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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number (SDN)	219293 (1)
Link to EDR	\\CDSESUB1\evsprod\NDA219293\0001
Submission Date	January 1, 2024
Submission Type	Standard
Brand Name	DANZITEN®
Generic Name	Nilotinib
Dosage Form and Strengths	Immediate Release tablets, 71 and 95 mg
Route of Administration	Oral
Proposed Indications	• Adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase • Adult patients with chronic phase (CP) and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior therapy that included imatinib.
Applicant	Slayback Pharma LLC
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1. EXECUTIVE SUMMARY

Slayback Pharma LLC submitted a 505(b)(2) NDA to seek approval of DANZITEN for the adult indications (R/I Ph+ CML-CP and AP, and newly diagnosed Ph+ CML-CP). The Applicant references Tasigna (nilotinib) Capsules, 150 and 200 mg as the listed drug (LD). DANZITEN is an immediate release tablet containing a different salt form (nilotinib tartrate) and lower strengths (i.e., 71 and 95 mg) as compared to Tasigna. The proposed recommended dosages for DANZITEN include 142 mg BID (for newly diagnosed (ND) Ph+ CML) and 190 mg BID (R/I Ph+ CML) for adult patients to be taken without regards to food.

Tasigna (nilotinib monohydrochloride monohydrate), a BCR-ABL kinase inhibitor, was approved in 2007 for the treatment of adult patients with chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) resistant to or intolerant (R/I) to prior therapy that included imatinib. Subsequently, Tasigna was approved for adult and pediatric patients ≥1 year of age with ND Ph+ CML-CP, and for pediatric patients ≥1 year of age with Ph+ CML-CP R/I to prior tyrosine-kinase inhibitor.

The recommended dosages for Tasigna include 300 mg twice daily (BID) (for ND Ph+ CML) and 400 mg BID (R/I Ph+ CML) for adults, and 230 mg/m^2 BID rounded to nearest 50 mg dose (up to maximum of 400 mg BID) for pediatric patients. Tasigna is recommended to be taken on an empty stomach (no food for at least 2 hours before and 1 hour after dose) due to a pronounced food effect. Tasigna is available as 50, 150, and 200 mg strength oral capsules.

The 505(b)(2) NDA is supported by 6 clinical pharmacology studies in healthy subjects to assess:

(i) Bioavailability/bioequivalence (BA/BE) of Danziten 71 mg compared to Tasigna 150 mg under overnight (e.g., at least 10 hours) fasting conditions,
(ii) BA/BE of Danziten 95 mg compared to Tasigna 200 mg under overnight fasting conditions,
(iii) BA/BE of Danziten 95 mg compared to Tasigna 200 mg under modified fasting (e.g., at least 2 hours before and 1 hour after dose) and fed conditions with a high-fat meal,
(iv) BA/BE of Danziten 95 mg compared to Tasigna 200 mg under modified fasting conditions with a low-fat meal,
(v) the effect of food on the PK of Danziten 95 mg under overnight fasting, modified fasting (, and fed conditions with a high-fat meal, and
(vi) the effect of food on the PK of Danziten 71 mg under fasting, modified fasting, and fed conditions with a high-fat meal.

Slayback Pharma LLC is relying on the clinical efficacy and safety of the LD, Tasigna by bridging Danziten systemic exposures to that of Tasigna. The key review questions focused on the establishment of a scientific bridge between the proposed Danziten 71 and 95 mg tablets and Tasigna 150 and 200 mg capsules, respectively, and the appropriateness of the dosage recommendations for the indicated adult patient population, the adequacy of QT prolongation assessment with Danziten, and the effect of food on the exposure of Danziten. Although bioequivalence was met for AUC, it was not met for Cmax for Danziten 71 mg (upper 90% confidence interval [CI] for Cmax was 125.43%) and 95 mg (upper 90% CI was 128.09%) tablets when compared to Tasigna 150 and 200 mg capsules respectively. However, there were minimal concerns for lower efficacy and no additional QT prolongation risk based on comparable steady state exposure metrics (AUC,ss and Cmax,ss).

1.1 Recommendations

From the Office of Clinical Pharmacology perspective, this NDA is approvable and there are no clinical pharmacology-related postmarketing requirements (PMR) or postmarketing commitments (PMC). The key review issues and recommendations are summarized below.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Adequate bridging between DANZITEN, 71 mg Tablets and Tasigna, 150 mg Capsules and DANZITEN, 95 mg Tablets and Tasigna, 200 mg Capsules was demonstrated with minimal concerns for lower efficacy and no additional QT prolongation risk based on comparable steady state exposure metrics (AUC,ss and Cmax,ss). Additionally, comparable steady state exposures metrics between DANZITEN, 95 mg Tablets and Tasigna, 150 mg Capsules based on various food conditions, demonstrating DANZITEN can be taken without regards to food. Therefore, a scientific bridge exists between DANZITEN Tablets and Tasigna Capsules to support the labeling recommendations.
General dosing instructions	Oral doses of 142 mg BID (for newly diagnosed Ph+ CML in CP) and 190 mg BID (resistant or intolerant Ph+ CML in AP/CP) for adult patients. DANZITEN can be taken with or without food.

Dosing and labeling for patient subgroups (intrinsic and extrinsic factors)	The following dosage recommendations for DANZITEN are based on the change in tablet strengths:
	• Hepatic Impairment:
	  ○ Newly diagnosed Ph+ CML: For any hepatic impairment, reduce DANZITEN dosage to 95 mg BID. Subsequently, increase DANZITEN dosage to 142 mg BID based on tolerability.
	  ○ Resistant or intolerant Ph+ CML in AP/CP: For mild or moderate hepatic impairment, reduce DANZITEN dosage to 142 mg BID. Subsequently, increase DANZITEN dosage to 190 mg BID based on tolerability. For severe hepatic impairment, reduce DANZITEN dosage to 95 mg twice daily. Subsequently, increase DANZITEN dosage to 142 mg BID and then 190 mg BID based on tolerability.
	• With concomitant use of strong CYP3A inhibitors: Avoid, or if necessary, reduce DANZITEN dosage to 142 mg once daily (resistant or intolerant Ph+ CML in AP/CP) or 95 mg once daily (for newly diagnosed Ph+ CML in CP).
	• With QTc prolonging drugs:
	  ○ If QTcF between 450 and 480 ms after two weeks, reduce DANZITEN dose to 190 mg once daily.
	  ○ Discontinue DANZITEN if following 190 mg once daily, QTcF returns to >480 ms.
	The recommendations for concomitant use of strong CYP3A inducers and proton pump inhibitors with DANZITEN are the same as those for the listed drug, i.e., avoid concomitant use with DANZITEN. As specified for the listed drug, instead of proton pump inhibitors, H2 blockers are recommended approximately 10 hours before or 2 hours after DANZITEN dose, or antacids are recommended approximately 2 hours before or 2 hours after DANZITEN dose.

	In addition, DANZITEN dose modifications for myelosuppression and non-hematologic toxicities were proportionally revised based on changes in tablet strengths of Danziten vs. LD.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

The following is a summary of the PK of Danziten.

Nilotinib single-dose maximum concentration (C_{max}), area under the time concentration curve (AUC), predicted steady-state maximum concentration ($C_{max,ss}$) and area under the time concentration curve (AUC_{ss}) in fasted subjects receiving the DANZITEN approved recommended dosages are presented in Table 1 and Table 2.

