

Physiologically based pharmacokinetic modeling and simulations to characterize the effect of cyclodextrins on the exposure of asciminib in lieu of clinical trials

Ioannis Loisios-Konstantinidis^{1*}, Felix Huth¹, Heidi Einolf², Matthias Hoch¹

¹Pharmacokinetic Sciences, Translational Medicine, Biomedical Research, Novartis, Basel, Switzerland; ²Pharmacokinetic Sciences, Translational Medicine, Biomedical Research, Novartis, New Jersey, USA; * Corresponding author: ioannis.loisios_konstantinidis@novartis.com

Introduction

In a clinical study, co-administration of multiple doses of an itraconazole (ITZ) oral solution containing hydroxypropyl-beta-cyclodextrin (HP-beta-CD) at a total of 8000 mg per dose with a 40 mg dose of asciminib (ABL001) decreased asciminib exposure by 40.2% in healthy subjects [1]. In addition, other cyclodextrins than HP-beta-CD are used as excipients in medicinal use or food/ drinks and include alpha-CD, beta-CD, gamma-CD, sulfobutylether (SBE)-beta-CD and randomly methylated-beta-CD [2]. In a post-marketing requirement FDA and EMA requested a PBPK modeling analysis to assess the clinical relevance of all cyclodextrins in medicinal use on the exposure of asciminib. The objective of this study was to establish a cutoff for the amount of each CD that would not reduce asciminib exposure by more than 20% (i.e., based on the bioequivalence criteria) using an in vitro-in silico-in vivo extrapolation approach.

Methods

PBPK modeling workflow

The Simcyp Population-based Simulator, Version 21 Release 1 (Certara Inc., Princeton, NJ) and the Simcyp North European Caucasian population was used for all simulations.

Asciminib

An established asciminib PBPK model with mechanistic oral absorption including the mechanistic permeability model (MechP) was used. The model was verified by its ability to recapitulate the effect of ITZ solution containing 8000 mg HP-beta CD on the PK of asciminib (Figure 1). Then, the PBPK model was applied to predict the cutoff amount of each CD that would not lead to an asciminib exposure decrease greater than 20% using three approaches

Cyclodextrins

PBPK models for each CD were developed using their respective solubility in FaSSiF, predicted regional permeability assuming logP of -10 and very fast degradation in colon with a rate constant of 500 h⁻¹ in line with the findings of Flourié et al 1993 [3].

Approach I: Mechanistic excipient binding model and MechP

The effect of drug binding to cyclodextrin on the solubility ($S_{bound,excip}$) has been incorporated within Simcyp into the global equation describing the total solubility (S_{Tot}) of the drug as follows:

$$S_{Tot}(t) = S_{0,scalar}(t) \cdot S_0 \cdot \left(1 + \frac{[BS](t)}{C_{H2O}} \cdot K_{m:w,unionized}(t) \right) + S_f(t) \cdot \left(1 + \frac{[BS](t)}{C_{H2O}} \cdot K_{m:w,ionized}(t) \right) + S_{bound,excip}(t)$$

However, the MechP model employs the free fraction hypothesis, meaning that only unbound drug permeates. Therefore, the impact of drug partitioning into bile salt micelles ($K_{m:w}$) and/or cyclodextrins results in a complex interplay between solubility (S_i), dissolution rate and effective permeability. Binding constant (KD) for each CD cyclodextrin were determined in vitro by performing solubility experiments in FaSSiF at multiple CD concentrations.

Approach II: Free fraction corrected regional effective permeability (linear)

Based on the quasi-equilibrium analysis of the effect of CD on the permeability of a co-administered drug, the membrane permeability (P_m) can be expressed as a linear function of the fraction of free drug (F) multiplied by the free membrane permeability ($P_{m(F)}$) [4].

$$P_m = F \cdot P_{m(F)} = \frac{1}{K_D \cdot C_{CD} + 1} \cdot P_{m(F)}$$

The regional permeability of asciminib in absence of micelles predicted by the MechP model was used as the effective permeability (P_{eff}) of the free drug. Then, the free fraction F was calculated using the KD and the average simulated cyclodextrin concentration in each segment of the GIT and regional P_{eff} was corrected for the free fraction and input into the PBPK model.

