Protagonist Therapeutics

PN-477: A Novel GLP-1R/GIPR/GCGR Triple Agonist Peptide Development Candidate

GLP-1R: Glucagon-Like Peptide-1 Receptor
GIPR: Gastric Inhibitory Polypeptide Receptor
GCGR: Glucagon Receptor

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Robust R&D Peptide Therapeutics Pipeline

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- **PN-477o: Once-daily ORAL GLP/GIP/GCG receptor triple agonist peptide as an anti-obesity development candidate***
- **PN-477sc: Once-weekly SC dosing**

Discovery → DC* ***IND-Enabling → Ph 1*** ***Ph 3 → NDA filings***

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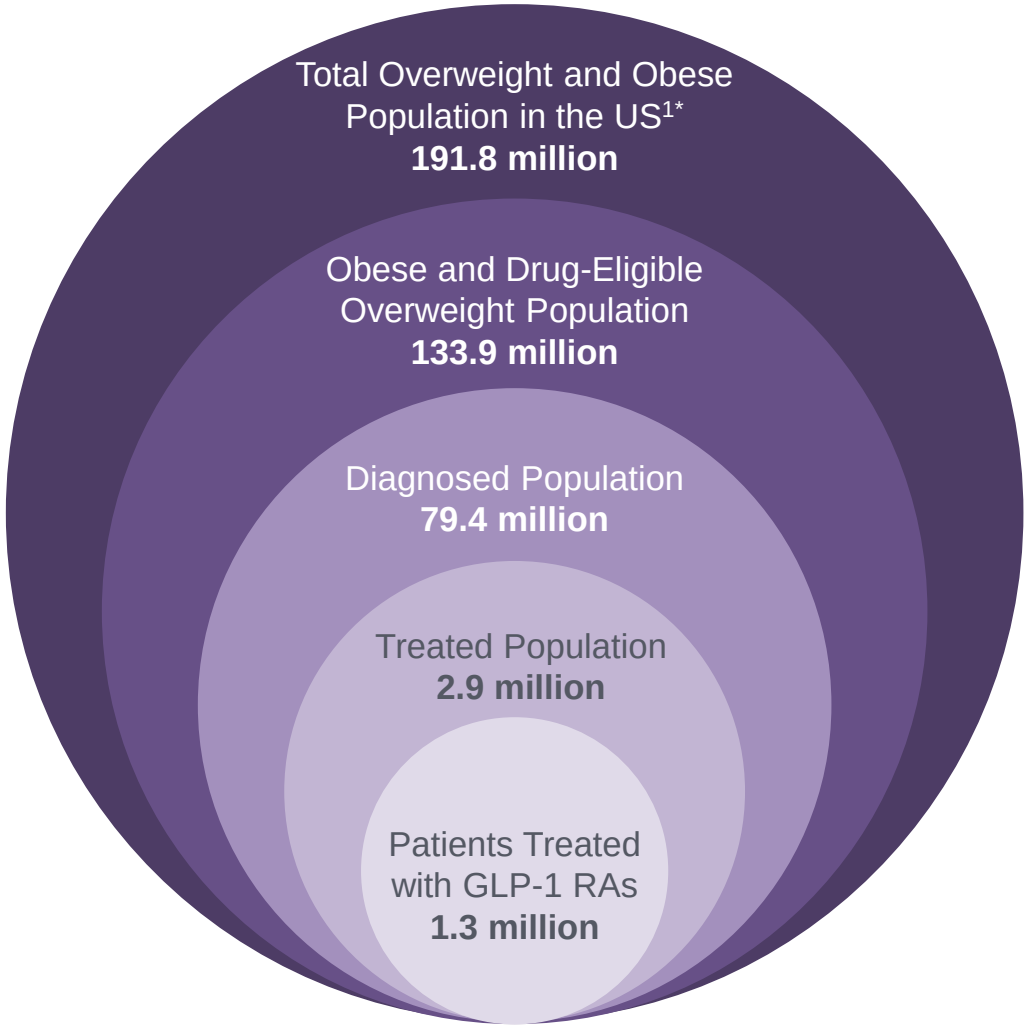
* Development candidate (DC); Ready for IND-Enabling Studies; ** Also in development for psoriatic arthritis, ulcerative colitis and Crohn's disease; sc: subcutaneous