Table 1: Nilotinib observed mean ±SD single-dose exposure in fasted subjects receiving DANZITEN

DANZITEN Dosage	**C_{max}**	**AUC**
142 mg	849 ± 366 ng/mL	17637 ± 7744 ng*hr/mL
190 mg	811 ± 300 ng/mL	15339 ± 6935 ng*hr/mL

Abbreviations: C_{max}= maximum concentration; AUC = area under the time concentration curve

Table 2: Nilotinib predicted mean ±SD steady-state exposure in fasted subjects receiving DANZITEN

DANZITEN Dosage	**$C_{max,ss}$**	**AUC_{ss}**
142 mg twice daily	2071 ± 761 ng/mL	14525 ± 5690 ng*hr/mL
190 mg twice daily	2229 ± 790 ng/mL	15662 ± 5738 ng*hr/mL

Abbreviations: $C_{max,ss}$= maximum concentration at steady state; AUC_{ss} = area under the time concentration curve at steady state

Absorption (from Danziten)

The median time (range) to reach peak plasma nilotinib concentrations (T_{max}) is 2.7 (1.0 to 4.7 hours) following single dose administration of DANZITEN 190 mg in fasted healthy subjects.

Effect of Food (from Danziten)

No clinically significant differences in nilotinib exposure were observed following administration of DANZITEN 142 mg or 190 mg with a high-fat meal (800 to 1000 calories, 50% fat) or a low-fat meal (400-500 kcal, 25% fat content) compared to fasted healthy subjects (refer to Section 3.3.4).

Elimination (from Danziten)

The mean elimination half-life of nilotinib is approximately 14 hours.

Refer to Section 3.2 and the clinical pharmacology review of the original NDA submission for Tasigna (NDA 022068) for other PK information of nilotinib.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dosing regimens of DANZITEN in adult patients with newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-CP and CML-AP is 142 mg BID and 190 mg BID with or without food, respectively. Refer to Section 3.3.2 and Section 3.3.4 regarding bridging of DANZITEN to Tasigna.

2.2.2 Therapeutic individualization

The following dosage recommendations for Danziten in specific populations are based on those evaluated with the LD, Tasigna given the adequate bridging between DANZITEN and Tasigna. Refer to Section 3.3.2 and Section 3.3.4 regarding bridging of DANZITEN to Tasigna.

- Avoid coadministration of strong CYP3A4 modulators. If concomitant use of strong CYP3A4 inhibitors cannot be avoided, reduce DANZITEN dosage to 142 mg once daily (resistant or intolerant Ph+ CML in AP/CP) or 95 mg once daily (for newly diagnosed Ph+ CML in CP).
- Avoid concomitant use of strong CYP3A inducers and PPI with DANZITEN. As an alternative to PPIs, use H2 blocker ~10 hours before or ~2 hours after DANZITEN dose, or antacids ~2 hours before or ~2 hours after DANZITEN dose.
- In newly diagnosed Ph+ CML with any hepatic impairment, reduce DANZITEN dosage to 95 mg BID. Subsequently, increase DANZITEN dosage to 142 mg BID in these patients based on tolerability.

  For patients resistant or intolerant Ph+ CML in AP/CP with mild or moderate hepatic impairment, reduce DANZITEN dosage to 142 mg BID. Subsequently, increase DANZITEN dosage to 190 mg BID based on tolerability. For patients resistant or intolerant Ph+ CML in AP/CP with severe hepatic impairment, reduce DANZITEN dosage to 95 mg twice daily. Subsequently, increase DANZITEN dosage to 142 mg BID and then 190 mg BID based on tolerability.

- Avoid coadministration of DANZITEN with agents that may prolong the QT interval.

2.3 Outstanding Issues

No outstanding issues.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

In the current NDA, the Applicant is seeking approval for DANZITEN via the 505(b)(2) approval pathway for the same adult indications as Tasigna. The Applicant references Tasigna Capsules, 150 and 200 mg (NDA 022068) as the listed drug. DANZITEN is an immediate release tablet containing a different salt form (nilotinib tartrate) and lower strengths (i.e., 71 and 95 mg) as compared to Tasigna. The proposed recommended dosages for DANZITEN include 142 mg BID (for ND Ph+ CML) and 190 mg BID (R/I Ph+ CML) for adult patients to be taken without regards to food. The Applicant is not currently seeking approval for DANZITEN for pediatric indications.

Tasigna as nilotinib monohydrochloride monohydrate capsules was approved in 2007 for the treatment of adult patients with chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) resistant to or intolerant (R/I) to prior therapy that included imatinib. Subsequently Tasigna was approved for adult and pediatric patients ≥1 year of age with the newly diagnosed Ph+ CML indication in CP, and for pediatric patients ≥1 year of age with Ph+ CML-CP R/I

to prior tyrosine-kinase inhibitor. Nilotinib used in Tasigna capsules is a hydrochloride salt form. Tasigna is available, for oral use, as 50 mg, 150 mg, and 200 mg strength capsules.

The recommended doses for Tasigna include 300 mg twice daily (BID) (for newly diagnosed Ph+ CML) and 400 mg BID (resistant or intolerant Ph+ CML) for adults, and 230 mg/m^2 BID rounded to nearest 50 mg dose (up to maximum of 400 mg BID) for pediatric patients. Tasigna should be taken on an empty stomach (no food for at least 2 hours before and 1 hour after dose).

3.2 General Pharmacology and Pharmacokinetic Characteristics

PK parameters for Danziten and Tasigna are as follows:

Danziten:

- 142 mg (Cmax,ss = 2071 ± 761 ng/mL, AUC,ss = 14525 ± 5690 ng*hr/mL)
- 190 mg (Cmax,ss = 2229 ± 790 ng/mL, AUC,ss = 15662 ± 5738 ng*hr/mL)
- Tmax = 2.7 hr (1.0 to 4.7 hrs) following 190 mg in fasted healthy subjects
- No Food effect: No change in exposure after either a high-fat and low-fat meal compared to fasted healthy subjects at the 142 mg and 190 mg dose levels.
- t1/2 = 14 hrs
- Metabolized by CYP3A4 (major) and CYP2C8 (minor)
- Primarily excreted via feces (93%) within 7 days.

Refer to Section 2.1, 3.3 and the Appendix for additional PK information for Danziten.

Tasigna:

- 300 mg (Cmax,ss = 1540 ng/mL (CV: 48%), AUC,ss = 13337 ng*hr/mL (CV: 46%))
- 400 mg (Cmax,ss = 2260 ng/mL (CV: 35%), AUC,ss = 18000 ng*hr/mL (CV: 33%))
- Tmax = 3 hrs
- Food effect: AUC increased 82% when dose was given 30 minutes after a high fat meal.
- Blood-to-serum ratio of 0.68
- t1/2 = 17 hrs (CV: 69%)
- CL = 29 L/h (CV: 61%)
- Metabolized by CYP3A4 (major) and CYP2C8 (minor)
- Primarily excreted via feces (93%) within 7 days.

Refer to the clinical pharmacology review of the original NDA submission for Tasigna (NDA 022068) for other PK information.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Effectiveness and safety of DANZITEN is based on establishment of a scientific bridge between both the highest and lowest strength of the listed drug (i.e., Tasigna) and the highest and lowest strength of DANZITEN in 2 BA/BE single dose studies (010-22 and 128-22) and supportive popPK analyses of nilotinib steady state PK (NDA 022068).