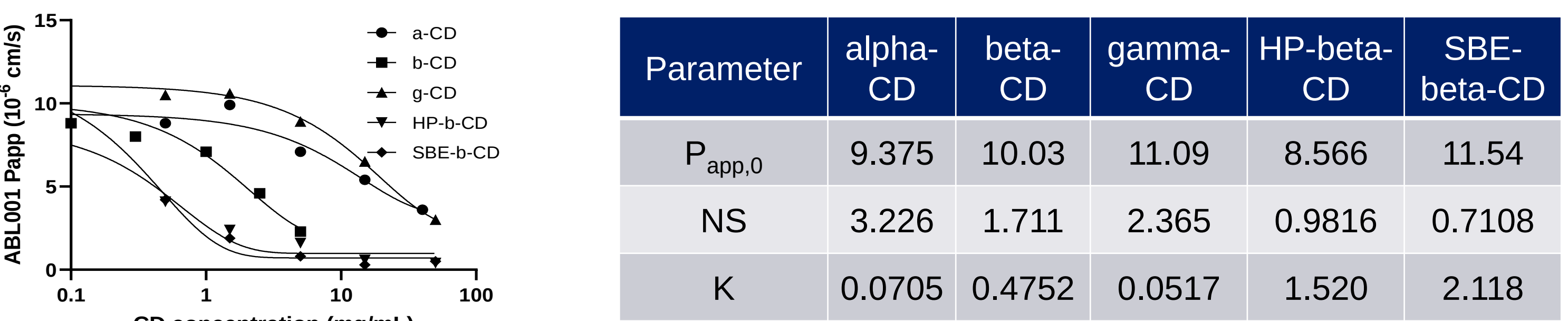
Approach II: Cyclodextrin concentration and apparent permeability in MDCK cells correlation (nonlinear)

In vitro apparent permeability (P_{app}) of asciminib was determined in a MDCK-based transwell experiment where increasing concentrations of the respective CDs were added to the donor compartment together with 10 μM of asciminib free base. The P_{app} versus CD concentration curves were fitted using the equation:

$$P_{app} = (P_{app,0} - NS) \cdot \exp(-K \cdot [CD]) + NS$$

Upon fitting, the average [CD] in each intestinal segment was used to back-calculate the regional P_{app} in the respective segment. The P_{app} was then converted to P_{eff} at each segment using an inhouse P_{app} - P_{eff} correlation. The P_{eff} values in each segment were used within Simcyp to simulate the effect of cyclodextrins on the PK of asciminib.

Figure 1: Fitted parameters of asciminib P_{app} in presence of increasing CD concentration



Results and Discussion

The PBPK model was able to describe the observed PK profile and parameters of asciminib with or without co-administration of ITZ/HP-beta CD solution with prediction errors less than 28% (Figure 2). Furthermore, the PBPK model was also able to capture the C_{max} and AUC_{inf} ratios of the interaction with the ITZ/HP-beta CD solution within 20% of the observed values. The verified PBPK model was applied to predict the effect of a wide range of dose of different cyclodextrins (i.e., alpha-, beta-, gamma-, HP-beta and SBE-beta-CD).

Figure 2: PBPK simulated versus observed PK profiles and parameters of the asciminib and ITZ/HP-beta CD interaction

