

Abstract

AdoXLong technology is designed to deliver sustained peptide circulation for at least one month. This new long-acting peptide platform is based on a biocompatible polymer chemically linked to peptides of interest while maintaining their mechanism of action.

AdoXLong was applied to semaglutide to develop a once-a-month liquid formulation.

In vitro, AdoXLong Sema demonstrates a high affinity to albumin. The intrinsic *in vitro* potency of GLP1-RA from AdoXLong Sema is well preserved and even slightly increased compared to semaglutide (Relative potency: 133%).

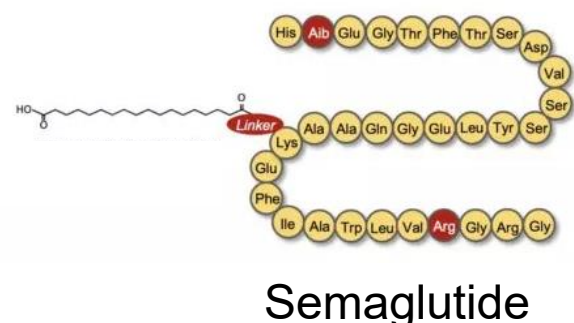
A decrease of AdoXLong Sema *in vitro* potency is observed in the presence of human serum albumin, confirming its high affinity to albumin.

Pharmacokinetic analysis of AdoXLong Sema after subcutaneous injection in rats shows an apparent half-life of 24h, i.e. 3.5 times that of semaglutide. These results were confirmed in pigs with an apparent half-life of 93h, i.e., 2 times that of semaglutide.

Introduction & Background

The prevalence of obesity in the general population worldwide is 14% in 2023 and is expected to increase to 24% in 2035. Two billion people are expected to be obese in 2035[1]. The associated impact on health-related complications and quality of life give rise to a large medical and economic burden.

Recent advances based on weekly treatment with incretin hormones, namely semaglutide and tirzepatide, are approved for obesity treatment with or without type 2 diabetes. Weight loss of up to 15 % from baseline have been obtained in clinical trials. However, a relatively high discontinuation rate has been observed with incretin treatment; 48% at 12 months and 70% at 24 months [2].



AdoXLong platform

AdoXLong is a long-acting peptide platform composed of a biocompatible polymer chemically linked to peptides of interest without modifying their mechanism of action. Pharmaceutical products derived from this technology are low viscosity aqueous solutions compatible with standard injection devices and administered subcutaneously using 29 Gauge or smaller needles.

The AdoXLong platform has been developed to address a critical challenge in diabetes and obesity treatments based on GLP-1 agonists, amylin, or other metabolic peptides: long-acting formulations. Moving from weekly to monthly administration would significantly improve long-term treatment persistence, while improving manufacturing capacity, thereby increasing the number of patients who can be treated.

AdoXLong was applied to semaglutide to develop a once-a-month liquid formulation.