Obesity: Unprecedented Pharmaceutical Opportunity in the US and Worldwide

Only ~2% of Eligible Patients Receive Drug Treatment



- Obesity is a global epidemic
  - In 2024, nearly **40% of Americans were obese or considered drug-eligible overweight**[1]
- Approved drugs: Injectable peptides
- Current challenges with anti-obesity drugs[1]
  - Early days & limited options
  - Adverse effects
  - Convenience; needle avoidance
- **'Oral' and 'more effective' agent an attractive option for a chronic condition**

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***Total Population:** overweight (25≤BMI<30) and obese (BMI≥30) **Drug-eligible Population:** obese (BMI≥30) and drug-eligible overweight (27≤BMI<30 with at least one weight-related comorbidity) **Treated Population:** receiving noradrenergic anoretics (54%), GLP-1 RAs (43%), noradrenergic FDCs (3%), lipase inhibitors (<1%).

[1] Clarivate Disease Landscape & Forecast – Obesity/Overweight (Nov 2024).

Desirable Features for Next Generation Anti-Obesity Candidate

- Currently approved therapies are injectables
  - Semaglutide (Wegovy®): Mono GLP-1R agonist – 13.7% body weight loss[1]
  - Tirzepatide (Zepbound®): Dual GLP-1R and GIPR agonist – 20.2% body weight loss[1]
- Retatrutide: An injectable triple agonist in Ph 3 development

Proprietary Peptide Technology

An ORAL Triple-Agonist Peptide (GLP-1R/GIPR/GCGR)

- Potential improvements
  - **Oral option**
  - Magnitude of body weight loss
    - Potential secondary benefits in co-morbidities (diabetes, CVD, OSA, CKD, MASH etc.)
  - Improving tolerability: mainly GI (nausea, vomiting)
  - Favorable fat vs. lean mass loss

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[1] Aronne LJ, NEJM 2025 (Ph3b open label head-to-head trial in non-diabetic obese patients)

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

Optionality for Oral or Subcutaneous Dosing

PN-477o

ORAL Triple-Agonist
Once-daily Dosing

PN-477sc

Injectable Triple-Agonist
Once-weekly Dosing

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PN-477 Triple Agonist (GLP-1R, GIPR, GCGR) Peptide as Development Candidate

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** ✓
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** ✓

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GI: Gastrointestinal; PK: Pharmacokinetic

PN-477: A Highly Potent Triple GLP-1/GIP/GCG Receptor Agonist Designed to Provide Weight Loss Profile of Retatrutide and GI Tolerability of Tirzepatide

	Human EC_{90} (nM)			Mouse EC_{90} (nM)		
	GLP-1R	GIPR	GCGR	GLP-1R	GIPR	GCGR
Semaglutide[1,‡] (Novo **Mono** GLP-1R)	74	NA†	NA†	6.1	NA†	NA†
Tirzepatide[2,‡] (Eli Lilly **Dual** GLP-1R/GIPR)	269	17x → 16	NA†	21	867	NA†
Retatrutide[3,‡] (Eli Lilly **Triple** GLP-1R/GIPR/GCGR)	103	6x → 17	83	8.3	493	102
PN-477	**49**	**17x → 2.7**	**56**	**17**	**133**	**1092**

‡Sourced from *MCE Cat. HY-114118 (Semaglutide); 1PlusChem Cat. 1P01MVTY (Tirzepatide); MCE Cat. HY-P3506 (Retatrutide)*

† ***NA: Not Active***

- Human EC_{50} potencies:

Human EC_{50} (nM)	GLP-1R	GIPR	GCGR
PN-477	4.6	0.39	15
Retatrutide	12.2	1.5	21

- Higher GIPR potency may be favorable for better GI tolerability[4,5]

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[1] Lau J, J Med Chem 2015; [2] Coskun T, Mol Metab 2018; [3] Coskun T, Cell Metab 2022; [4] Campbell JE, Cell Metabolism 2023; [5] El K, Sci Adv 2021

PN-477 is Orally Stable in Gastrointestinal Fluids

In Vitro Metabolic Stability

Compound	Simulated Gastric Fluid $T_{1/2}$ (hr)	Simulated Intestinal Fluid $T_{1/2}$ (hr)
PN-477	**> 24**	**15.9**
Retatrutide	**< 0.5**	**< 0.5**
Tirzepatide	**< 0.5**	**< 0.5**
Semaglutide	**< 0.5**	**< 0.5**

