



# Translational PK/PD modeling to support First-In-Human clinical trial of a MAT2A inhibitor

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## Background

The deletion of metabolic gene methylthioadenosine phosphorylase (MTAP) occurs, globally, in 15% of human cancers [1] with unmet needs. Deletion of the MTAP gene with synthetic lethal inhibition of methionine adenosyl-transferase IIA (MAT2A) leads to the death of tumor cells. S095035 is a potent and selective small-molecule antagonist of MAT2A that targets MTAP-null cancer cells.

**Objectives** : To translate PK & PK/PD and predict efficacious exposure and dose in patients ahead of S095035 entering clinical development.

## Workflow for efficacious human dose projection based on preclinical studies

### 1) PK modeling of single dose intravenous/oral (IV/PO) PK studies

S095035 plasma PK data from single-dose IV/PO studies were modeled using a joint IV/PO compartmental model including absorption. The human distribution and elimination PK parameters were predicted using estimated allometric scaling coefficients (Table 1). With this translational PK model, simulations of human PK profiles were performed for doses ranging from 10 mg to 500 mg.

### 2) PK/PD in xenograft mouse models : pancreatic cancer KP4-K MTAP-null model and colon cancer HCT-116 MTAP-null model

Xenograft-tumor bearing mice were treated with several S095035 dose levels ranging from 0.3 mg/kg to 20 mg/kg. The tumor volumes were measured every 3-4 days on each animal (control group and treated group, n = 12 mice per groups) over the duration of treatment (up to 18 days). On the last day of the study, PK samples were collected at 1h, 6h, 12h and 24h after administration. A sequential modeling approach was used (PK modeling, then tumor growth modeling in the absence of treatment, then PK/PD). Different tumor growth models were tested: simple, exponential, double exponential and exponential with linear growth model (e.g Simeoni 2004 [2]). A proportional and a saturable effect of S095035 plasma concentrations were tested on tumor growth.

### 3) Prediction of efficacious exposure and dose in Human

Based on the PK/PD correlations, the efficacious steady-state exposure results in the AUC needed to achieve 90% of maximum tumor growth inhibition (EAUC90[0-24h]). To account for heterogeneity in tumor sensitivity to S095035, the geometric mean of efficacious exposures in mice was projected with a plasma protein binding correction (PPB) into efficacious exposure of S095035 in humans. A range of bioavailabilities (conservative 50% to more representative in animal species at 85%) was used to predict the efficacious dose-range in humans.