In vitro studies

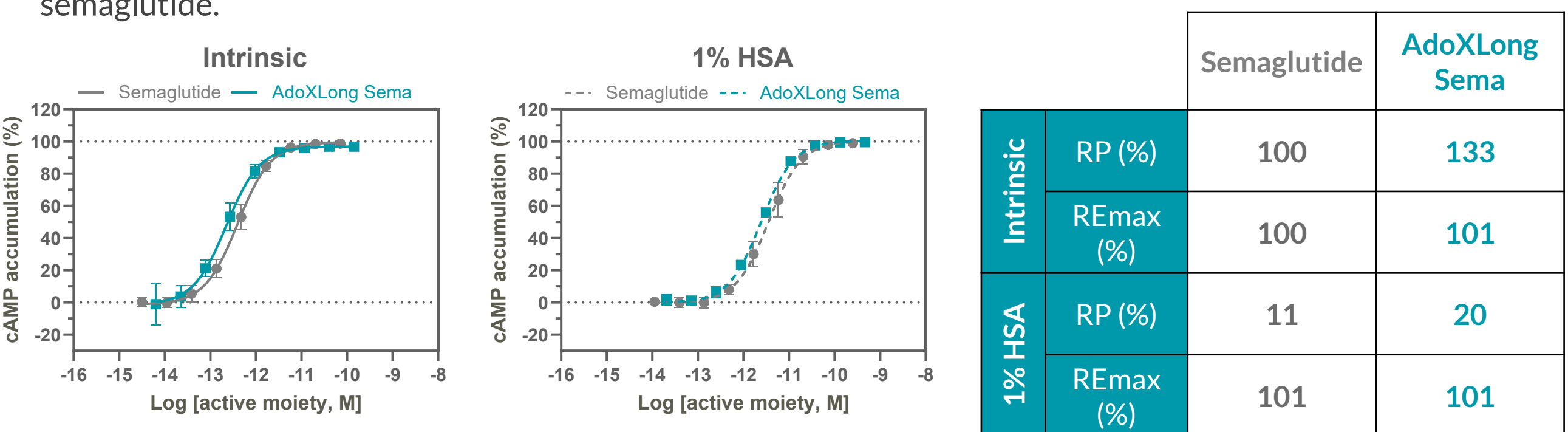
Methods

Functional potencies for molecules were determined in Chinese hamster ovary (CHO)-K1 cells stably expressing human GLP-1R. Cells were treated with defined molecules standards in presence of casein, supplemented, or not, with 1% (w/v) human serum albumin (HSA). Accumulated cAMP levels were measured using alphascreen cAMP technology. Potency and efficacy of active moieties were normalized by the intrinsic potency and efficacy of semaglutide to calculate RP(%) and REmax(%), respectively.

SE-HPLC analysis was done using PBS as the mobile phase, at 0.5mL/min and 30°C on a Tosoh TSK Gel column. UV measurements at 214 nm were used to monitor peptide elution.

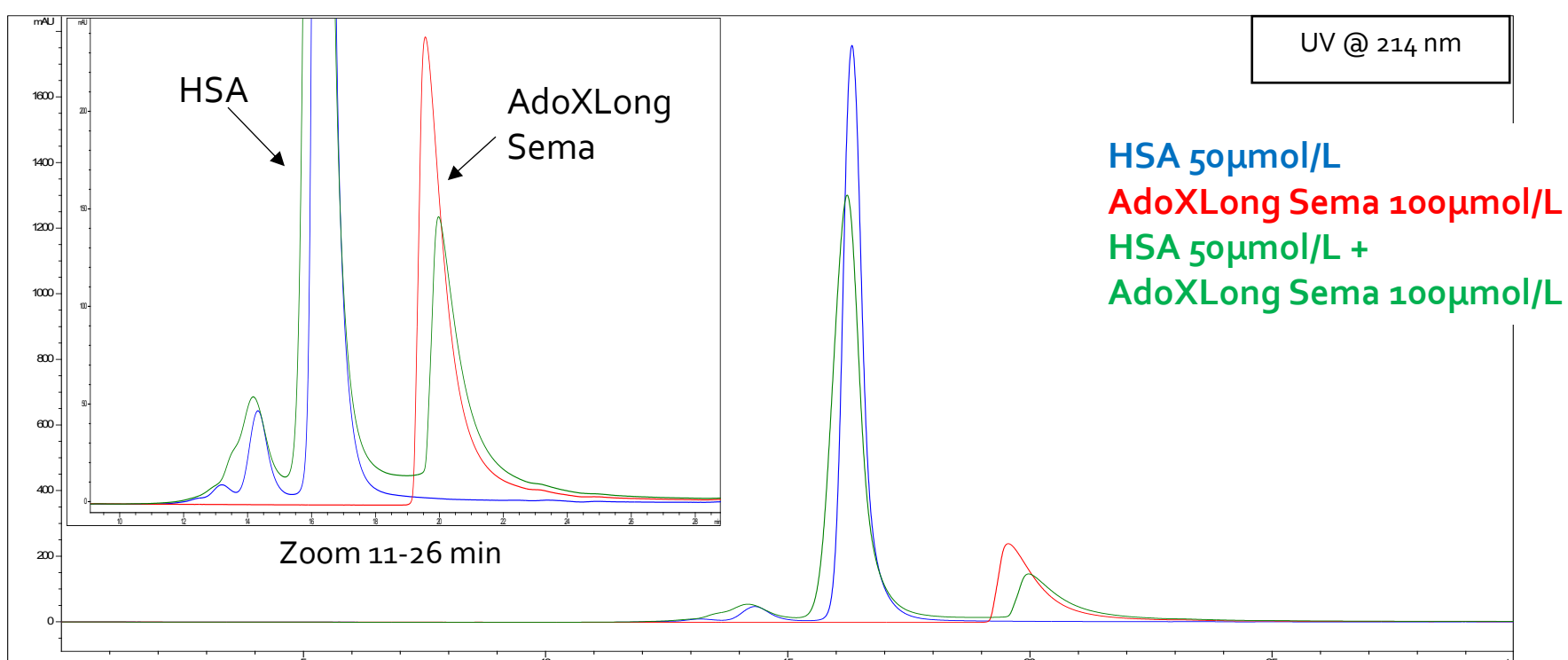
In vitro GLP-1R potency and efficacy

- The intrinsic relative potency (RP) and efficacy (REmax) of AdoXLong Sema is well preserved *in vitro*.
- A decrease of AdoXLong Sema activity is observed in the presence of HSA, confirming its high affinity to albumin. Interestingly, residual potency in the presence of albumin is slightly higher than the one of semaglutide.