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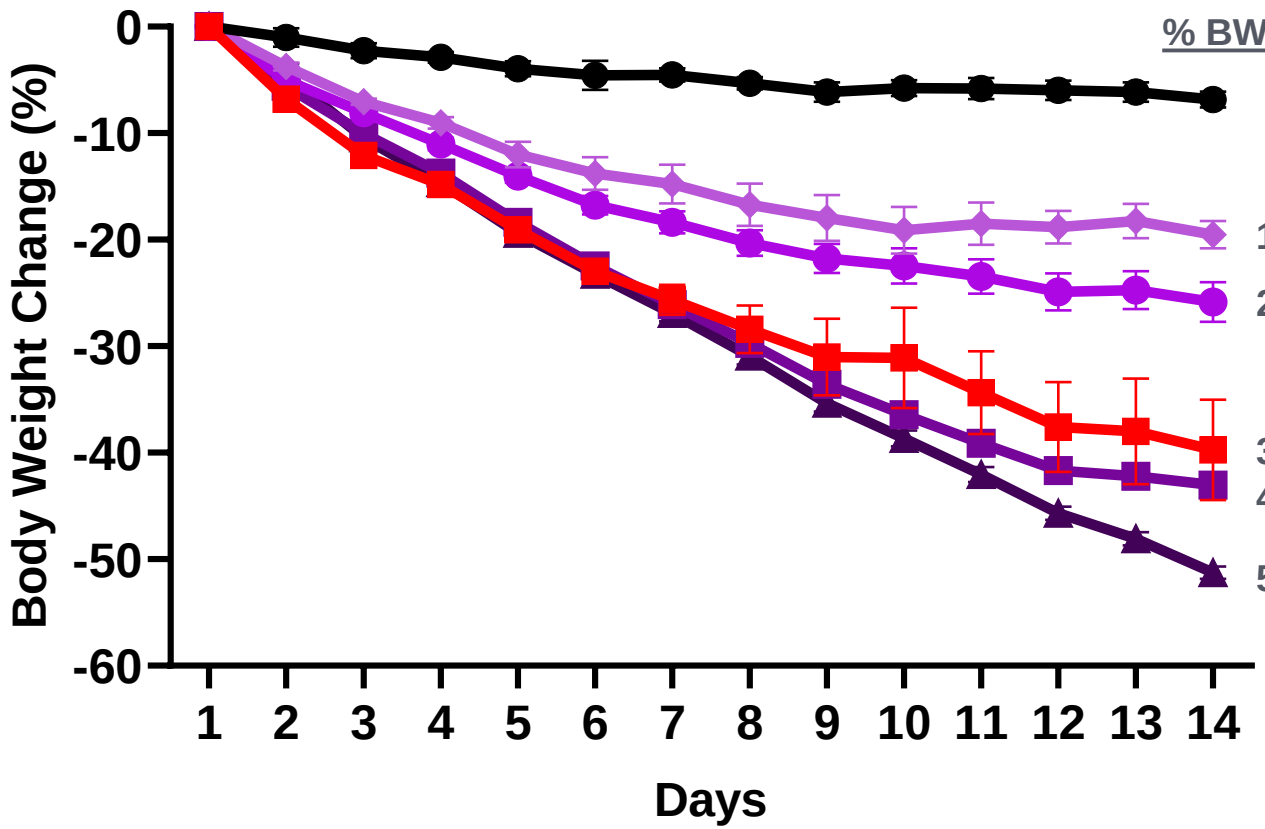
Dose Proportional Body Weight Loss of Up to 50% with Oral PN-477o

DIO Mice Study #1

% Body Weight Change, PO: Days 1-14



% BWL by D14	
6.8	Vehicle Control (PO, QD)
19.5	PN-477o (PO 3 mg/kg, QD)
25.9	PN-477o (PO 10 mg/kg, QD)
39.7	Retatrutide (**SC** 30 nmol/kg, Q3D)*
43.1	PN-477o (PO 30 mg/kg, QD)
51.3	PN-477o (PO 90 mg/kg, QD)

* Retatrutide SC 30 nmol/kg dose is the highest dose reported for DIO mouse efficacy study;Cell Metabolism 34, 1234–1247, September 6, 2022

BWL: Body Weight Loss; DIO: Diet Induced Obese; Data points depict mean ± SEM. PO = oral, SC = subcutaneous, QD = once a day, Q3D = every 3 days