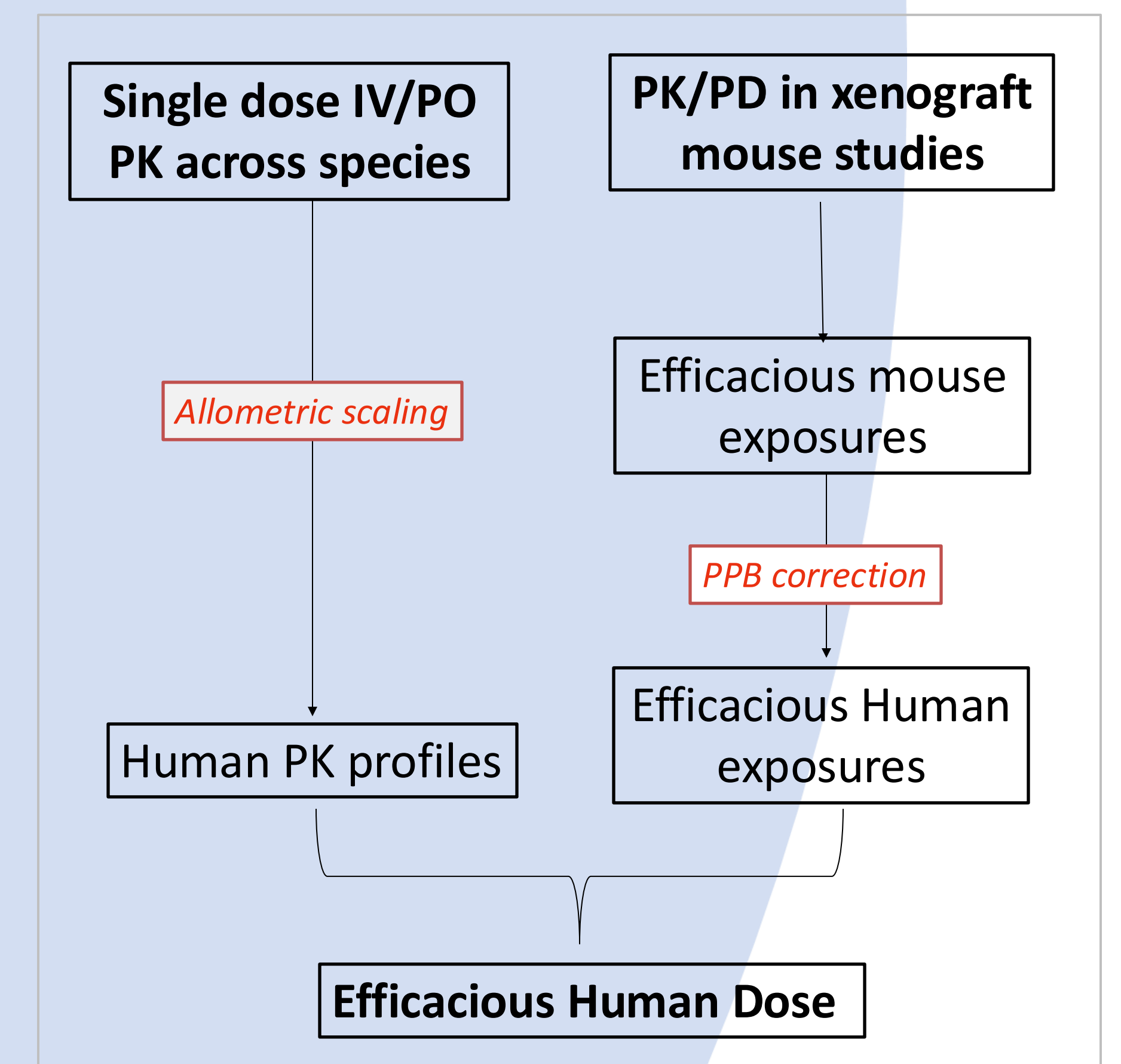


Figure 1: Modeling framework

Model estimations and simulations were performed using the Monolix Suite 2019R2. Allometric scaling were performed using MicrosoftExcel365 (2006 FDA guidance [3]) and Simcyp v2018R1 allometric tools.

## Results

### 1) PK modeling of single-dose intravenous/oral (IV/PO) PK studies

All IV/PO PK studies (mouse, rat, dog, monkey) were modeled using a 2-compartment PK model and first-order absorption. Table 1 summarizes the translated PK parameters in humans, associated with a predicted effective half-life of 27 hours.

### 2) PK/PD in xenograft mouse models : pancreatic cancer KP4-K MTAP-null model and colon cancer HCT-116 MTAP-null model

For both xenograft-tumor bearing mouse models, a linear 2-compartment PK model including first-order absorption was used. Based on modeling in absence of the treatment, the longitudinal tumor growth was modeled using an exponential (KG) in HCT-116 MTAP-null model and a double exponential growth (KG') in KP4-K MTAP-null model. In both models, a saturable effect of S095035 (IC50 [RSE%] = 25.6 [7.26] and IC50 [RSE%] = 220 [43.2] ng/mL) better described the TGI (Figure 2). In mice, the respective EAUC90[0-24h] in KP4-K MTAP-null model and HCT-116 MTAP-null model were 5,444 h.ng/mL and 30,888 h.ng/mL with a geometric mean of 12,967 h.ng/mL that corresponded to a human exposure at steady state of 12,100 h.ng/mL.