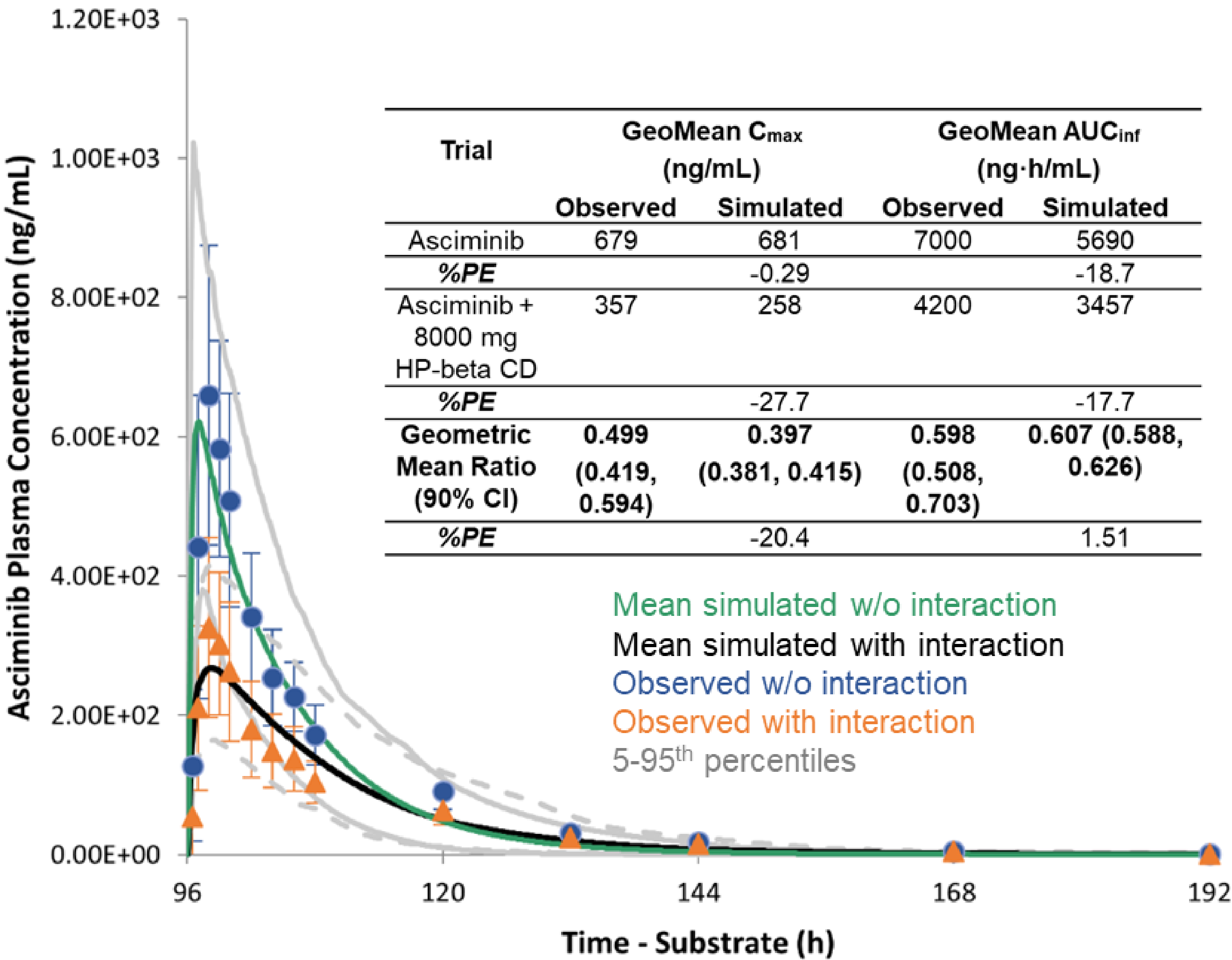


Table 1: Proposed CD cut-off values with no clinically relevant effect on the exposure of asciminib

Trial Design	Geometric Mean C _{max} (ng/mL)	Geometric Mean AUC _{inf} (ng·h/mL)
Asciminib 40 mg	681	5690
Asciminib + 500 mg beta-CD	620	5594
Geometric Mean Ratio (90% CI)	0.957 (0.951, 0.962)	0.982 (0.980, 0.984)
Asciminib + 2,000 mg HP-beta-CD	432	4684
Geometric Mean Ratio (90% CI)	0.666 (0.647, 0.686)	0.822 (0.812, 0.833)
Asciminib + 2,000 mg SBE-beta-CD	445	4766
Geometric Mean Ratio (90% CI)	0.687 (0.667, 0.707)	0.837 (0.827, 0.847)

Conclusions

The PBPK model predicted that alpha-, beta- or gamma-CD is not expected to have an effect on the PK of asciminib at their maximum soluble dose or dose available in oral products (including food and drinks).

For HP-beta and SBE-beta cyclodextrin a maximum dose of 2,000 mg was predicted to not have a relevant effect (i.e., less than 20% decrease) on the exposure of asciminib.

Both, FDA and EMA, accepted the results of this comprehensive PBPK modeling analysis without the need to conduct any clinical study or additional in vitro experiments.

References

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