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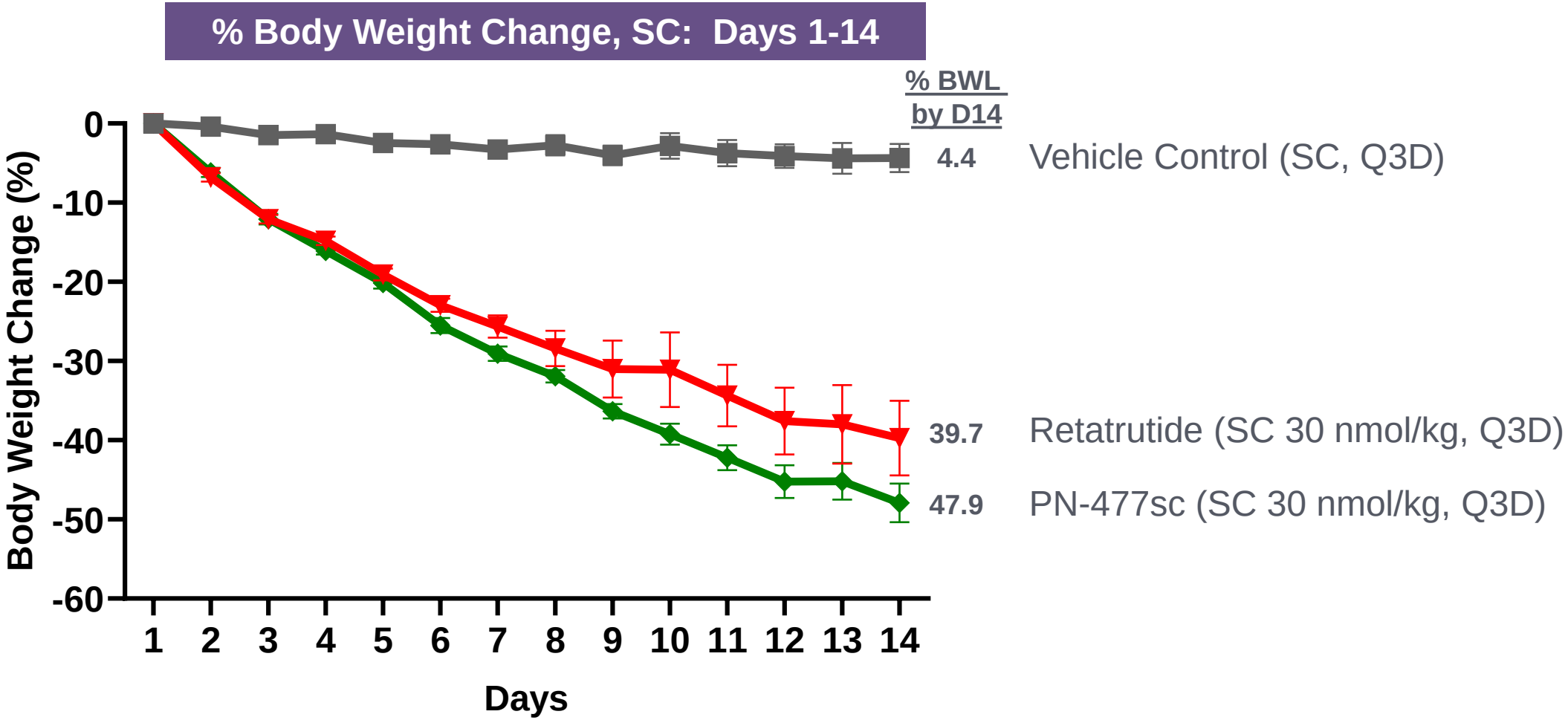
Subcutaneous PN-477sc Achieves Body Weight Loss Comparable to Retatrutide

DIO Mice Study #1



BWL: Body Weight Loss; DIO: Diet Induced Obese; Data points depict mean ± SEM. SC = subcutaneous, QD = once a day, Q3D = every 3 days

