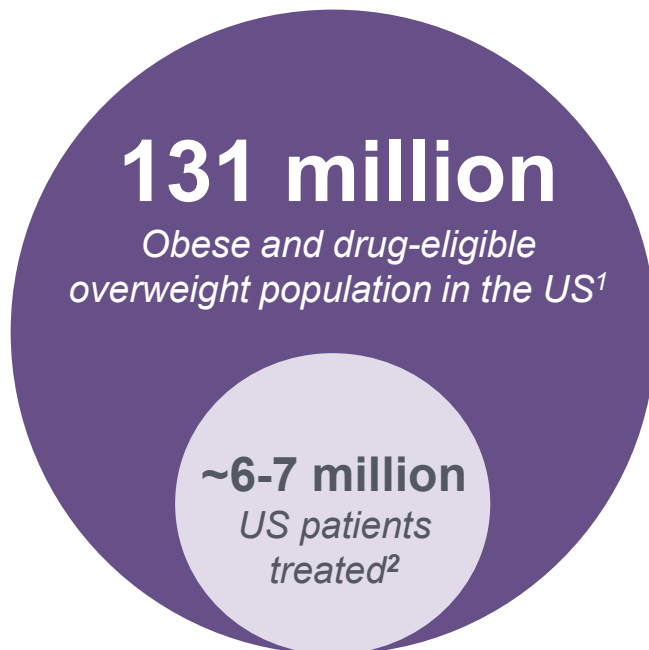
Metabolic Pipeline: Addressing the Need For Unimolecular Oral Anti- Obesity Therapies

Triple-G, Dual-G, and AmylinR Agonists

Obesity: Unprecedented Pharmaceutical Opportunity in the US and Worldwide

Only ~5% of Eligible Patients Receive Drug Treatment¹

*Massive Untapped
Opportunity in Obesity Care*



- Obesity is a global epidemic
 - In 2024, nearly **40% of Americans were obese** or considered drug-eligible overweight³
- Low Treatment Penetration
 - Only ~5% of eligible patients receive drug treatment¹
- Current challenges with anti-obesity drugs
 - Convenience; needle avoidance
 - Early days & limited options
 - Adverse effects

‘Oral’ and ‘more effective’ agents:
An attractive option for a chronic condition
and affiliated co-morbidities

Four of the Current Top 10 Best-Selling Drugs are Peptide-Based Therapies¹

<u>2015</u>	1 peptide branded therapy in top 10			<u>2025</u>	4 peptide branded therapies in top 10	
Humira	\$14.0B	mAb	→	Keytruda	\$31.7B	mAb
Harvoni	\$13.9B	SM		Mounjaro	\$23.0B	Peptide
Enbrel	\$8.7B	Fusion		Ozempic	\$19.2B	Peptide
Remicade	\$8.4B	mAb		Dupixent	\$17.7B	mAb
Rituxan	\$7.1B	mAb		Skyrizi	\$17.6B	mAb
Lantus	\$7.0B	Peptide		Eliquis	\$14.4B	SM
Avastin	\$6.8B	mAb		Darzalex	\$14.4B	mAb
Herceptin	\$6.6B	mAb		Biktarvy	\$14.3B	SM
Revlimid	\$5.8B	SM		Zepbound	\$13.5B	Peptide
Sovaldi	\$5.3B	SM		Wegovy	\$12.0B	Peptide

1 → 4

Peptides among the top 10

\$7B → \$68B

Combined top-10 peptide sales

~10x

Growth over the decade

PN-477: A Novel Triple GLP-1/GIP/GCG Receptor Agonist Peptide

Optionality for Oral or Subcutaneous Dosing

Potential Improvements

- **Magnitude** and **quality** of body weight loss
 - Potential secondary benefits in co-morbidities (diabetes, CVD, OSA, CKD, MASH etc.)
 - Favorable fat vs. lean mass loss
- Improving **tolerability**: mainly GI (nausea, vomiting)
- Maximize **optionality** of one drug substance with two formulations (oral or sc injectable)

