Population Pharmacokinetic (PopPK) Modeling for a Novel Nilotinib Formulation

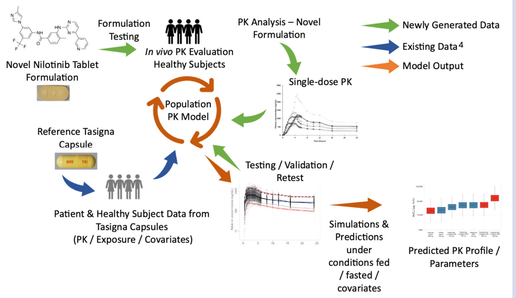
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INTRODUCTION

- Introduction of the second-generation tyrosine kinase inhibitor (TKI) nilotinib brought important benefits to treatment of chronic myeloid leukemia (CML).[1]
- Nilotinib overcomes resistance due to wide range of breakpoint cluster region—Abelson fusion gene (BCR-ABL) mutants to imatinib.[2,3] However, treatment with this TKI could be simplified by decreasing the strong effect of food which increases its bioavailability that is correlated with QT prolongation.[4,5] This effect has resulted in specialized dosing instructions:
  - A boxed warning in the Tasigna® capsule label states that food must be avoided for ≥2 hours before and ≥1 hour after the dose is taken.[6]
- Azurity has developed a new film-coated oral tablet formulation of nilotinib which, when administered at half the dose strength of the currently approved Tasigna capsule formulation, results in bioequivalent (BE) systemic drug exposure.
- This report summarizes results from a validated population pharmacokinetic (PopPK) model (**Figure 1**) to predict and simulate:
  - The steady-state PK of the new nilotinib tablet; and
  - How administration with food affects systemic exposure to nilotinib delivered via the new nilotinib tablet formulation vs. that of the currently approved Tasigna capsules.

Figure 1. Overview of Population Pharmacokinetic (PopPK) Model Development and PK Simulation



References

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5. Tian X, et al. J Clin Pharmacol. 2018;58(12):1533-1540.
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METHODS

Predictions Carried Out With the PopPK Model

The final model was used to predict concentration-time profiles for nilotinib delivered via nilotinib tablets or Tasigna capsules at steady state following twice-daily (BID) dosing under varied fasted and non-fasted conditions. Simulations included both fixed and random effects.

50 healthy subjects (50% male) randomly selected from the analysis dataset formed the basis for simulations. From these individual profiles, area under the curve at steady state (AUC_{ss}), maximum plasma concentration at steady state (C_{maxss}), and minimum concentration at steady state (C_{minss}) were derived and used for formal BE testing, performed with an appropriate analysis of variance model on the log-transformed individual estimates for the PK parameters.

100 study replicates were simulated to establish the probability of BE between the two formulations under fasted conditions in a steady-state study setting.

Data Sources: Pooled PopPK data from 14 bioavailability/bioequivalence clinical studies in healthy subjects.

Prandial State Definitions for Assessment of Food Effects*

Fasted: Tasigna capsules or nilotinib tablets were administered after an overnight fast of ≥10 hours (h).

Fed: After an overnight fast of ≥10 h, subjects consumed a high-fat high-calorie non-vegetarian breakfast 30 minutes prior to dosing and completed within 30 minutes.

Modified fasting with a low-fat meal: Fasting for ≥10 h overnight and administration of study drug 2 h after the start consumption of a low-fat meal (400-500 kcal, about 25% fat content).

Modified fasting with a high-fat meal: Fasting for ≥10 h overnight and administration of study drug 2 h after the start consumption of a high-fat meal (800-1000 kcal, non-vegetarian, about 50% fat content).

*Subjects did not consume additional food until ≥4 h post-dose for all conditions.

Analyses

- The analysis used a nonlinear mixed effects model.
- Individual estimates of PK parameters of interest were evaluated for relationships with potential covariates, specifically body weight, age, sex, creatinine clearance, total bilirubin, alanine transaminase, aspartate transaminase, nilotinib tablet/Tasigna capsule formulation, formulation lot number, and nilotinib dose.
- Covariates that demonstrated statistical significance were retained in the final model.
- Standard goodness-of-fit diagnostics, visual predictive checks, and non-parametric bootstrap analyses were used to evaluate the performance, robustness as well as predictive ability of the final model.

RESULTS

Observations

The PK analysis dataset included 30,089 PK observations from 502 subjects. A total of 1311 observations were below the limit of quantification and excluded from the analysis. Thus, 28,779 observations from 502 subjects were included.

PK Analysis

- Nilotinib PK after oral administration was characterized by a two-compartment model with linear elimination and zero-order absorption with lag-time.
- **Table 1** shows steady-state PK (90% confidence interval) of nilotinib tablets and Tasigna capsules administered twice-daily under different food conditions.
- Among covariates evaluated, body weight and sex were found to have statistically significant effects on nilotinib clearance. Females receiving nilotinib tablets under fasted conditions had slightly higher relative bioavailability (BA) (11.6%) vs. males.