Body Weight Loss and Body Composition Improvements Comparable to Retatrutide

DIO Mouse Study #2; Subcutaneous PN-477sc vs Retatrutide

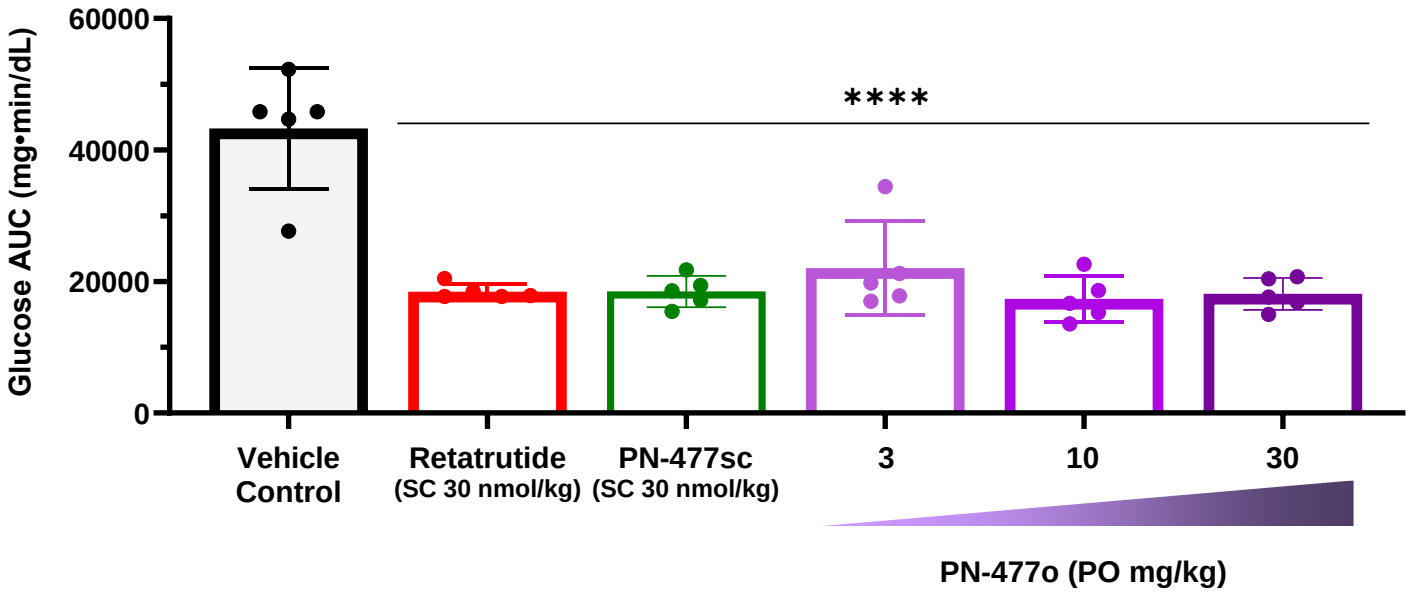
Body Composition	Retatrutide SC 30 nmol/kg Q3D	PN-477sc SC 30 nmol/kg Q3D
% Body Weight Loss (D22)	-31.5	-30.3
% Fat Mass Loss (D22)	-67.0	-70.0
% Lean Mass Loss (D22)	-16.8	-13.2
Lean Mass/Fat Mass Ratio		
- Baseline	1.3	1.4
- Day 22	3.3	3.9

DIO: Diet Induced Obese; SC: subcutaneous, Q3D: every 3 days

PN-477 (Oral and SC) Improves Glycemic Control after Glucose Challenge

DIO Mice Study #3

OGTT in DIO Mice
Single Dose, PO and SC, 2-hr PD



- Glycemic control is significantly improved in DIO mice after PN-477 PO or SC when compared to the vehicle control
- Profiles consistent with retatrutide

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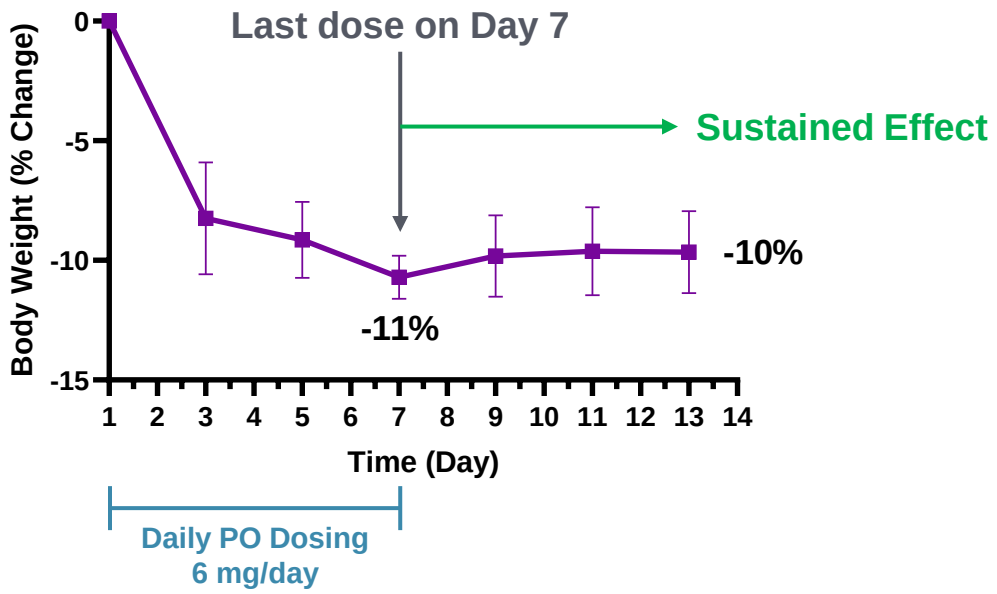
****p<0.0001; One way ANOVA; n=7. Bars depict mean ± SEM. Retatrutide was synthesized by Protagonist.
OGTT: oral glucose tolerance test; DIO: diet induced obese; PO: oral; SC: subcutaneous; PD: Pharmacodynamics; AUC: area under curve