Interaction with albumin measured by SE-HPLC analysis

- SE-HPLC shows a decrease in AdoXLong semaglutide peak area at 20 minutes upon addition of 50μmol/L of HSA. Concurrently, in presence of AdoXLong semaglutide, the HSA peak at 16 minutes broadens and shifts to earlier elution times, indicating the formation of larger HSA-AdoXLong semaglutide complexes.
- This supports the high affinity of AdoXLong semaglutide for HSA observed previously.



In vivo PK studies

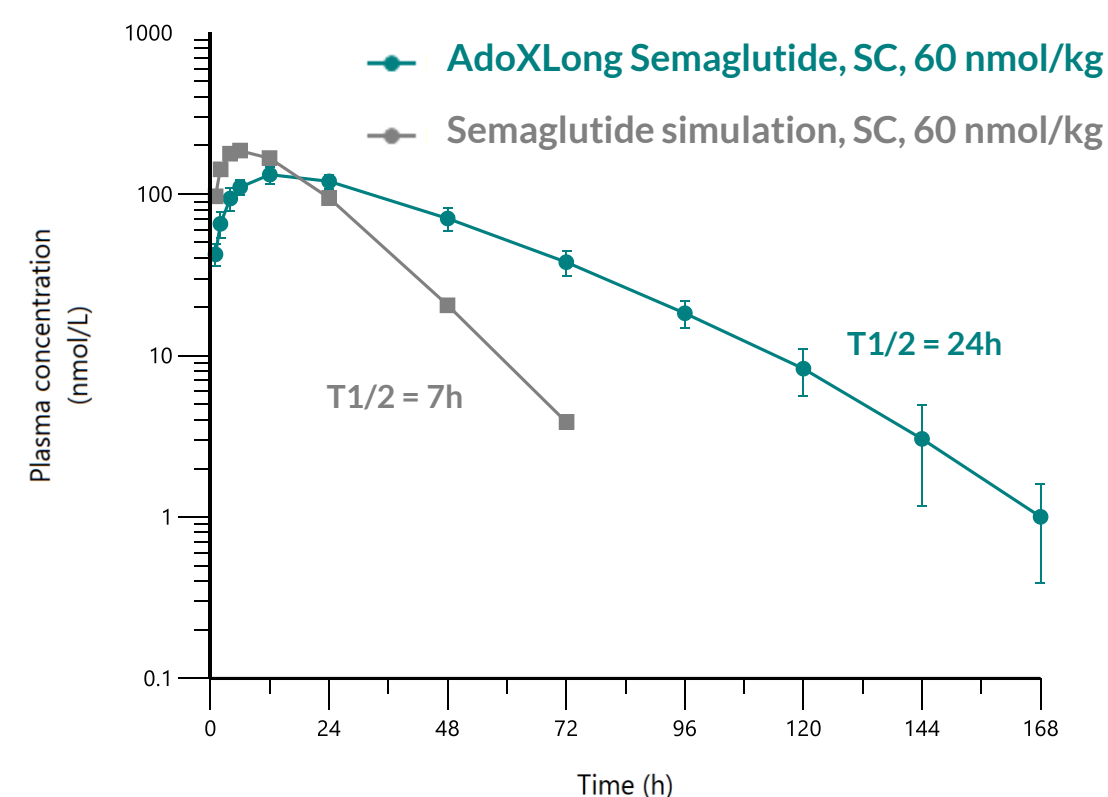
Methods

AdoXLong Sema was tested in rats (N=5) and in pigs (N=6) following a subcutaneous (SC) and intravenous (IV) injection (in pig only). Plasmatic AdoXLong Sema concentrations were evaluated by ELISA.