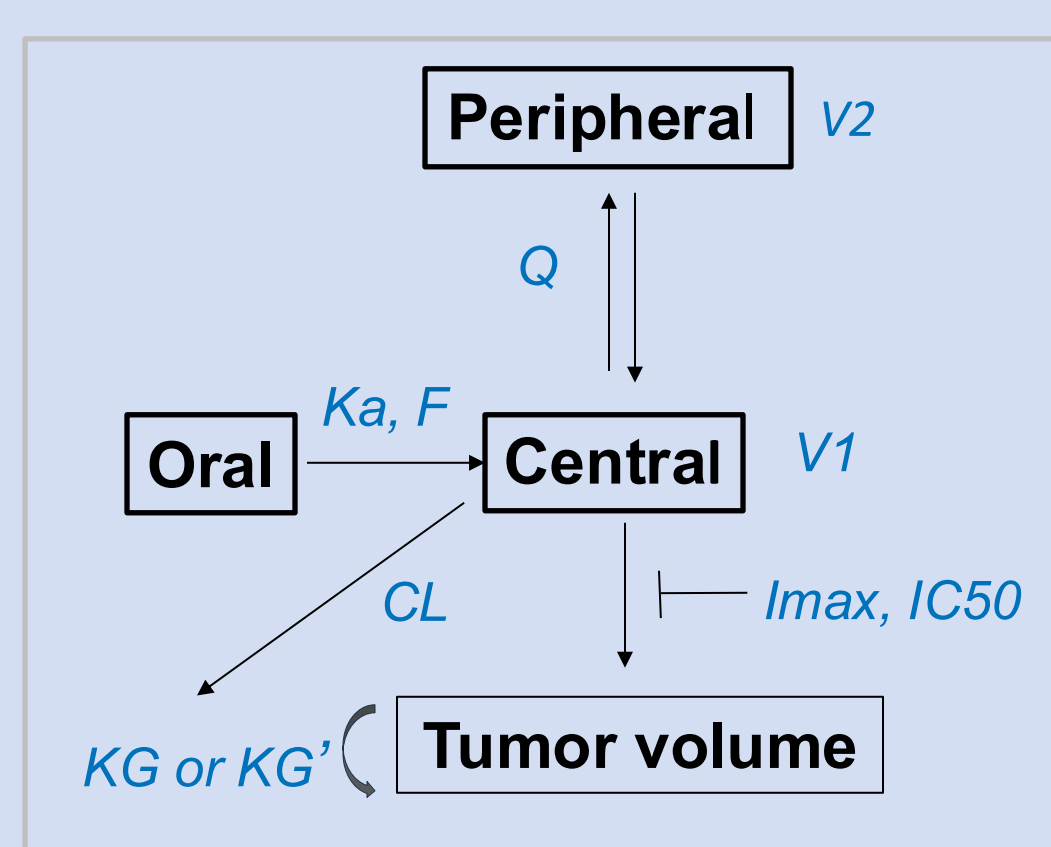


Figure 2: PK/PD model in xenograft mouse

| Parameters | Units  | Value      | Coefficient of allometric scaling | R <sup>2</sup> of allometric scaling |
|------------|--------|------------|-----------------------------------|--------------------------------------|
| CL         | L/h/kg | 0.0597     | 0.604                             | 0.949                                |
| V1         | L/kg   | 0.321      | 0.809                             | 0.978                                |
| Q          | L/h/kg | 0.303      | 1.09                              | 0.960                                |
| V2         | L/kg   | 2.07       | 1.21                              | 0.980                                |
| Ka         | H-1    | 0.362      | -0.264                            | 0.970                                |
| F          | %      | 50% to 85% | -                                 | -                                    |

Table 1: PK parameters model in human

|  | PPB corrected projection<br>F= 85%                 | PPB corrected projection<br>F= 50%                 |
|--|--|--|
| PK parameters in Human                   | Table 1 with target at AUC 12,100 h.ng/mL          |  |
| Predicted Cmax (ng/mL)                   | 802  | 808  |
| Predicted Cmin (ng/mL)                   | 336  | 368  |
| Simulated AUC <sub>0-24h</sub> (h.ng/mL) | 12140  | 12200  |
| Simulated TGI in Human (%)               | 67% (HCT-116 parameters)<br>72% (KP4-K parameters) | 67% (HCT-116 parameters)<br>71% (KP4-K parameters) |

Table 2: Prediction of efficacious S095035 Human doses to reach EAUC90 at steady state