**ORAL Triple-Agonist
Once-daily Dosing**

PN-477_o

**Injectable Triple-
Agonist
Once-weekly Dosing**

PN-477_{sc}

PN-477 Oral Triple Agonist (GLP-1R, GIPR, GCGR) Peptide

Novel Chemical Entity, Oral Triple Agonist, Potent, and Stable in GI Fluids

Attribute	Criteria
Potency	✓ nM potency vs GLP-1R, GIPR, GCGR
Stability	✓ Stable in simulated gastric and intestinal fluids ✓ Stable in serum ✓ Metabolic stability ✓ Thermostability
Efficacy Model	✓ Mouse Diet Induced Obesity (DIO) model
<i>in vivo</i> Pharmacodynamics	✓ Glucose control with glucose tolerance test
<i>in vivo</i> Pharmacokinetics	✓ Oral bioavailability demonstrated in mouse, rat, dog, cynomolgus monkey ✓ GI stability and Oral PK supports once-a-day oral dosing ✓ PK profile supports once-a-week subcutaneous dosing

GI: Gastrointestinal; PK: Pharmacokinetic

PN-477 is More Potent than Retatrutide

	Human EC ₅₀ (nM)		
	GLP-1R	GIPR	GCGR
Tirzepatide ^{1,‡} (Eli Lilly Dual GLP-1R/GIPR)	23.1	1.7	NA [†]
Retatrutide ^{2,‡} (Eli Lilly Triple GLP-1R/GIPR/GCGR)	14.6	1.6	19.2
PN-477	6.4	0.4	14.8

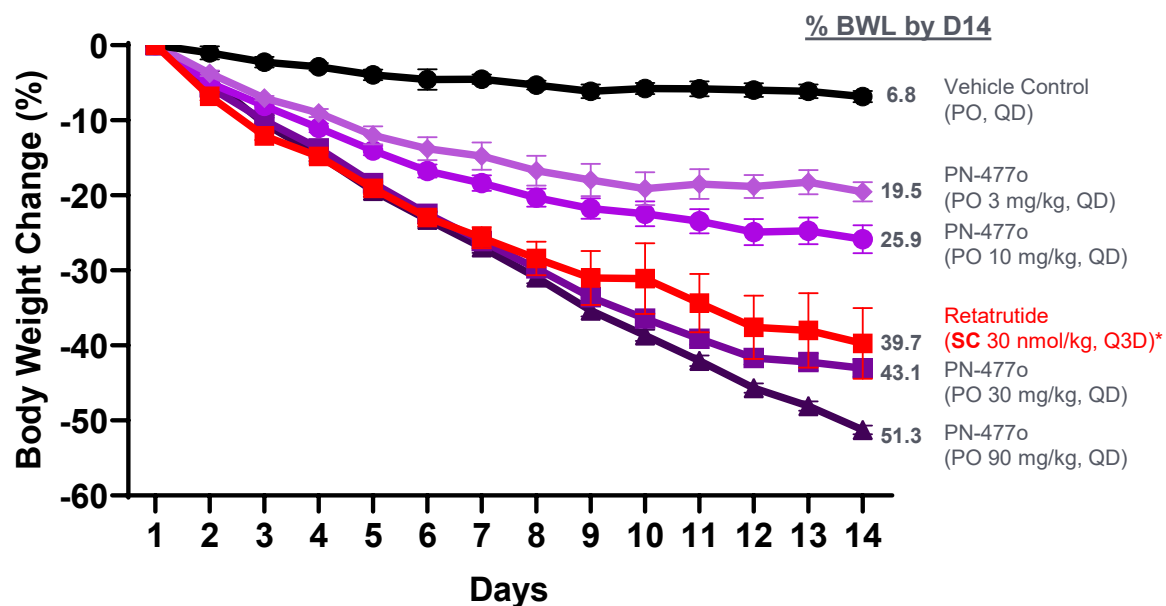
- cAMP assay: PN-477 is more potent than retatrutide for GLP-1R and GIPR
 - GLP-1R : GIPR potency ratio for PN-477 is similar to tirzepatide