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. A scientific bridge has been established between both the highest and lowest strength of the listed drug (i.e., Tasigna) and the highest and lowest strength of DANZITEN in 2 BA/BE studies (010-22 and 128-22) to support the DANZITEN dosages of 142 mg BID for newly diagnosed adult patients with Ph+ CML, and 190 mg BID for adult patients with resistant or intolerant Ph+ CML in CP.

Study 010-22 demonstrated that the bioavailability of the highest strength of DANZITEN, 2 x 95 mg is comparable to the highest strength of Tasigna, 2 x 200 mg under overnight (i.e., at least 10 hours) fasted conditions. The 90% confidence intervals (CI) of the geometric mean ratio (GMR) for PK parameters, AUC_{0-t}, and $AUC_{0-\infty}$ were within bioequivalence limits of 80% to 125% (Table 3: refer to Appendix 4.1 for details). It was noted that the upper 90% CI of the GMR for Cmax was above 125% (128.09%).

Table 3: Geometric mean summary BA/BE statistics for Study 010-22 (n=92)

Parameter (unit)	DANZITEN, 2 x 95 mg (Test, %CV)	Tasigna 2 x 200 mg (Reference, %CV)	Geometric Mean Ratio (GMR) of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	13763 (39)	13360 (41)	1.03	97.75, 108.57
$AUC_{0-\infty}$ (h*ng/mL)	14183 (40)	13790 (42)	1.03	97.52, 108.46
Cmax (ng/mL)	760 (38)	637 (40)	1.19	110.99, 128.09
Tmax (hr)*	2.67 (1, 4.67)	4 (1.33, 5.67)	-	-
t1/2 (hr)	13.3 (33)	12.4 (30)	-	-

Source: Reviewer's analysis, *Median (Min, Max)

Study 128-22 demonstrated that the bioavailability of the lowest strength of DANZITEN, 2 x 71 mg is comparable to the lowest strength of Tasigna Capsules, 2 x 150 mg under overnight (i.e., at least 10 hours) fasted conditions, in that the 90% confidence intervals (CI) of the geometric mean ratio (GMR) for PK parameters, AUC_{0-t}, and $AUC_{0-\infty}$ were within bioequivalence limits of 80% to 125% (Table 4: refer to Appendix 4.1 for details). It was noted that the upper 90% CI of the GMR for Cmax was above 125% (125.43%).

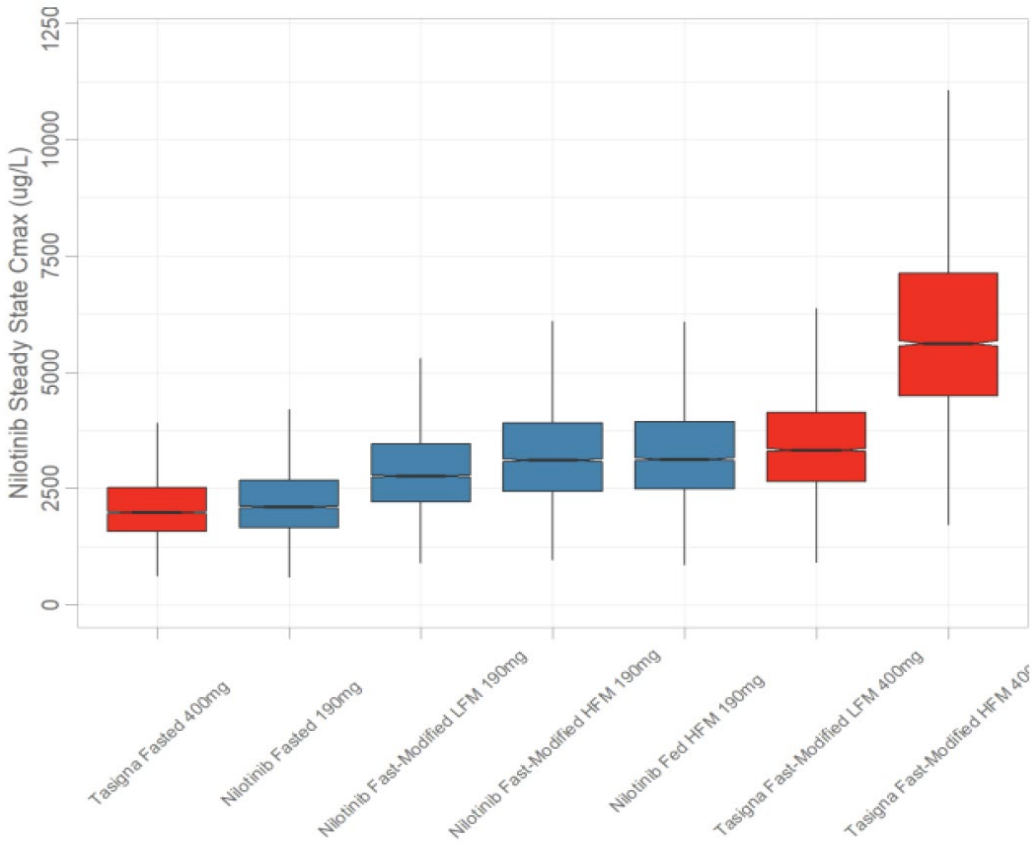
Table 4: Geometric mean summary BA/BE statistics for Study 128-22 (n=87)

Parameter (unit)	DANZITEN, 2 x 71 mg (Test, %CV)	Tasigna 2 x 150 mg (Reference, %CV)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	15783 (43)	15841 (44)	1.00	94.03, 105.59
$AUC_{0-\infty}$ (h*ng/mL)	16119 (43)	16990 (51)	0.95	88.30, 101.94
Cmax (ng/mL)	782 (43)	666 (69)	1.17	109.90, 125.43
Tmax (hr)*	2.67 (1, 4.67)	3.67 (1.33, 12)	-	-
t1/2 (hr)	12.5 (29)	13.8 (53)	-	-

Source: Reviewer's analysis, *Median (Min, Max)

Tasigna is associated with concentration-dependent QT prolongation. Per the label, after a single dose of Tasigna 800 mg (two times the maximum approved recommended dosage) given with a high fat meal to healthy subjects, the maximum mean placebo-adjusted QTcF changes were 18.0 msec (90% CI: 9.65, 25.8). Given higher C_{max} (upper 90% CI of the GMR above 125%) of DANZITEN following single dose administration for the highest dose (95 mg) and lowest dose (71 mg) vs. Tasigna, additional population PK (popPK) analysis was conducted to show no additional QT prolongation risk based on predicted steady state Cmax of Danziten 190 mg that were within those of Tasigna 400 mg under various food conditions (Figure 1; Table 5).

Figure 1. Boxplots of the simulated steady state Cmax for Danziten 190 mg and Tasigna 400 mg under overnight fasted, modified fasting with a low-fat or high-fat meal, and fed conditions



Source: Applicant's PopPK analysis report, Figure 52 on page 300. The box represents the interquartile interval, the black line corresponds to the median. The upper whisker extends to the largest value no further than 1.5x IQR from the hinge. The lower whiskers extend to the smallest value at most 1.5xIQR of the hinge. Boxplots are color coded by product, red for Tasigna and blue for Danziten. Abbreviations: HFM = High Fat Meal; IQR = interquartile range; LFM = Low Fat Meal. Fasted referred to overnight (e.g., at least 10 hours) fasting; Modified fast referred to fasting at least 1 hour before and 2 hours after meal.