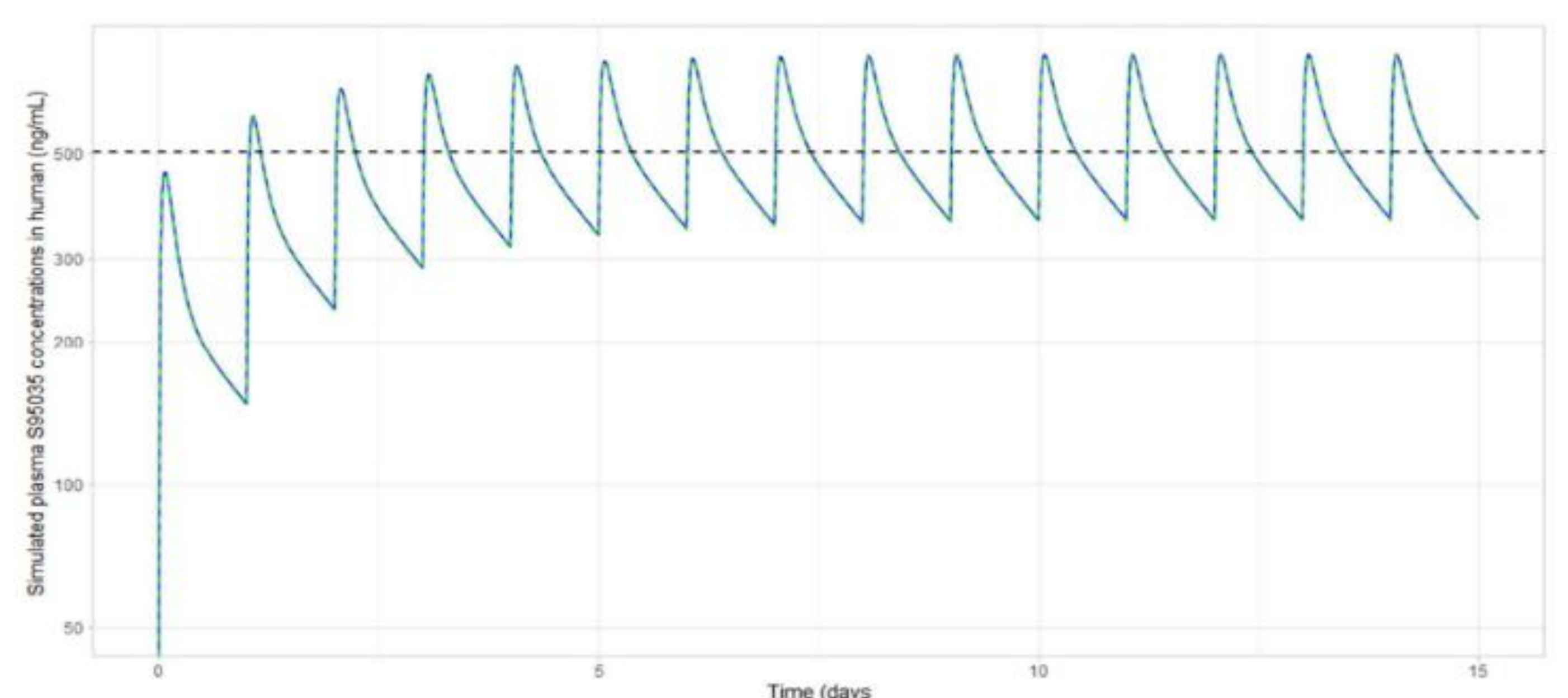


Figure 3: Simulations Plasma Concentrations-Time profile of S095035 in Human

## Conclusion

S095035 is anticipated to have low clearance and moderate distribution volume in Human. The projected human PK parameters support once daily (QD) dosing of S095035. Nevertheless, differences in tumor sensitivity to S095035 suggest that a dose up to 200 mg could be required to achieve an anti-tumor effect. It is important to provide an active dose range to support FIH study design and translational PK/PD modeling is the right tool for this assessment. In oncology, the pre-clinical PK and tumor volume data can inform on the efficacious exposure and dose in Human.

## References

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- [2] Simeoni M, Magni P, Cammia C, De Nicolao G, Croci V, Pesenti E, Germani M, Poggesi I, Rocchetti M. Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. *Cancer Res*. 2004 Feb 1;64(3):1094-101. doi: 10.1158/0008-5472.can-03-2524. PMID: 14871843.
- [3] 2006 FDA guidance's