PN-477 is a novel, orally stable, and potent Triple-G agonist peptide, with a potency profile that combines the best of retatrutide for weight loss (GCGR activity), and of tirzepatide for tolerability (GLP-1R:GIPR potency ratio)

Oral and Subcutaneous PN-477 Promote Significant Body Weight Loss

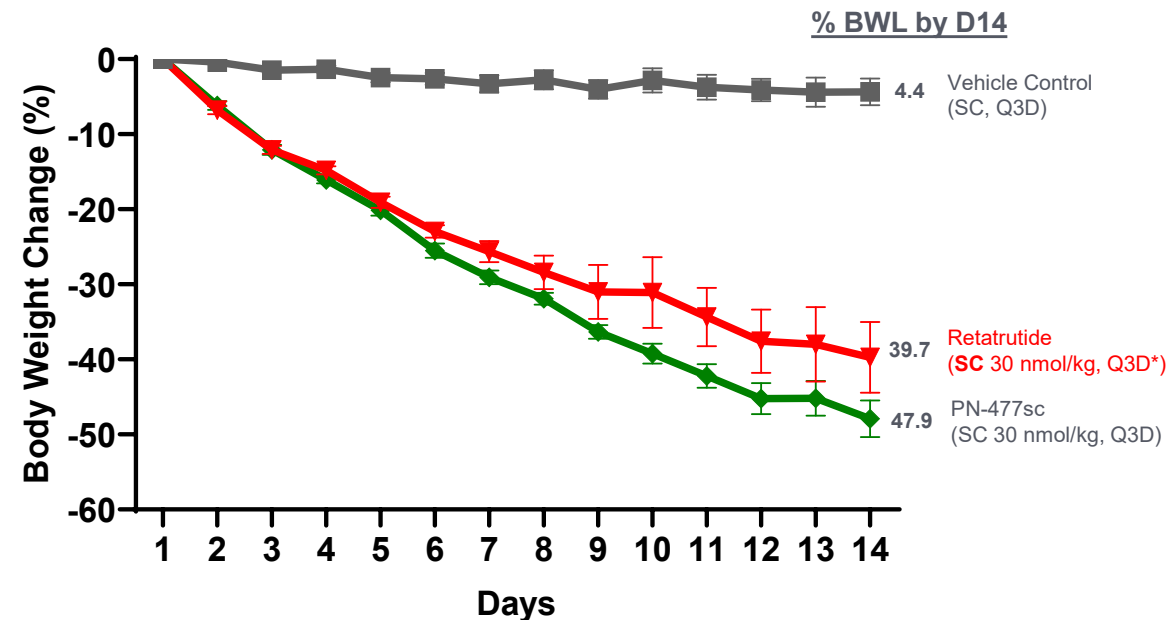
Pre-Clinical Efficacy Study Using DIO Mice

