Abstract

Ultralong-Acting Amylin Agonist Elicits Sustained 12-Week Weight Loss in DIO Rats After Single Dose

John A. Hangasky PhD, Rocío DV. Fernández PhD, Gary W. Ashley PhD, Christian Weyer MD, MAS, Daniel V. Santi MD, PhD

Background: Amylin agonists are a promising class of anti-obesity peptides that have therapeutic potential both in monotherapy and combination therapy settings (as an alternative or add-on to incretin therapy). To date, most amylin agonist candidates rely on lipidation to extend half-life, enabling once-weekly dosing via reduced clearance. We have developed a half-life extension platform in which an anti-obesity peptide is covalently tethered via a base-catalyzed β-elimination linker to a mesoporous tetra-PEG microsphere (MS) hydrogel creating a biodegradable subcutaneous depot. A key distinguishing feature of this approach is that the half-life is no longer governed by clearance, but by the release of the peptide from the SC depot, enabling ultralong pharmacokinetics with more predictable nonclinical-to-clinical translation. Here we report a potent amylin agonist, PPX8142, that when conjugated to MSs and administered as a single subcutaneous (SC) dose shows an extended half-life and sustained efficacy, both alone and in combination with semaglutide.

Methods: The potency of PPX8142 was assessed in cell lines cultured in 0.1% casein and expressing either human amylin (hAMY3) or human calcitonin (hCT) receptors. A MS conjugate of PPX8142 (MS~PPX8142) was prepared and the in vitro peptide release kinetics were measured under accelerated conditions. Pharmacokinetics were evaluated in lean rats following a single SC dose. Diet-induced obese (DIO) rats received a single SC dose of MS~PPX8142 at escalating dose levels, either alone or in combination with daily semaglutide delivered at submaximal dose, with longitudinal monitoring of food intake and body weight.

Results: PPX8142 demonstrated high potency at both the hCT and hAMY3 receptors and exhibited excellent chemical stability under physiological conditions. Under accelerated in vitro conditions, MS~PPX8142 showed controlled peptide release, extrapolating to a release half-life of approximately 7 weeks under physiological conditions. In lean rats, a single subcutaneous dose of MS~PPX8142 achieved sustained systemic exposure for at least 10 weeks. In DIO rats, single dose administration produced a large and significant reduction in body weight compared to vehicle control, which was sustained for 12 weeks when given alone or in combination with submaximal daily semaglutide (Figure).

Conclusion: These results constitute preclinical proof-of-concept that substantial half-life extension, well beyond that achievable with lipidation, can be achieved with our platform. MS~PPX8142 demonstrated sustained systemic exposure and dose-dependent weight loss without the use of lipidation. These data support further evaluation of MS~amylin conjugates as potent, ultralong-acting amylin agonists with potential for once-monthly or once-quarterly dosing.

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Background

Amylin agonists are a promising class of anti-obesity peptides that have therapeutic potential both in monotherapy and combination therapy settings (as an alternative or add-on to incretin therapy). To date, most amylin agonist candidates rely on lipidation to extend half-life, enabling once-weekly dosing via reduced clearance. We have developed a half-life extension platform in which an anti-obesity peptide is covalently tethered via a base-catalyzed β-elimination linker to a mesoporous tetra-PEG microsphere (MS) hydrogel creating a biodegradable subcutaneous depot. A key distinguishing feature of this approach is that the half-life is no longer governed by clearance, but by the release of the peptide from the SC depot, enabling ultralong pharmacokinetics with more predictable nonclinical-to-clinical translation. Here we report a potent amylin agonist that, when conjugated to MSs and administered as a single subcutaneous (SC) dose, shows an extended half-life and sustained efficacy, both alone and in combination with semaglutide.

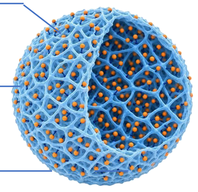
Prolynx's Technology

Prodrug Components:

Hydrogel Microspheres
Tetra-PEG polymer (95% water) that can be injected with a small gauge needle and placed subcutaneously

Active Drug Covalently Linked
Covalent linkage to hydrogel matrix enables tightly controlled release of unmodified native drug from depot

Tunable Release and Depolymerization
Finely tuned β-eliminative rate achieves desired release profile for smoother PK and predictable >100 days half-life

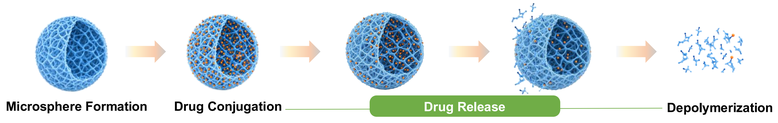


Resulting Pharmacokinetics:

Continuous pump-like release of drug
Results in a smooth PK profile with no burst, thus improving GI tolerability

Ultra-long half-life
Determined by the slow release of drug into the circulation, not reduced clearance (as with lipidation)

Potential for monthly and quarterly dosing
Half-life extension is not limited by the half-life of human albumin, breaking past current dose frequency barriers



Prolynx Approach to Drug Development

Identification of API → Modulation and tuning of linker profile → Demonstration of PK and in vivo efficacy

The Prolynx approach to creating novel, long-acting prodrugs relies on three important, universal concepts:

- Identification of novel, potent, highly stable APIs.
- Incorporation of the tunable linker system to develop a prodrug with both the desired release kinetics and depot residence time to achieve the target pharmacokinetics.
- Demonstration of extended half-life and efficacy of the designed prodrug in animal models to directly inform human clinical trials.