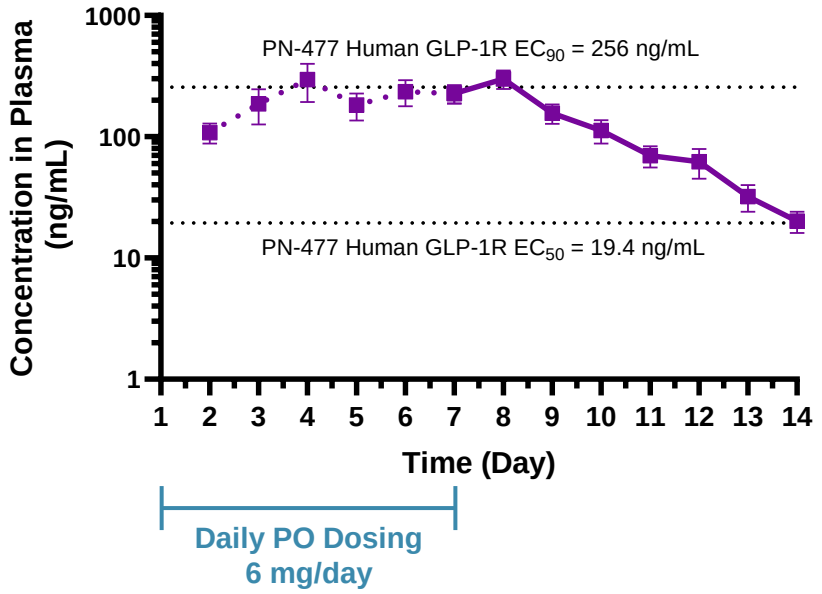
11% BW Loss by Day 7 in Cynomolgus Monkeys after 7-Day Oral Dosing of PN-477o

Weight Loss Sustained for 6 Days After Last Dose

Cyno % BW Change, PO



Cyno PK C_{trough} Day 1-7, PO



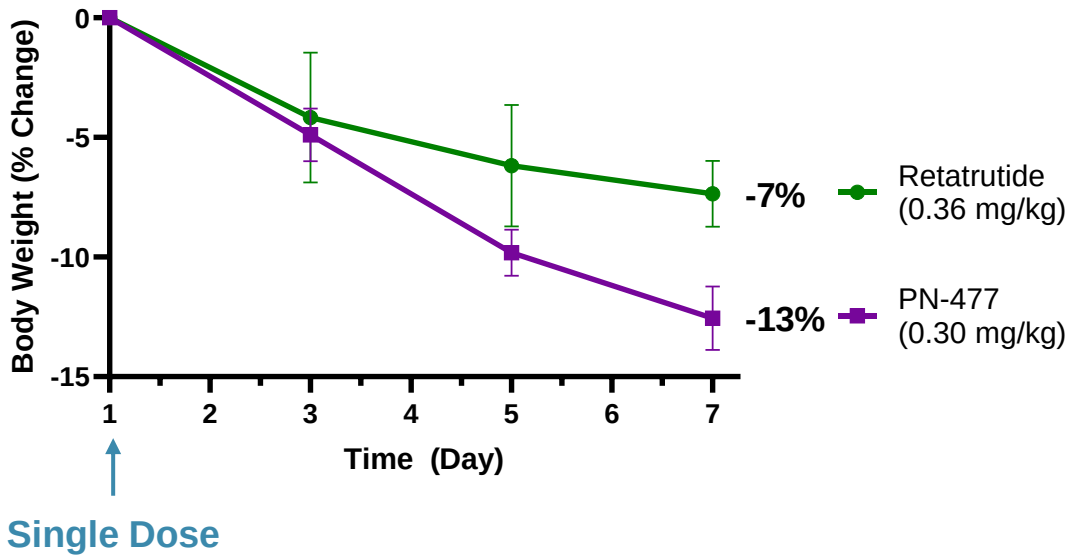
- PN-477o PK profile suggests once daily human dosing
- Body weight loss was sustained for 6 days post-last dose