% Body Weight Change, PO: Days 1-14



- Dose-Dependent Body Weight Loss of Up to 50% with Oral PN-477o

% Body Weight Change, SC: Days 1-14

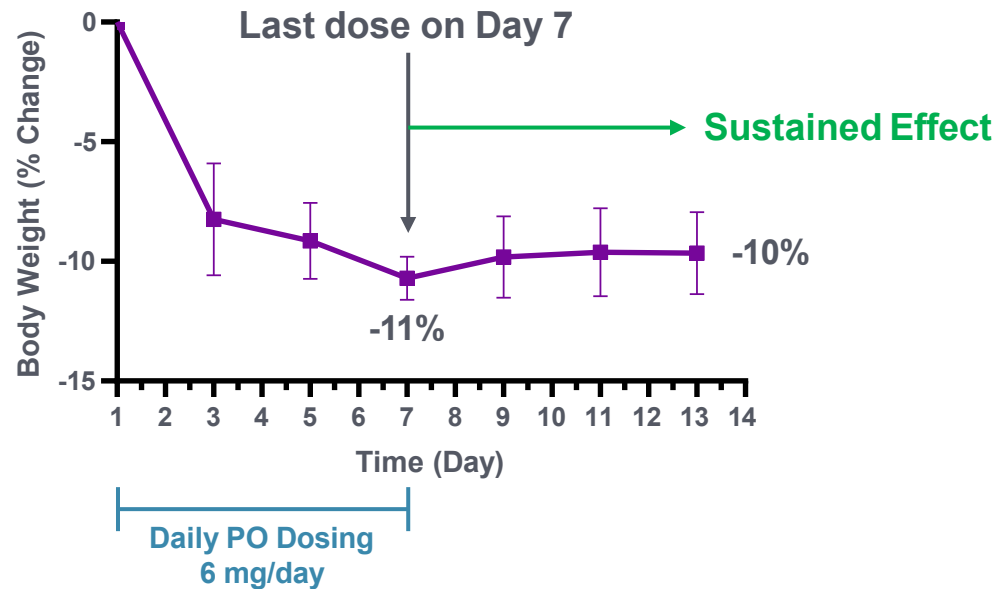


- Subcutaneous PN-477sc Achieves Body Weight Loss Comparable to Retatrutide

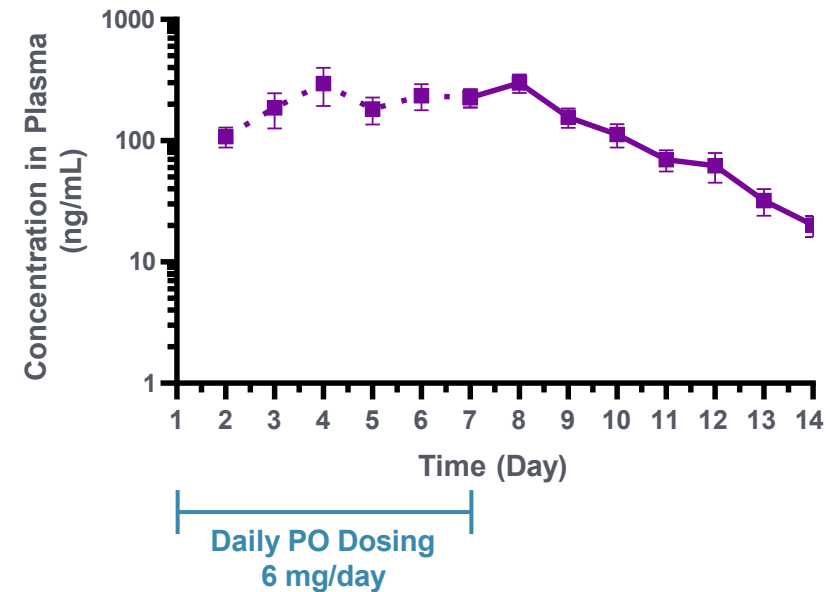
11% BW Loss by Day 7 in Normal Cynomolgus Monkeys after 7-Day Oral Dosing of PN-477

