# Semaglutide Depot (SG Depot), a Long-Acting Injection of Semaglutide Administered Once Every Four Weeks to Demonstrate Pharmacokinetic Modeling and Human-based Allometric Scaling

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## Introduction and Objective

Semaglutide Depot is a microspheres-based extended-release drug product intended for once every 28 days SC administration. Semaglutide Depot efficacy and pharmacokinetic (PK) profile were evaluated in mice (db/db) and in minipig models. PK modeling was utilized to provide human-based allometric scaling towards a first in human clinical trial.

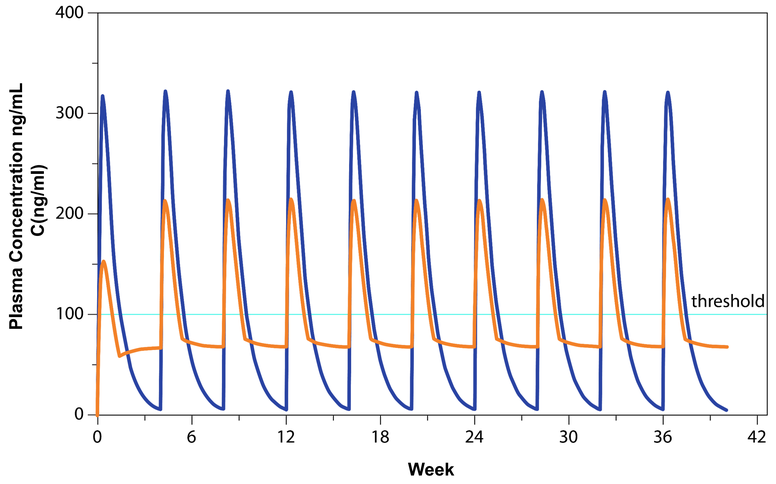
## Design/Methods

- Allometric scaling was done using PK data from nonclinical trials (rodent and non-rodent) to predict human drug exposure for a range of drug doses. Phoenix non-linear mixed effect modeling software was used to perform individual, population and pooled data analyses.
- Litrature based assumptions of drug half-life and allometric scaling were verified using empirical data. Due to the sparsness of the empirical data, the following assumptions were made to ensure plausible efficient modeling:
  1. Depot and API share the same volume of distribution and global clearance, hence only the absorption process must be modelled separately.
  2. For mice, Semaglutide Depot data show two distinct absroption and eliminations processes.
  3. For minipigs these process are confounded.

## Results

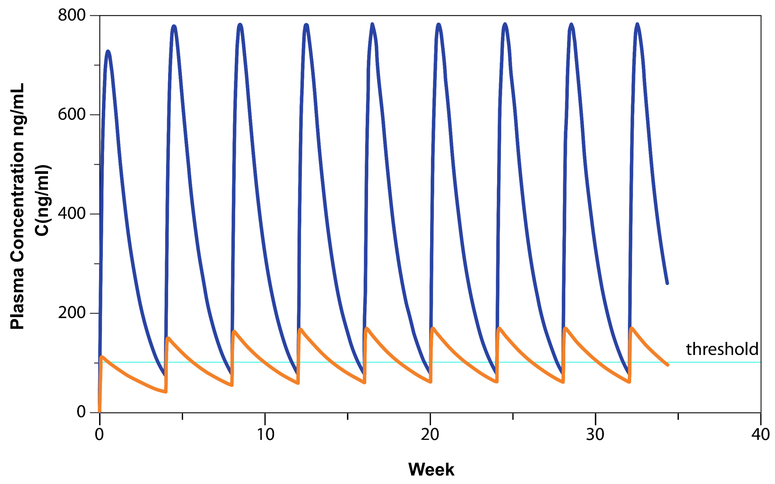
- Based on the model properties and mice or minipigs PK data, Semaglutide Depot administration to humans in dose of 4-8 mg every 4 weeks would lead to the target mean steady state plasma level of 100ng/ml.
- In both animal models, extrapolation to humans demonstrated a significant formulation effect on the PK profile, when compared to the plasma profile of identical posology of non-formulated API.
- Semaglutide Depot showed significantly lower Cmax values and reduced fluctuations in the Semaglutide plasma concentrations (lower Cmax/Cmin), which is anticipated to be translated into reduced side effects and better dose stability of the formulated product as compared to immediate release Semaglutide.

***Figure 1:*** Simulated Human PK Profiles of 4 mg Semaglutide Formulations at Steady State, based on mice data




Simulated steady state plasma concentration-time curves for 4 mg Semaglutide administered every 28 days as immediate-release API (**Blue**) versus extended-release depot formulation (**Orange**). Model predictions derived from allometric scaling of preclinical data (mice) using nonlinear mixed-effects modeling. The depot formulation maintains plasma concentrations above the therapeutic threshold (100 ng/mL, dashed line) while demonstrating attenuated Cmax and reduced peak-trough fluctuation (Cmax/Cmin ratio).

***Figure 2:*** Simulated Human PK Profiles of 8 mg Semaglutide Formulations at Steady State, based on mini-pigs data




Simulated steady state plasma concentration-time curves for 8 mg Semaglutide administered every 28 days as API (**Blue**) versus depot microspheres (**Orange**). The depot formulation achieves sustained therapeutic concentrations (mean 104 ng/mL) with flattened pharmacokinetic profile, maintaining target engagement while potentially mitigating concentration-dependent adverse effects.

## Conclusions

Based on the pre-clinical results Semaglutide Depot given once every 28 days in doses of 4 to 8 mg is expected to reach the target human PK profile equivalent to four weekly Semaglutide injections while offering an improved safety profile. Phase I/IIa clinical study is planned to explore Semaglutide Depot PK, safety and efficiency in humans including these dose ranges.

Disclosure: Galina Zats, Nadav Bleich Kimelman, Shai Rubnov (co-inventor of SG Depot) and Uri Danon are employed by Mapi Pharma. Ehud Marom is a co-inventor of SG Depot, founder and CEO of Mapi Pharma.

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