Table 5: Simulated steady-state exposures of Danziten vs. Tasigna under overnight fasting conditions

Steady state, BID dosing (PopPK simulated, n = 50) DANZITEN 190 mg / Tasigna 400 mg	
	GMR [90% CI]
Cmax,ss (ng/mL)	1.06 [0.97,1.2]
AUCss (ng*h/mL)	1.04 [0.949,1.17]
Cmin,ss (ng/mL)	1.02 [0.89,1.18]
Steady state, BID dosing (PopPK simulated, n = 50) Nilotinib tablets 142 mg / Tasigna 300 mg	
	GMR [90% CI]
Cmax,ss (ng/mL)	1.06 [0.97,1.17]
AUCss (ng*h/mL)	1.03 [0.95,1.13]
Cmin,ss (ng/mL)	1 [0.888,1.15]

Source: Adapted from Summary of Clinical Pharmacology Studies, Table 2.7.2-1, and Table 2.7.2-5, and Applicant's PopPK analysis report, Table 10.

Refer to Sections 4.2.1, 4.2.2, and 4.2.3 for additional details on the popPK analysis. According to the IRT review, as long as the Cmax,ss from Danziten at the highest therapeutic dose is not higher than the listed product, Tasigna, the previously characterized concentration-QT relationship can be extended to predict the QT effects of Danziten.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes. Dose adjustments are recommended for patients with hepatic impairment (HI).

No dedicated organ impairment studies have been conducted with DANZITEN. The HI information was borrowed from the listed drug based on the establishment of a scientific bridge, and DANZITEN dose adjustments were modified based on the different strengths compared to Tasigna:

- In newly diagnosed Ph+ CML with any HI, it is recommended to reduce DANZITEN dose to 95 mg BID, and then increase to 142 mg BID based on tolerability.
- For patients resistant or intolerant Ph+ CML with mild or moderate HI, it is recommended to reduce DANZITEN dose to 142 mg BID, and subsequently increase to 190 mg BID based on tolerability. For patients resistant or intolerant Ph+ CML with severe HI, it is recommended to reduce DANZITEN dose to 95 mg BID and then increase to 142 mg BID followed by 190 mg BID, based on tolerability.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food Effect

DANZITEN may be taken with or without food based on the conducted single dose food effect studies and supportive popPK analysis of nilotinib steady state PK.

In Study 006-23, the AUC_{0-t} and $AUC_{0-\infty}$ increased by 59% and Cmax increased by 48% when DANZITEN 190 mg (2 x 95 mg tablets) was administered with a high-fat meal (994 calories, 50% fat: 65 g fat, 38 g proteins, and 63 g carbohydrates) compared to DANZITEN administered under overnight fasted conditions (Table 6: Refer to Appendix 4.1 for details). Additionally, the AUC_{0-t}, $AUC_{0-\infty}$, and Cmax

increased by 65% when DANZITEN 190 mg was administered under modified fasting (at least 2 hours after a high-fat meal consisting of 994 calories, 50% fat: 65 g fat, 38 g proteins, and 63 g carbohydrates) compared to DANZITEN under fasted conditions (Table 7: Refer to Appendix 4.1 for details).

Table 6: Summary statistics (Study 006-23, fed, high-fat meal vs fasting)

Parameter (unit)	DANZITEN, 2 x 95 mg (Test, Fed)	DANZITEN 2 x 95 mg (Reference, Fasting)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	28468	17927	1.59	145.80, 172.95
$AUC_{0-\infty}$ (h*ng/mL)	29493	18499	1.59	146.8, 173.16
Cmax (ng/mL)	1244	840	1.48	134.76, 162.91

Source: Reviewer's analysis

Table 7: Summary statistics (Study 006-23, modified fasting vs fasting,)

Parameter (unit)	DANZITEN, 2 x 95 mg (Test, Modified Fasting)	DANZITEN 2 x 95 mg (Reference, Fasting)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	29197	17927	1.63	149.25, 177.71
$AUC_{0-\infty}$ (h*ng/mL)	30561	18499	1.65	151.81, 179.76
Cmax (ng/mL)	1391	840	1.66	150.35, 182.50

Source: Reviewer's analysis

In Study 007-23, the AUC_{0-t} and $AUC_{0-\infty}$ increased by 56% and Cmax increased by 44% when DANZITEN (2 x 71 mg tablets) was administered with a high-fat meal (994 calories, 50% fat: 65 g fat, 38 g proteins, and 63 g carbohydrates) compared to DANZITEN under overnight fasted conditions (Table 8: Refer to Appendix 4.1 for details). Additionally, the AUC_{0-t}, $AUC_{0-\infty}$, and Cmax increased by 62-64% when DANZITEN was administered under modified fasting (at least 2 hours after high-fat meal consisting of 994 calories, 50% fat: 65 g fat, 38 g proteins, and 63 g carbohydrates) compared to DANZITEN under overnight fasted (at least 10 hours prior and 4 hours after dosing) conditions (Table 9: Refer to Appendix 4.1 for details).

Table 8: Summary statistics (Study 007-23, fed, high-fat meal vs fasting)

Parameter (unit)	DANZITEN, 2 x 71 mg (Test, Fed)	DANZITEN 2 x 71 mg (Reference, Fasting)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	20582	13356	1.54	143.14, 165.91
$AUC_{0-\infty}$ (h*ng/mL)	21164	13692	1.58	143.51, 166.48
Cmax (ng/mL)	943	657	1.44	130.56, 157.88

Source: Reviewer's analysis

Table 9: Summary statistics (Study 007-23, modified fasting vs fasting, high-fat meal)

Parameter (unit)	DANZITEN, 2 x 71 mg (Test, Modified Fasting)	DANZITEN 2 x 71 mg (Reference, Fasting)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	21615	13356	1.62	150.33, 174.24
$AUC_{0-\infty}$ (h*ng/mL)	22165	13692	1.62	150.30, 174.35
Cmax (ng/mL)	1078	657	1.64	149.29, 180.54

Source: Reviewer's analysis

Per the label, it is recommended to take Tasigna twice daily at approximately 12-hour intervals on an empty stomach. No food should be consumed for at least 2 hours before the dose is taken and no food should be consumed for at least one hour after the dose is taken. Therefore, the labeling allows modified fasting conditions which includes fasting as well as taking any meal, including a high-fat meal beyond the 3-hour specified fasting window.

To further assess the potential clinical impact of this food effect on Danziten, population PK analysis was conducted which showed steady state AUC (Figure 2), Cmax (Figure 1), and Cmin (Figure 3) of Danziten 190 mg were within those of Tasigna 400 mg under various food conditions. Food increases PK exposures of Danziten as well as Tasigna. The PK exposures of Danziten taken under modified fasting, low fat meal (MF-LFM), modified fasting, high fat meal (MF-HFM), and fed conditions are similar to those of Tasigna taken under MF-LFM and significantly lower than when Tasigna is taken under MF-HFM conditions. Therefore, population PK analysis justifies administration of Danziten with or without food. Refer to Sections 4.2.1, 4.2.2, and 4.2.3 for additional details on the popPK analysis.

During development of Danziten, the Applicant conducted additional studies that compared exposures of Danziten vs. Tasigna under various food conditions. Study 011-22 demonstrated that the bioavailability of DANZITEN, 2 x 95 mg, under fed (high-fat meal) conditions was lower than that of Tasigna, 2 x 200 mg under modified fasting conditions (at least 1 hour before or 2 hours after a high-fat meal). Additionally, the DANZITEN, 2 x 95 mg, under modified fasting conditions (at least 1 hour before or 2 hours after a high-fat meal) was lower than that of Tasigna, 2 x 200 mg, under the same modified fasting conditions. The upper 90% CI of the GMR for primary PK parameters, Cmax (53.45%), AUC_{0-t},(59.27%) and $AUC_{0-\infty}$ (59.29%) were below the bioequivalence limits of 80% (Table 10 and Table 11: refer to Appendix 4.1 for details).