Weight Loss Sustained for 6 Days After Last Dose

% BW Change, PO



PK C_{trough} Day 1-7, PO

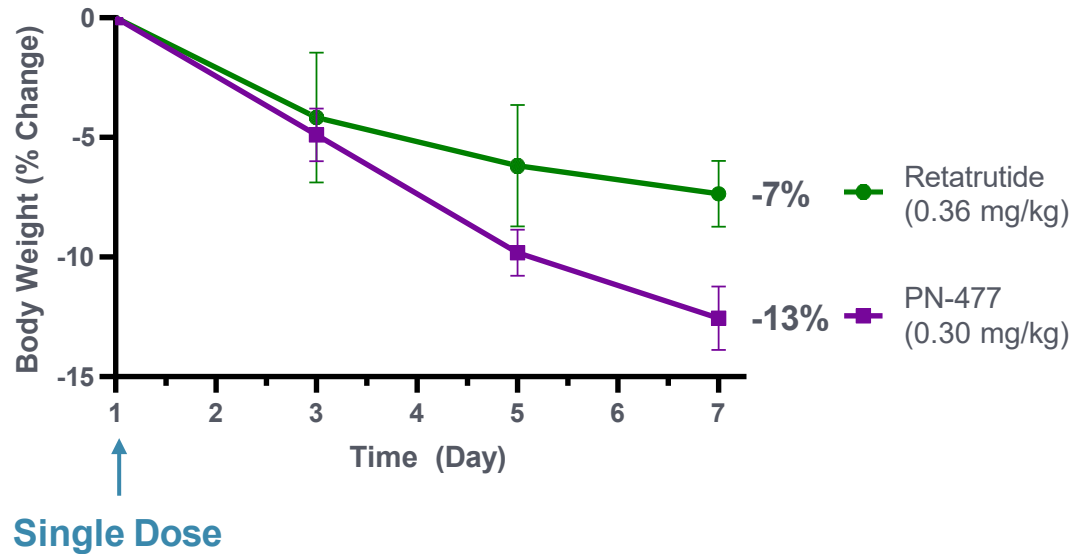


Oral PN-477 PK profile suggests **once daily human dosing and sustained weight loss**

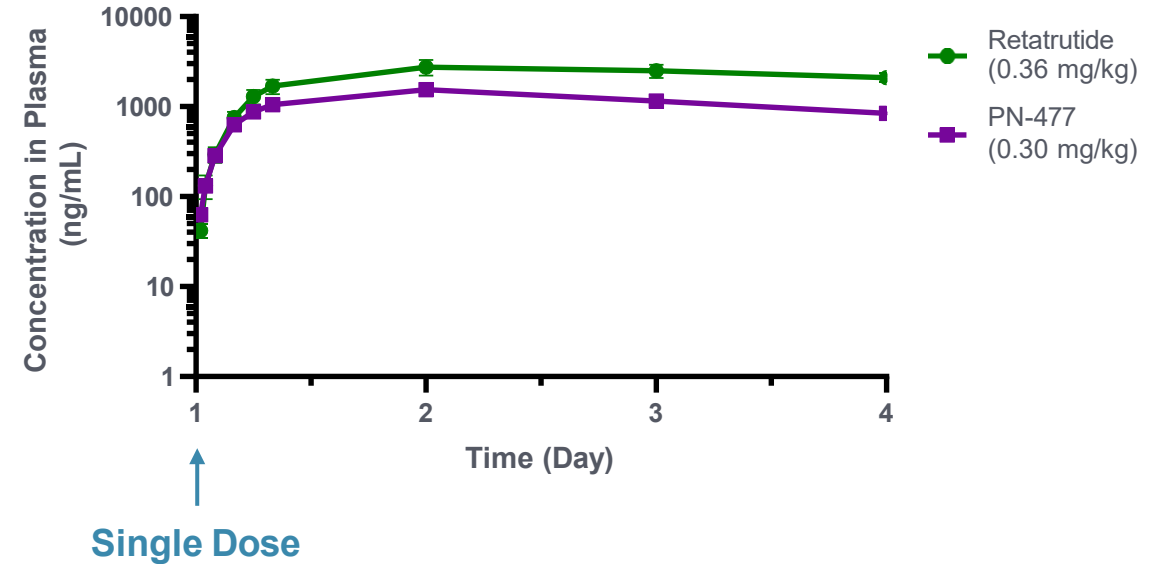
13% BW Loss Normal Cynomolgus Monkeys by 7-Days Post-Single SC Dose of PN-477