BW: Body Weight; PO: oral; PK: Pharmacokinetics

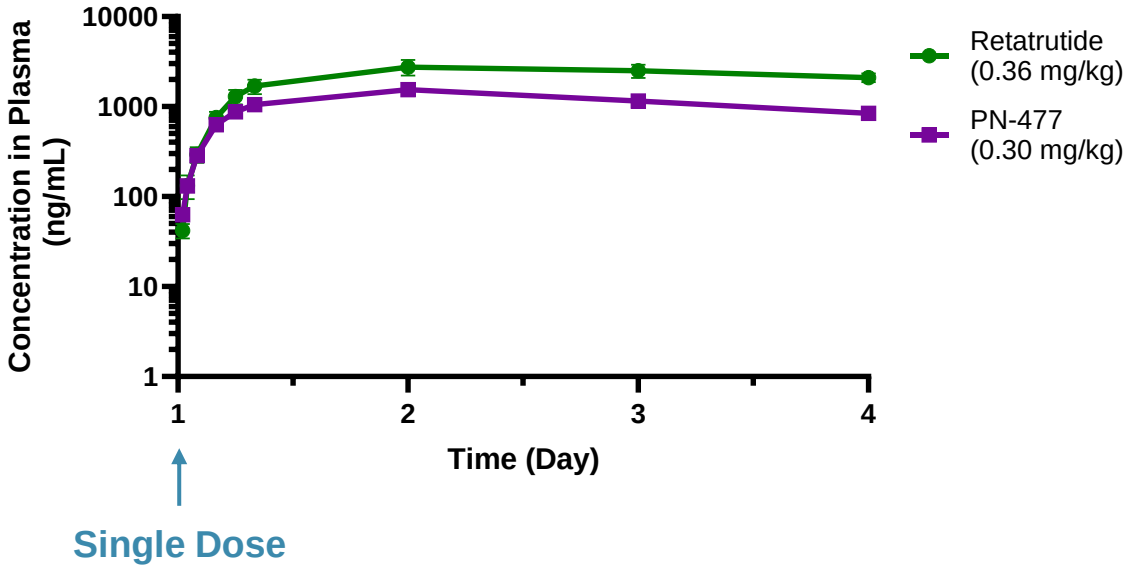
13% BW Loss by Day 7 in Normal Monkeys after Single SC Dose of PN-477

PN-477 Vs. Retatrutide

Cyno % BW Change, SC



Cyno PK, SC



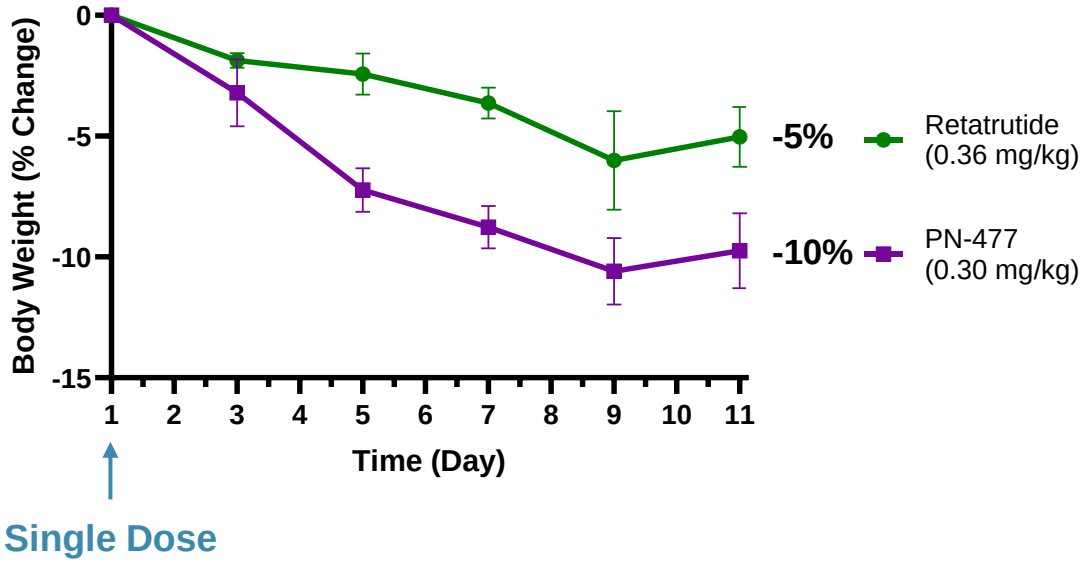
PN-477sc PK profile suggests once weekly human dosing