Table 10: Summary statistics for Study 011-22 (fed vs modified fasting, high-fat meal)

Parameter (unit)	DANZITEN, 2 x 95 mg (Test, Fed)	Tasigna 2 x 200 mg (Reference, Modified Fasting)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	24101	43322	0.56	52.22, 59.27
$AUC_{0-\infty}$ (h*ng/mL)	24592	44228	0.56	52.14, 59.29
Cmax (ng/mL)	1236	2496	0.50	45.88, 53.45

Source: Reviewer's analysis

Table 11: Summary statistics for Study 011-22 (modified fasting, high-fat meal)

Parameter (unit)	DANZITEN, 2 x 95 mg (Test, Modified Fasting)	Tasigna 2 x 200 mg (Reference, Modified Fasting)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	23463	43322	0.54	50.80, 57.74
$AUC_{0-\infty}$ (h*ng/mL)	23849	44228	0.54	50.54, 57.74
Cmax (ng/mL)	1316	2496	0.53	48.81, 56.95

Source: Reviewer's analysis

Based on the results of Study 011-22 showing the significant difference in nilotinib exposures under modified fasting conditions that may result in lower efficacy of Danziten vs. Tasigna, Study 052-23 was a follow-up study to address these concerns. Study 052-23 demonstrated that the bioavailability of DANZITEN, 2 x 95 mg was comparable to Tasigna Capsules, 2 x 200 mg, after modified fasting conditions (2 hours after a low-fat meal). The 90% CI of the GMR for primary PK parameters, Cmax, AUC_{0-t}, and $AUC_{0-\infty}$ were within the bioequivalence limits of 80% to 125% (Table 12: refer to Appendix 4.1 for details).

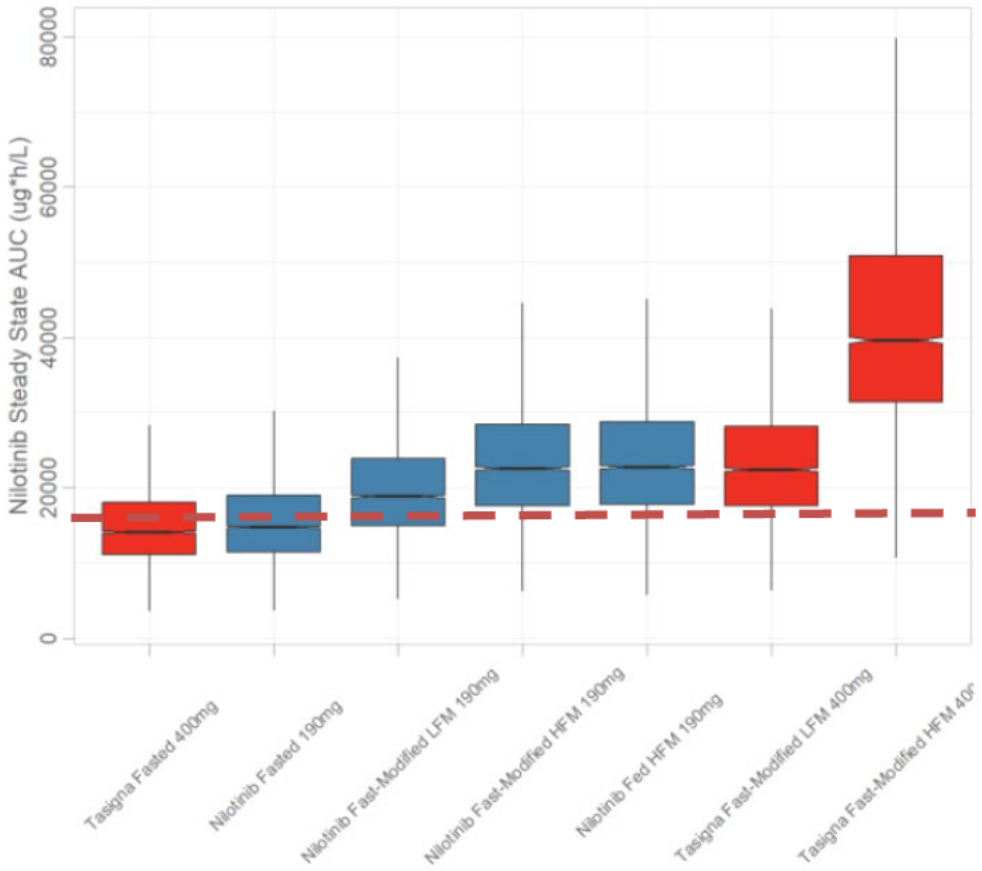
Table 12: Summary statistics for Study 052-23 (modified fasting, low-fat meal)

Parameter (unit)	DANZITEN, 2 x 95 mg (Test, Modified Fasting)	Tasigna 2 x 200 mg (Reference, Modified Fasting)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	22301	26544	0.84	80.08, 88.14
$AUC_{0-\infty}$ (h*ng/mL)	23077	27598	0.84	79.67, 87.76
Cmax (ng/mL)	1213	1429	0.85	80.09, 89.94

Source: Reviewer's analysis

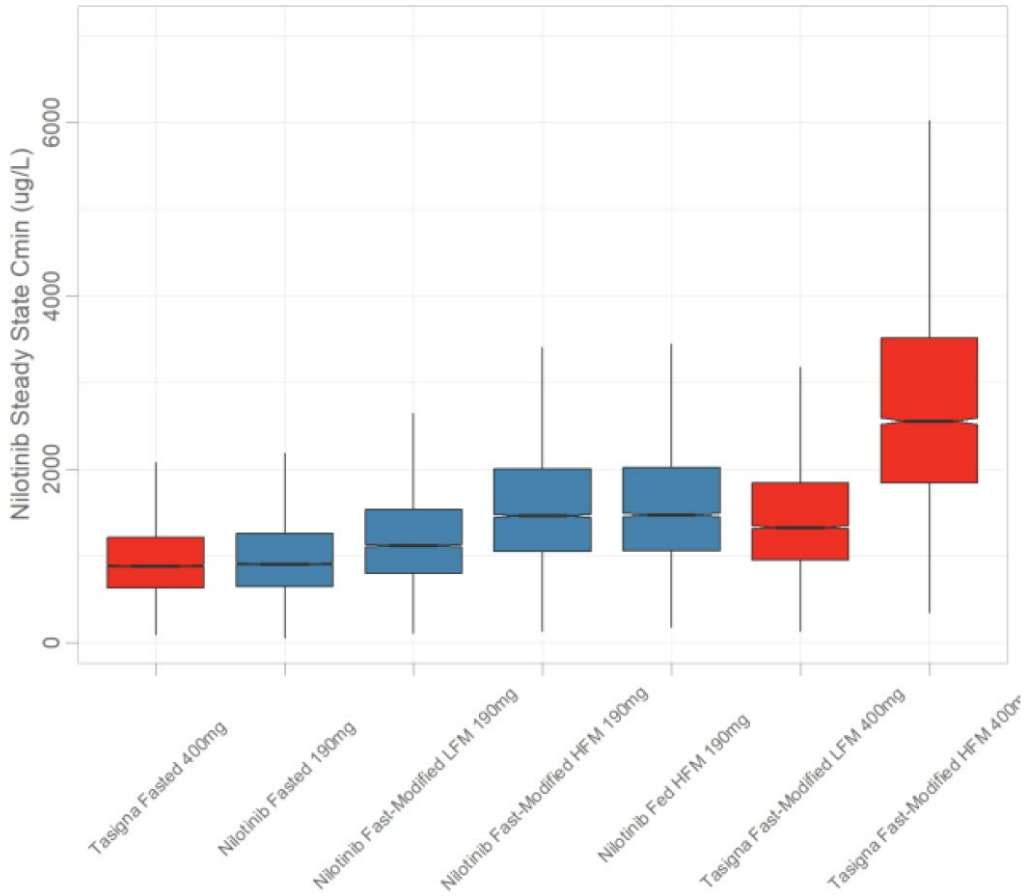
Furthermore, additional popPK analysis was conducted to show minimal concerns for lower efficacy with Danziten vs. Tasigna based on predicted steady state AUC of Danziten 190 mg that were within those of Tasigna 400 mg under various food conditions (Figure 2).