% BW Change, SC



PK, SC

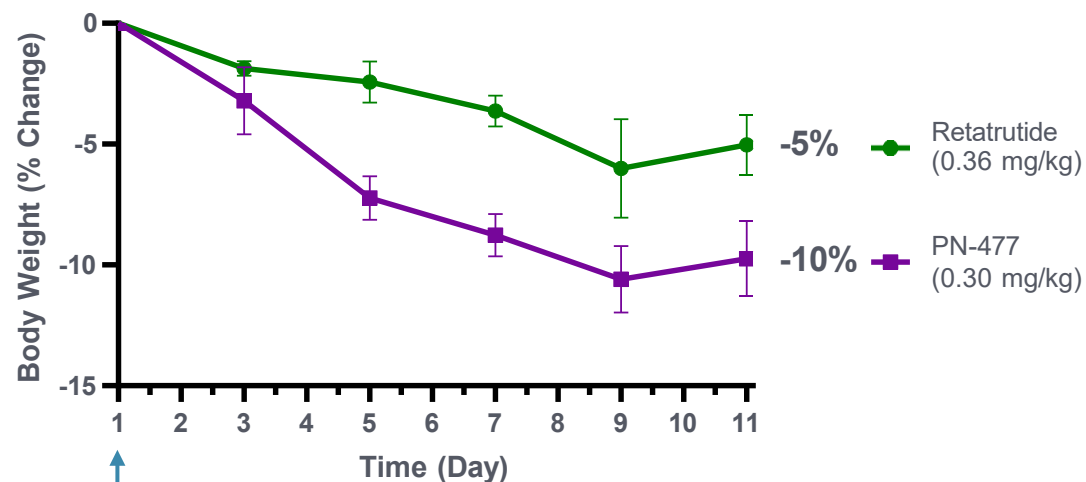


PK profile of subcutaneous PN-477 in cynomolgus monkeys suggests **once weekly human dosing**