BW: Body Weight; PK: Pharmacokinetics; SC: subcutaneous

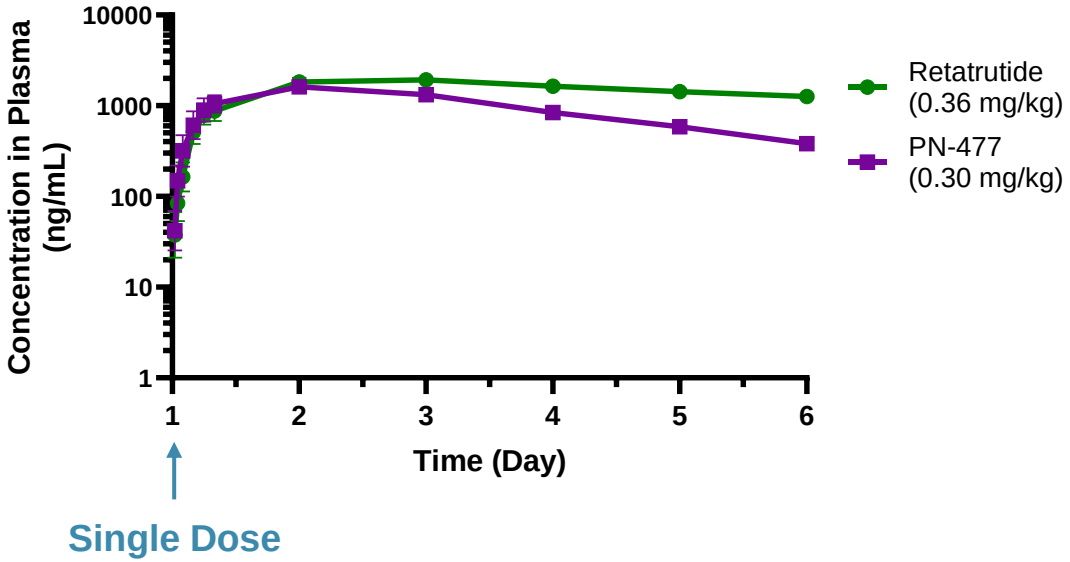
10% BW Loss by Day 11 in Normal Beagle Dogs after Single SC Dose of PN-477

PN-477 Vs. Retatrutide

Dog % BW Change, SC



Dog PK, SC



PN-477sc PK profile suggests once weekly human dosing

BW: Body Weight; PK: Pharmacokinetics; SC: subcutaneous

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

- Novel, orally stable, and potent triple agonist (GLP-1R, GIPR, 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
  - 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
- IND-enabling studies underway

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Major Upcoming Catalysts in 2H 2025 and 2026

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

	1H 2025	2H 2025	1H 2026	2H 2026
Rusfertide (Takeda)	❖ PV day[1] ✓ ❖ **VERIFY topline results[2]** ✓ ❖ **ASCO VERIFY plenary presentation[3]** ✓	❖ **NDA filing[4]** ❖ ASH Meeting[4]	❖ Medical Conferences	❖ **US Approval (PV)**
Icotrokinra (Johnson&Johnson Innovative Medicine)	❖ Medical Conferences ✓ ❖ **Ph2b UC ANTHEM[2]** ✓ ❖ Study initiation: • Ph3 ICONIC-PsA 1[2] ✓ • Ph3 ICONIC-PsA 2[2] ✓ • Ph3 ICONIC-ASCEND (H2H vs. Stelara) ✓ ❖ Ph3 PsO ADVANCE 1 ✓ ❖ Ph3 PsO ADVANCE 2 ✓	❖ **Psoriasis NDA filing[4]** ❖ Medical Conferences	❖ Medical Conferences	❖ **US Approval (Psoriasis)** ❖ Ph3 ICONIC-PsA 1 Primary Completion
Discovery	**1. PN-477o** ✓ **2. PN-477sc** ✓ Anti-obesity DCs[5]	❖ **Oral Hepcidin** DC[4] ❖ **PN-881 Ph1 initiation[4]**	❖ **PN-477 Ph1 initiation[6]**	

1. February 6, 2025 2. March 2025 3. June 1, 2025 4. Q4 2025 5. June 30, 2025 6. Q2 2026

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Thank You