Figure 2. Boxplots of the simulated steady state AUC for Danziten 190 mg and Tasigna 400 mg under overnight fasted, modified fasting with a low-fat or high-fat meal, and fed conditions



Source: Applicant's PopPK analysis report, Figure 52 on page 300. The box represents the interquartile interval, the black line corresponds to the median. The upper whisker extends to the largest value no further than 1.5x IQR from the hinge. The lower whiskers extend to the smallest value at most 1.5xIQR of the hinge. Boxplots are color coded by product, red for Tasigna and blue for Danziten. Abbreviations: HFM = High Fat Meal; IQR = interquartile range; LFM = Low Fat Meal. Fasted referred to overnight (e.g., at least 10 hours) fasting; Modified fast referred to fasting at least 1 hour before and 2 hours after meal. The red dotted line denotes the mean $AUC_{0\text{-}12h,ss}$ (%CV) of 18000 ng·h/mL (33%) obtained from the Tasigna labeling.

Figure 3. Boxplots of the simulated steady state Cmin for Danziten 190 mg and Tasigna 400 mg under overnight fasted, modified fasting with a low-fat or high-fat meal, and fed conditions



Source: Applicant's PopPK analysis report, Figure 52 on page 300. The box represents the interquartile interval, the black line corresponds to the median. The upper whisker extends to the largest value no further than 1.5x IQR from the hinge. The lower whiskers extend to the smallest value at most 1.5xIQR of the hinge. Boxplots are color coded by product, red for Tasigna and blue for Danziten. Abbreviations: HFM = High Fat Meal; IQR = interquartile range; LFM = Low Fat Meal. Fasted referred to overnight (e.g., at least 10 hours) fasting; Modified fast referred to fasting at least 1 hour before and 2 hours after meal.

Drug-Drug Interactions

No drug-drug interaction studies were performed with DANZITEN for this application. The drug-drug interaction information was borrowed from the listed drug based on the establishment of a scientific bridge. Concomitant use of strong CYP3A4 modulators should be avoided with DANZITEN. If concomitant use strong CYP3A4 inhibitors cannot be avoided, DANZITEN dose should be reduced to 142 mg once daily (resistant or intolerant Ph+ CML) or 95 mg once daily (for newly diagnosed Ph+ CML).

Proton pump inhibitors should be avoided. Alternately, H2 blocker may be used ~10 hours before or ~2 hours after DANZITEN dose, or antacids ~2 hours before or ~2 hours after DANZITEN dose.

4. APPENDICES

4.1 Studies Conducted

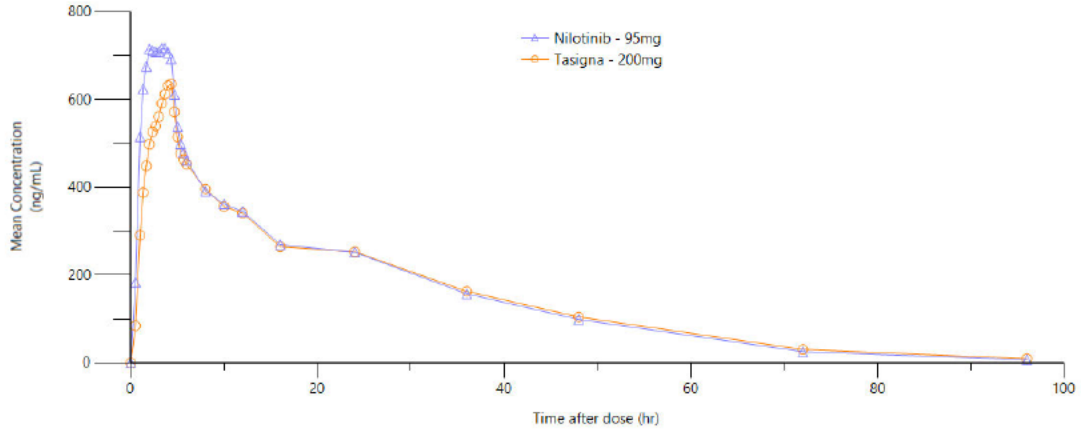
4.1.1 Study 010-22

The Applicant conducted an open label, single-dose, randomized, two-treatment, two-sequence, two-period, single dose fully replicate crossover study to compare the bioavailability of DANZITEN 190 mg (test) against the approved Tasigna® 400 mg (reference) under overnight fasting conditions (Table 13).

Table 13: Design of Study 010-22

<table>
<tr><td>Purpose</td><td colspan="7">Relative bioavailability of DANZITEN, 95 mg (test) against the approved Tasigna®, 200 mg (reference)</td></tr>
<tr><td>Study Design</td><td colspan="7">Randomized, two-treatment, two-sequence, two-period, single dose fully replicate crossover. Washout period of 10-11 days. Subject fasted overnight for at least 10 hours prior to dosing and till 4 hours post dose.</td></tr>
<tr><td>Study Population</td><td colspan="7">96 were enrolled into the study. 92 subjects completed the study.</td></tr>
<tr><td>Proposed Dose</td><td colspan="7">A single oral dose Tasigna® (nilotinib) 2 x 200 mg capsules or DANZITEN, 2 x 95 mg was administered with 240 mL of water.</td></tr>
<tr><td>Instruction for Concomitant Medication (DDI Potential)</td><td colspan="7">• Not to consume drugs known to prolong the QT interval
• Not to consume drugs that strong CYP3A Inhibitors/Inducers
• Not to consume drugs that are proton pump inhibitors (PPI) and to use H2 blockers approximately 10 hours before or 2 hours after the dose</td></tr>
<tr><td>PK Sampling Schedule</td><td colspan="7">Pre-dose, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours post dose</td></tr>
<tr><td>ECG Monitoring Schedule</td><td colspan="7">26 and 21 hours pre-dose, 0, 3 to 4, 96 hrs post-dose</td></tr>
<tr><td>ECG Monitoring Results (Increase in QTcF)</td><td colspan="7"><table>
<tr><th>Dose and Condition</th><th><0 msec</th><th><10 msec</th><th>10-20 msec</th><th>20-30 msec</th><th>30-60 msec</th><th>>60 msec</th></tr>
<tr><td>DANZITEN 190 mg fasted</td><td>30.5% (29/95)</td><td>46.3% (44/95)</td><td>20% (19/95)</td><td>3.2% (3/95)</td><td>0% (0/95)</td><td>0% (0/95)</td></tr>
<tr><td>Tasigna 400 mg fasted</td><td>37.6% (35/93)</td><td>39.8% (37/93)</td><td>18.3% (17/93)</td><td>3.2% (3/93)</td><td>1.1% (1/93)</td><td>0% (0/93)</td></tr>
</table></td></tr>
<tr><td>Safety Signals</td><td colspan="7">• No AEs or SAEs reported.</td></tr>
</table>