10% BW Loss by Day 11 in Normal Beagle Dogs after Single SC Dose of PN-477

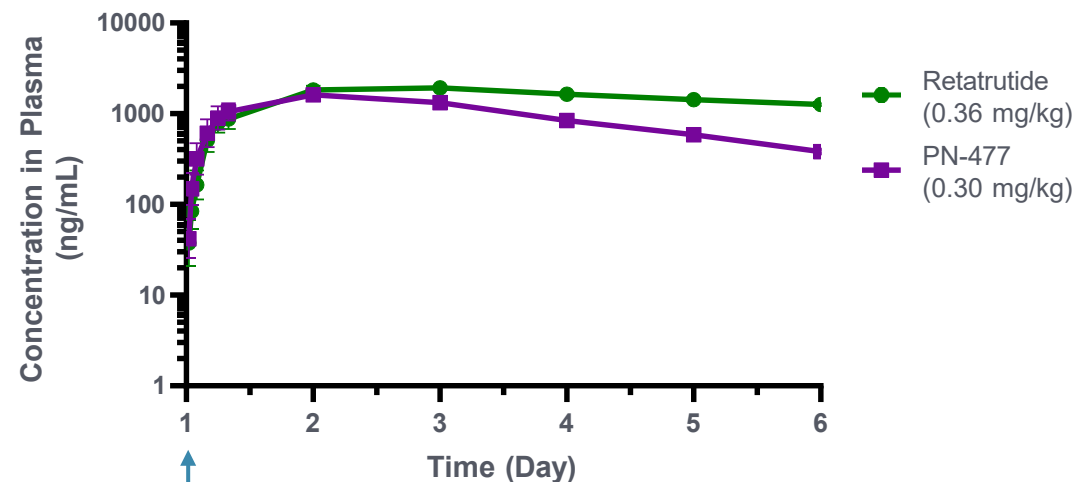


% BW Change, SC



Single Dose

PK, SC



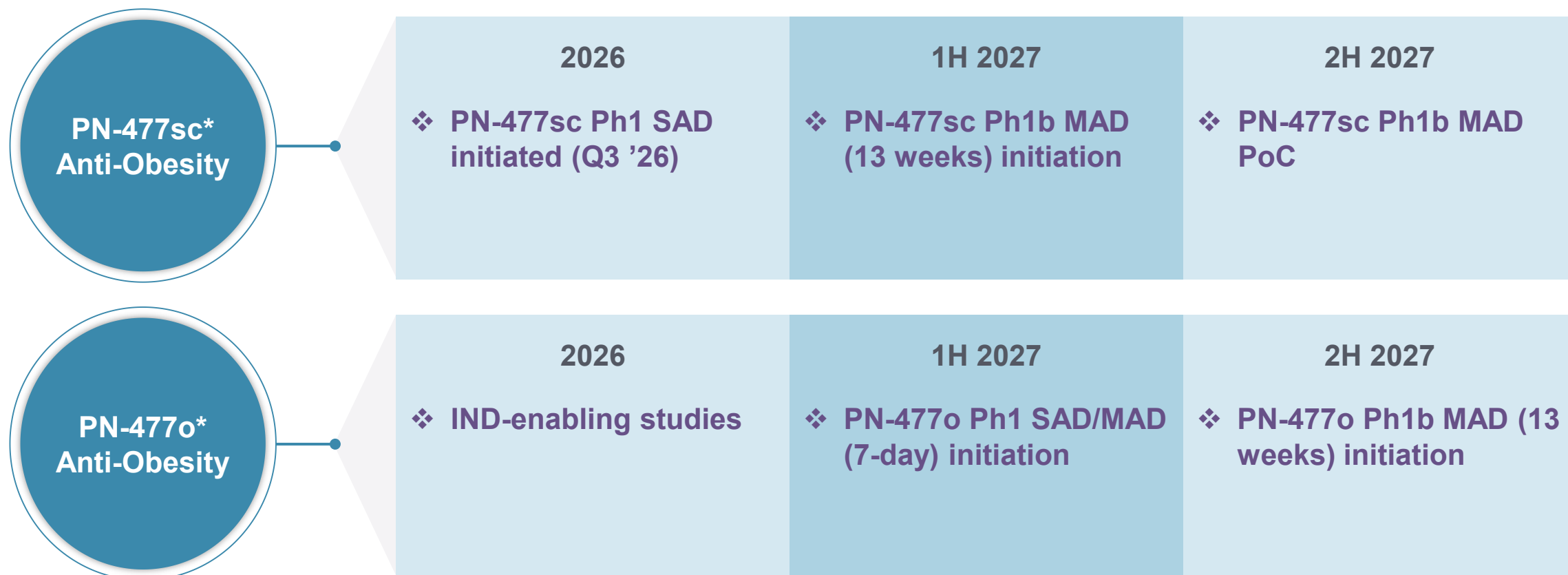
Single Dose

Data from a single subcutaneous dose of PN-477 in normal weight dogs supports once-weekly dosing in humans

PN-477: A Potential Best-in-Class Triple Agonist Anti-Obesity Peptide With Convenience of Once-Daily Oral and Once-Weekly SC Dosing

- Novel, orally stable, and potent triple agonist (GLP-1R, GIPR, and GCGR)
- Engineered balance of GLP-1R, GIPR, GCGR absolute and relative potencies
 - Designed to provide maximal weight loss and optimal body composition of retatrutide and GI tolerability of tirzepatide
- Weight loss in DIO mice benchmarks favorably versus retatrutide
 - Dose-proportional body weight loss of up to 50% in DIO mouse model achieved with oral administration of PN-477o
 - PN-477sc provides similar body weight loss as retatrutide with equivalent SC dose
 - Preferential fat mass to lean mass loss observed; similar to retatrutide
- Weight loss after single dose of PN-477sc benchmarks favorably versus retatrutide in normal dogs and monkeys
- PK profiles after Oral and SC dosing in normal dogs and monkeys support:
 - **PN-477o**: Once-daily ORAL Triple-Agonist Peptide
 - **PN-477sc**: Once-weekly injectable Triple-Agonist Peptide
- Phase 1 study initiated with PN-477sc

PN-477: Near-Term Clinical Development Plan



*PN-477sc: weekly sc dosing; PN-477o: once-daily oral dosing

PN-458: A Highly Potent Oral Dual GLP-1/GIP Receptor Agonist

Potential Weight Loss Profile and GI Tolerability of Tirzepatide

	Human EC ₅₀ (nM)		
	GLP-1R	GIPR	GCGR
Tirzepatide^{1,‡} (Eli Lilly Dual GLP-1R/GIPR)	23.1	1.7	NA [†]
PN-458	7.8	0.86	NA[†]