Results

MS~Amylin Sustains Dose-Dependent Body Weight Loss for 12 Weeks

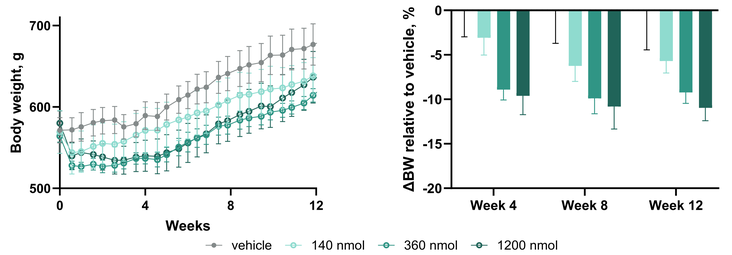


Figure 1. Body weights of DIO rats treated with MS~Amylin. In vitro receptor profiling of the MS~Amylin peptide shows potent agonism of the hAMY3 and hCT receptors. The MS~Amylin peptide is chemically stable under physiological conditions and resists fibril formation. Left: Absolute body weight and Right: Percent body weight relative to vehicle (●). DIO rats (n=5–6/group) on high fat diet, with an average starting body weight of 570 g, were administered subcutaneous single agent MS~Amylin at a fixed dose of 140 nmol (○), 360 nmol (○) or 1200 nmol (○). Body weights and food intake were measured two to three times per week. Body composition was assessed by DEXA scan at week 4. Data points represent mean ± SEM.

- MS~Amylin elicits sustained, dose-dependent body weight loss as a monotherapy in DIO rats.
- After 4 weeks, MS~Amylin reduced cumulative food intake by up to 14% compared to vehicle.

MS~Amylin has Potential as an Adjunct to Incretin Therapy

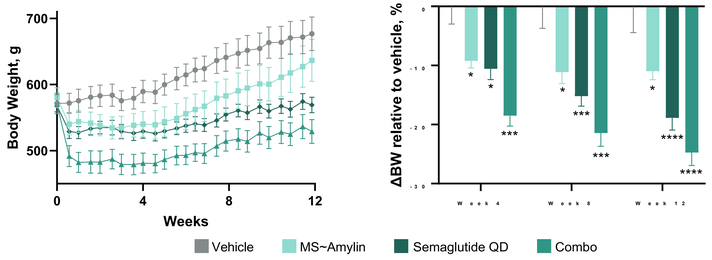


Figure 2. Body weights of DIO rats treated with MS~Amylin and semaglutide. Left: Absolute body weight and Right: Percent body weight relative to vehicle (●). DIO rats (n=5–6/group) on 60% high fat diet, with an average starting body weight of 570 g, were administered subcutaneous single agent MS~Amylin (■) at a fixed dose of 1200 nmol, daily 5 nmol/kg semaglutide (◆) or the combination (▲). Body weights and food intake were measured two to three times per week; animals dosed with semaglutide were weighed daily. Body composition was assessed by DEXA scan at week 4. Data points represent mean ± SEM. Data at weeks 4, 8 and 12 were analyzed by two-way ANOVA, followed by Dunnett's post hoc test (* $p \leq 0.05$; *** $p \leq 0.0002$; **** $p < 0.0001$).

- Co-administration of MS~Amylin and submaximal semaglutide resulted in greater weight loss (27%) compared to MS~Amylin (11%) or semaglutide (18%).
- DEXA scan of animals shows the combination of MS~Amylin and semaglutide results in a favorable shift in body composition reducing fat mass and preserving lean mass.

Results

MS~Amylin Shows a Long Terminal Half-Life

Table 1. Terminal half-life of Amylin Agonists

	$t_{1/2}$, days	
Amylin Agonist	**Rat**	**Human**
MS~Amylin	42	TBD
Cagrilintide	~1.1 [1]	6.6 – 8.1 [2]
Petrelintide	~1.4 [3]	8.9 – 10.7 [4]
Eloralintide	~2.2 [5]	12.9 – 15.3 [5]

TBD, to be determined

- MS~Amylin's half-life is controlled by release from the depot and is expected to be largely species-independent.

Conclusions

1. MS~Amylin demonstrated sustained systemic exposure and dose-dependent weight loss sustained for up to 12 weeks in DIO rats.
2. MS~Amylin enhanced semaglutide-induced weight loss, supporting its potential as a long-acting adjunct to incretin therapy.
3. The data support further evaluation of MS~Amylin conjugates as potent, ultralong-acting amylin agonists with potential for once-monthly or once-quarterly dosing.
4. The results constitute preclinical proof-of-concept that substantial half-life extension, well beyond that achievable with lipidation, can be achieved with our platform.

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Disclosures
All authors are employees of Prolynx Inc. and may hold stock/equity in the company.