Concentration-Time profile for DANZITEN (Nilotinib) 95 mg and Tasigna® 200 mg



Geometric Mean PK Parameters (n=92)

Parameter (unit)	DANZITEN, 2 x 95 mg (Test, %CV)	Tasigna 2 x 200 mg (Reference, %CV)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	13763 (39)	13360 (41)	1.03	97.75, 108.57
$AUC_{0-\infty}$ (h*ng/mL)	14183 (40)	13790 (42)	1.03	97.52, 108.46
Cmax (ng/mL)	760 (38)	637 (40)	1.19	110.99, 128.09
Tmax (hr)*	2.67 (1, 4.67)	4 (1.33, 5.67)	-	-
t1/2 (hr)	13.3 (33)	12.4 (30)	-	-

*Median (Min, Max)

4.1.2 Study 128-22

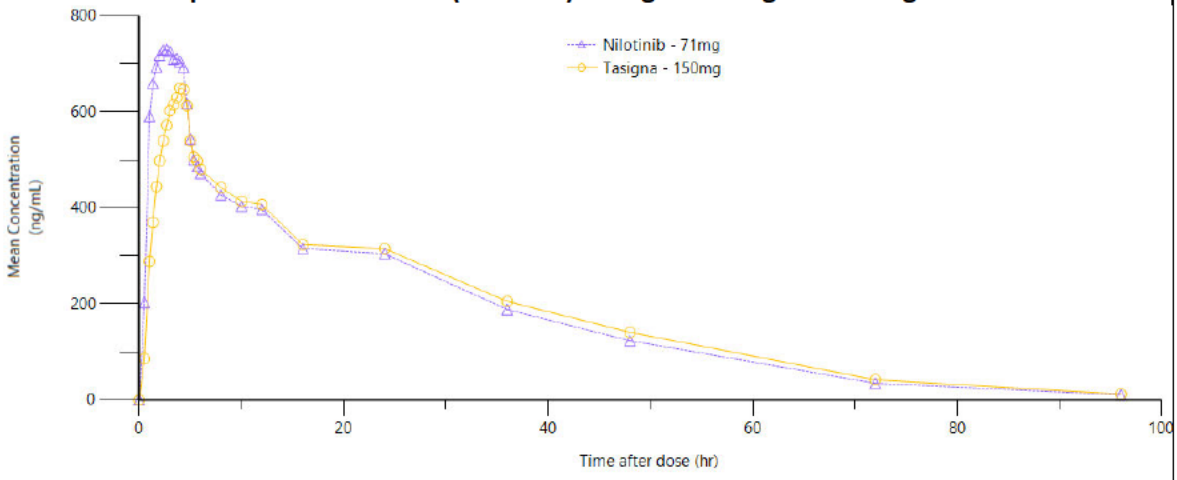
The Applicant conducted an open label, single-dose, randomized, two-treatment, two-sequence, two-period, single dose fully replicate crossover study to compare the bioavailability of DANZITEN 142 mg (test) against the approved Tasigna® (nilotinib) 300 mg (reference) under overnight fasting conditions (Table 14).

Table 14: Design of Study 128-22

Purpose	Relative bioavailability of DANZITEN, 71 mg (test) against the approved Tasigna®, 150 mg (reference)
Study Design	Randomized, two-treatment, two-sequence, two-period, single dose fully replicate crossover. Washout period of 11 days. Subject fasted overnight for at least 10 hours prior to dosing and till 4 hours post dose. Subjects with QT > 440 ms excluded.
Study Population	90 were enrolled into the study. 87 subjects completed the study.
Proposed Dose	A single oral dose Tasigna® 2 x 150 mg capsules or DANZITEN, 2 x 71 mg tablets was administered with 240 mL of water.
Instruction for Concomitant	• Not to consume drugs known to prolong the QT interval • Not to consume drugs that strong CYP3A Inhibitors/Inducers • Not to consume drugs that are proton pump inhibitors (PPI) and to use H2

<table>
<tr><td>Medication (DDI Potential)</td><td>blockers approximately 10 hours before or 2 hours after the dose</td></tr>
<tr><td>PK Sampling Schedule</td><td>Pre-dose, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours post dose</td></tr>
<tr><td>ECG Monitoring Schedule</td><td>0, 3 to 4, 96 hrs post-dose</td></tr>
<tr><td>ECG Monitoring Results (Increase in QTcF)</td><td>
<table>
<tr><th>Dose and Condition</th><th><0 msec</th><th><10 msec</th><th>10-20 msec</th><th>20-30 msec</th><th>30-60 msec</th><th>>60 msec</th></tr>
<tr><td>DANZITEN 142 mg fasted</td><td>28.7% (25/87)</td><td>44.8% (39/87)</td><td>23% (20/87)</td><td>3.4% (3/87)</td><td>0% (0/87)</td><td>0% (0/87)</td></tr>
<tr><td>Tasigna 300 mg fasted</td><td>34.4% (31/90)</td><td>42.2% (38/90)</td><td>21.1% (19/90)</td><td>2.2% (2/90)</td><td>0% (0/90)</td><td>0% (0/90)</td></tr>
</table>
</td></tr>
<tr><td>Safety Signals</td><td>• DANZITEN: Itching all over (n=1), Chest pain (n=1), Pain (n=1), Rash (n=1), Headache (n=1), Loose motions (n=1), Dizziness (n=1).
• Tasigna: Itching all over (n=1), Chest pain (n=1), Rash (n=1), Headache (n=1), Dizziness (n=1), Dry cough (n=1).</td></tr>
</table>

Concentration-Time profile for DANZITEN (Nilotinib) 71 mg and Tasigna® 150 mg



Geometric Mean PK Parameters (n=87)

Parameter (unit)	DANZITEN, 2 x 71 mg (Test, %CV)	Tasigna 2 x 150 mg (Reference, %CV)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	15783 (43)	15841 (44)	1.00	94.03, 105.59
$AUC_{0-\infty}$ (h*ng/mL)	16119 (43)	16990 (51)	0.95	88.30, 101.94
Cmax (ng/mL)	782 (43)	666 (69)	1.17	109.90, 125.43
Tmax (hr)*	2.67 (1, 4.67)	3.67 (1.33, 12)	-	-
t1/2 (hr)	12.5 (29)	13.8 (53)	-	-

*Median (Min, Max)

4.1.3 Study 011-22

The Applicant conducted an open label, single-dose, randomized, three-treatment, three-sequence, three-period, single dose fully replicate three-way crossover study to compare the bioavailability of DANZITEN 190 mg (test) against the approved Tasigna® 400 mg (reference) under modified fasting and fed conditions after a high-fat meal (Table 15).