[‡]Sourced from 1PlusChem Cat. 1P01MVTY (Tirzepatide); MCE Cat. HY-P3506 (Retatrutide)

[†] NA: Not Active

- PN-458 has higher potency than tirzepatide for GLP-1R and GIPR

PN-458 Dual Agonist (GLP-1R, GIPR) Peptide

Novel Chemical Entity, Oral Dual Agonist, Potent, and Stable in GI Fluids

Attribute	Criteria
Potency	✓ nM potency vs GLP-1R, GIPR
Stability	✓ Stable in simulated gastric and intestinal fluids ✓ Stable in serum ✓ Metabolic stability ✓ Thermostability
Efficacy Model	✓ Mouse Diet Induced Obesity (DIO) model
In vivo Pharmacodynamics	✓ Glucose control with glucose tolerance test
In vivo Pharmacokinetics	✓ Oral bioavailability demonstrated in mouse, rat, dog, cynomolgus monkey ✓ GI stability supports once-a-day oral dosing ✓ Plasma PK profile supports once-a-week subcutaneous dosing

GI: Gastrointestinal; PK: Pharmacokinetic

Two Anti-Obesity Assets Create Strategic Flexibility

Preclinical Data Support Best-in-Class Potential For Both Programs

PN-477

TRIPLE AGONIST

GLP-1R / GIPR / GCGR agonist peptide

DESIGN GOAL	Maximize weight loss magnitude and quality (preferential fat mass loss)
BENCHMARK	Retatrutide-class profile
FORMATS	Once-daily oral, once-weekly SC
PRECLINICAL	Significant body weight loss in DIO mice, dogs, and cynomolgus monkeys

PN-458

DUAL AGONIST

GLP-1R / GIPR agonist peptide

DESIGN GOAL	Balance weight loss with GI tolerability
BENCHMARK	Tirzepatide-class profile
FORMATS	Once-daily oral
PRECLINICAL	Significant body weight loss in DIO mice, dogs, and cynomolgus monkeys

What's Next?

Protagonist Therapeutics

Expected Clinical Trial Initiations, Data Readouts, and Development Candidate Nominations



	1H 2026	2H 2026	2027
ICOTYDE™ Partner: J&J	ICOTYDE™ approved for moderate to severe plaque psoriasis	❖ Commercial ❖ EMA CHMP Positive Opinion: July 2026	❖ Commercial
MIMRYLO™ Partner: Takeda	❖ NDA accepted; priority review granted ❖ Opted-out	MIMRYLO™ approved for erythrocytosis in PV	❖ Commercial
PN-881*	Oral IL-17 antagonist ❖ Ph1 ongoing	❖ Ph1 completion	❖ Comprehensive Ph2b PsO Initiation (early Q1 '27) ❖ Ph1 data ❖ Evaluation of potential additional Ph2 study (e.g., PsA, HS)
PN-477sc* PN-477o*	Anti-obesity DCs ❖ IND-enabling studies	❖ PN-477sc Ph1 SAD initiation	❖ PN-477sc Ph1b MAD Initiation and PoC ❖ PN-477o Ph1 SAD (1H '27) ❖ PN-477o Ph1b MAD initiation (2H '27)
PN-8047*	Oral Hepcidin DC ❖ IND-enabling studies	❖ IND-enabling studies	❖ Ph1 SAD/MAD initiation ❖ Ph1 PD PoC (Mid '27) ❖ Ph2 PV initiation (2H '27)
PN-458o*			Dual GLP/GIP DCs ❖ Ph1 SAD initiation (Mid '27) ❖ Ph1 MAD initiation (2H '27)
Discovery*	❖ Oral IL-4Rα antagonist ❖ Amylin oral mono/poly-agonists		

Thank you