Table 1. Simulated Steady-State PK of Nilotinib Tablets and Tasigna Capsules

	Low-Dose		High-Dose	
	Nilotinib Tablets 142 mg	Tasigna Capsules 300 mg	Nilotinib Tablets 190 mg	Tasigna Capsules 400 mg
	Mean (90% Confidence Intervals)			
Steady-State PK	BID Dosing - Overnight Fast			
C_{min}	926 (806 - 1030)	900 (811 - 980)	1000 (892 - 1120)	970 (884 - 1080)
C_{max}	2070 (1930 - 2200)	1950 (1810 - 2090)	2250 (2090 - 2430)	2120 (1980 - 2270)
AUC	14600 (13400 -15600)	13900 (12900 -14900)	15700 (14600 - 17000)	15000 (14100 - 16200)
Steady-State PK	BID Dosing – Low-Fat Meal - Modified Fasting			
C_{min}	1130 (1010 - 1250)	1350 (1240 - 1520)	1230 (1100 - 1360)	1470 (1340 - 1660)
C_{max}	2680 (2490 - 2880)	3230 (3030 - 3490)	2980 (2770 - 3200)	3600 (3390 - 3890)
AUC	18400 (17100 - 19900)	21800 (20600 - 23600)	20300 (18900 - 22000)	24100 (22700 - 26100)
Steady-State PK	BID Dosing – High-Fat Meal – Modified Fasting			
C_{min}	1460 (1320 - 1650)	2590 (2360 - 2870)	1610 (1460 - 1820)	2830 (2580 - 3130)
C_{max}	2980 (2740 - 3240)	5500 (5160 - 5930)	3290 (3030 - 3580)	6010 (5630 - 6480)
AUC	21700 (20200 - 23500)	39000 (36500 - 42100)	23900 (22300 - 25900)	42500 (39700 - 45900)
Steady-State PK	BID Dosing – High-Fat - Fed Conditions			
C_{min}	1360 (1240 - 1490)	nc	1620 (1470 – 1780)	nc
C_{max}	2790 (2600 - 3020)	nc	3320 (3100 - 3600)	nc
AUC	20300 (18900 - 22000)	nc	24100 (22500 - 26200)	nc

AUC, area under the curve at steady state; C_{max}, maximum concentration; C_{min}, minimum concentration; nc, not calculated

Model Predictions for Fasted Conditions

Simulations showed that BE criteria were met for all exposure metrics (AUC_{ss}, C_{maxss}, and C_{minss}) for all evaluated scenarios under fasted conditions (**Table 2**). Results indicated that:

- 190 mg nilotinib tablets were predicted to be bioequivalent to 400 mg Tasigna capsules and 142 mg nilotinib tablets were predicted to be bioequivalent to 300 mg Tasigna capsules.
- The PopPK model predicted the median and 5th and 95th percentile of observed nilotinib concentrations with good accuracy for both formulations.

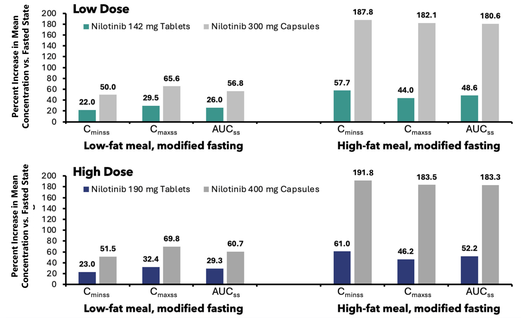
Table 2. BE Test of the Steady-State Parameters Between Nilotinib Tablets vs. Tasigna Capsules: Fasted Conditions

Scenario (N=50)	Exposure	Geometric Mean Ratio (90% CI)
190 mg Nilotinib film-coated tablets vs. 400 mg Tasigna capsules	AUC_{ss} (ng•h/mL)	1.04 (0.949, 1.17)
	C_{maxss} (ng/mL)	1.06 (0.97, 1.2)
	C_{minss} (ng/mL)	1.02 (0.89, 1.18)
142 mg Nilotinib film-coated tablets vs. 300 mg Tasigna capsules	AUC_{ss} (ng•h/mL)	1.03 (0.95, 1.13)
	C_{maxss} (ng/mL)	1.06 (0.97, 1.17)
	C_{minss} (ng/mL)	1 (0.888, 1.15)

Effect of Food on Nilotinib Exposure

Consumption of a low- or high-fat meal under modified fasting conditions indicated much greater increases in exposure with Tasigna capsules vs. nilotinib tablets (**Figure 2**).

Figure 2. Effects of Food on Exposure for Nilotinib Tablets vs. Tasigna Capsules



CONCLUSIONS

- **The final model was suitable to simulate and compare the PK of nilotinib tablets vs. Tasigna capsules at steady state.**
- **Reduced-dose nilotinib film-coated tablets (142 and 190 mg) demonstrated BE and provided equivalent exposures to 300 and 400 mg Tasigna capsules in the fasted state.**
- **The effects of food in increasing exposure to nilotinib were greatly lower with nilotinib tablets vs. Tasigna capsules.**
- **While the modeling results for steady-state conditions have yet to be validated in a prospective PK study, it should be noted that prospective, single-dose studies in healthy volunteers have produced results consistent with the model for all of the fasted and fed conditions considered.**
- **The results indicate that the novel tablet formulation of nilotinib is likely to improve convenience by allowing patients with CML to take their medication without adhering to specific dosing instructions related to timing of administration and food intake.**

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