Rat study

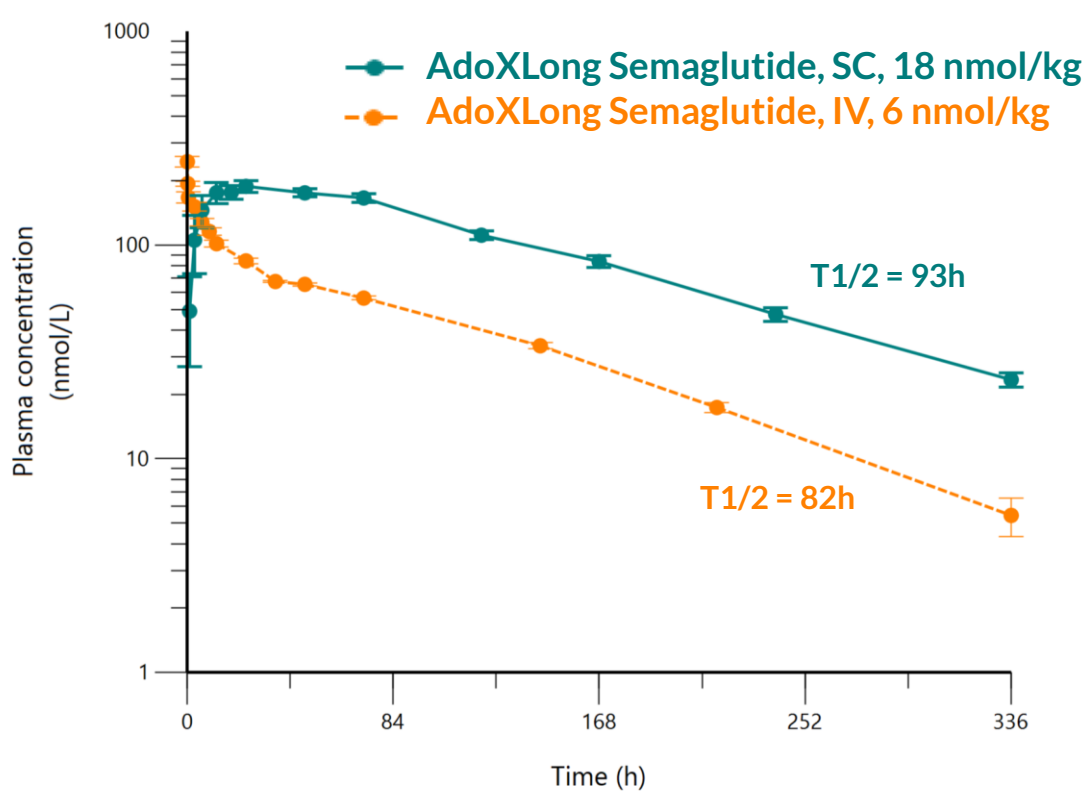
After SC administration in rats:

- AdoXLong Sema demonstrates a prolonged half-life of 24h.
- This increase corresponds to 3.5-fold half-life of semaglutide.



Mean±SE PK profile after single SC administration to rats (n=5) at 60 nmol/kg versus SC semaglutide simulated at the same dose (simulated from Tae Suk Lee et al., J Chromatogr B Analyt Technol Biomed Life Sci. 2023 Apr 15;1221:123688)

Pig study



Mean±SE PK profiles after single IV or SC administration to farm pigs (n=6) at 6 and 18 nmol/kg respectively

After IV and SC administration in farm pigs:

- AdoXLong Sema demonstrates a prolonged half-life of 82 h (IV) and 93 h (SC).
- This increase corresponds to 2-fold half-life of semaglutide[3].
- The SC bioavailability of AdoXLong Sema is 91%.

Conclusion

The AdoXLong platform shows a preservation of human GLP1-R activity *in vitro* in the presence or absence of human serum albumin. AdoXLong Sema half-life *in vivo* is significantly prolonged after subcutaneous administration in rats and in farm pigs compared to semaglutide. Moreover, the bioavailability after SC administration of AdoXLong Sema is higher than 90% in pig.

AdoXLong provides an effective approach for sustained systemic delivery of circulation-prolonging peptides, supporting the feasibility of once-monthly AdoXLong Sema administration in humans.

[1] World Obesity Atlas 2023

[2] Weiss T et al. Real-World Adherence and Discontinuation of Glucagon-Like Peptide-1 Receptor Agonists Therapy in Type 2 Diabetes Mellitus Patients in the United States. Patient Prefer Adherence. 2020 Nov 27;14:2337-2345.

[3] Patent WO2021144476