Table 15: Design of Study 011-22

Purpose	Relative bioavailability of DANZITEN, 95 mg (test) against the approved Tasigna® Capsules, 200 mg (reference) under modified fasting and fed conditions
Study Design	Randomized, three-treatment, three-sequence, three-period, single dose fully replicate three-way crossover. Washout period of 10 days.
Study Population	36 were enrolled into the study. 32 subjects completed all three periods of the study.
Proposed Dose	In two of the groups, either a single oral dose Tasigna® (nilotinib) 2 x 200 mg capsules or a single oral dose of DANZITEN 2 x 95 mg was administered after subjects fasted overnight for 10 hours prior to consuming a high-fat, high calories breakfast and till 4 hours post dose. The drug was administered after 2 hours of consumption. In one of the groups, a single oral dose of DANZITEN 2 x 95 mg was administered after subjects fasted overnight for 10 hours prior to consuming a high-fat, high calories breakfast 30 minutes before dosing and till 4 hours post dose. In all situations, the meals were consumed and completed within 30 minutes. Additionally, the drugs were administered with 240 mL of water.
Instruction for Concomitant Medication (DDI Potential)	• Not to consume drugs known to prolong the QT interval • Not to consume drugs that strong CYP3A Inhibitors/Inducers • Not to consume drugs that are proton pump inhibitors (PPI) and to use H2 blockers approximately 10 hours before or 2 hours after the dose
PK Sampling Schedule	Pre-dose, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours post dose
ECG Monitoring Schedule	26 and 21 hours pre-dose, 0, 5 to 6, 96 hrs post-dose

ECG Monitoring Results (Increase in QTcF)

Dose and Condition	<0 msec	<10 msec	10-20 msec	20-30 msec	30-60 msec	>60 msec
DANZITEN 190 mg modified fasted (HFM)	18.2% (6/33)	51.5% (17/33)	24.2% (8/33)	6.1% (2/33)	0% (0/33)	0% (0/33)
DANZITEN 190 mg fed	32.4% (11/34)	38.2% (13/34)	17.6% (6/34)	11.8% (4/34)	0% (0/34)	0% (0/34)
Tasigna 400 mg modified fasted (HFM)	5.7% (2/35)	14.3% (5/35)	45.7% (16/35)	22.9% (8/35)	5.7% (2/35)	0% (0/35)

Safety Signals	• **DANZITEN**: No AEs reported. • **Tasigna**: Nausea (n=1), Abdominal pain (n=1), Headache (n=2).

Geometric Mean PK Parameters (fed (n=33) vs modified fasting (n=32), high-fat meal)

Parameter (unit)	DANZITEN, 2 x 95 mg (Test, Fed, %CV)	Tasigna 2 x 200 mg (Reference, Modified Fasting, %CV)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	24101 (34)	43322 (28)	0.56	52.22, 59.27
$AUC_{0-\infty}$ (h*ng/mL)	24592 (34)	44228 (30)	0.56	52.14, 59.29
Cmax (ng/mL)	1236 (25)	2496 (26)	0.50	45.88, 53.45
Tmax (hr)*	4.67 (2.67, 10)	4.67 (3.33, 12)	-	-
t1/2 (hr)	12.6 (37)	14.6 (32)	-	-

*Median (Min, Max)

Geometric Mean PK Parameters (fed (n=33) vs modified fasting (n=32), high-fat meal, n=32)

Parameter (unit)	DANZITEN, 2 x 95 mg (Test, Modified Fasting, %CV)	Tasigna 2 x 200 mg (Reference, Modified Fasting, %CV)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	23463 (29)	43322 (28)	0.54	50.80, 57.74
$AUC_{0-\infty}$ (h*ng/mL)	23849 (29)	44228 (30)	0.54	50.54, 57.74
Cmax (ng/mL)	1316 (24)	2496 (26)	0.53	48.81, 56.95
Tmax (hr)*	4.67 (3, 10)	4.67 (3.33, 12)	-	-
t1/2 (hr)	11.9 (32)	14.6 (32)	-	-

*Median (Min, Max)

4.1.4 Study 052-23

The Applicant conducted an open label, single-dose, randomized, two-treatment, two-sequence, two-period, single dose crossover study to compare the bioavailability of DANZITEN 190 mg (test) against the approved Tasigna® 400 mg (reference) under modified fasting conditions after a low-fat meal (Table 16).

Table 16: Design of Study 052-23

Purpose	Relative bioavailability of DANZITEN 190 mg (test) against the approved Tasigna® 400 mg (reference) under modified fasting conditions
Study Design	Randomized, two-treatment, two-sequence, two-period, single dose fully crossover. Washout period of 10 days.
Study Population	90 were enrolled into the study. 86 subjects completed all two periods of the study.
Proposed Dose	In two of the groups, either a single oral dose Tasigna® (nilotinib) 2 x 200 mg capsules or a single oral dose of DANZITEN 2 x 95 mg tablets was administered

<table>
<tr><td></td><td>after subjects fasted overnight for 10 hours prior to consuming a low-fat, high calories breakfast and till 4 hours post dose. The drug was administered after 2 hours of consumption.

In all situations, the meals were consumed and completed within 30 minutes. Additionally, the drugs were administered with 240 mL of water.</td></tr>
<tr><td>Instruction for Concomitant Medication (DDI Potential)</td><td>• Not to consume drugs known to prolong the QT interval
• Not to consume drugs that strong CYP3A Inhibitors/Inducers
• Not to consume drugs that are proton pump inhibitors (PPI) and to use H2 blockers approximately 10 hours before or 2 hours after the dose</td></tr>
<tr><td>PK Sampling Schedule</td><td>Pre-dose, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours post dose</td></tr>
<tr><td>ECG Monitoring Schedule</td><td>0, 5 to 6, and 96 hrs post dose</td></tr>
<tr><td>ECG Monitoring Results (Increase in QTcF)</td><td>
<table>
<tr><th>Dose and Condition</th><th><0 msec</th><th><10 msec</th><th>10-20 msec</th><th>20-30 msec</th><th>30-60 msec</th><th>>60 msec</th></tr>
<tr><td>DANZITEN 190 mg modified fasted (LFM)</td><td>24.7% (22/89)</td><td>46.1% (41/89)</td><td>27% (24/89)</td><td>2.2% (2/89)</td><td>0% (0/89)</td><td>0% (0/89)</td></tr>
<tr><td>Tasigna 400 mg modified fasted (LFM)</td><td>15.3% (13/85)</td><td>58.8% (50/85)</td><td>22.4% (19/85)</td><td>3.5% (3/85)</td><td>0% (0/85)</td><td>0% (0/85)</td></tr>
</table>
</td></tr>
<tr><td>Safety Signals</td><td>• DANZITEN: Itching in lower limb (n=1), Itching of skin (n=1), Backache (n=1), Tachycardia (n=1), Vomiting (n=2), Nausea (n=2), Headache (n=7), Dizziness (n=1).
• Tasigna: Itching all over (n=1), Fever (n=2), Backache (n=2), Body pains (n=1), Vomiting (n=1), Nausea (n=1), Abdominal pain (n=1), Diarrhea (n=1), Aphthous ulcer (n=1), Constipation (n=1), Headache (n=9), Dizziness (n=2), Dry cough (n=1), Cold (n=1).</td></tr>
</table>

Geometric Mean PK Parameters (fed vs modified fasting, low-fat meal, n=86)

Parameter (unit)	DANZITEN, 2 x 95 mg (Test, Modified Fasting, %CV)	Tasigna 2 x 200 mg (Reference, Modified Fasting, %CV)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	22301 (32)	26544 (40)	0.84	80.08, 88.14
$AUC_{0-\infty}$ (h*ng/mL)	23077 (33)	27598 (41)	0.84	79.67, 87.76
Cmax (ng/mL)	1213 (28)	1429 (40)	0.85	80.09, 89.94
Tmax (hr)*	3.33 (1.33, 5.33)	3.33 (1.33, 4.67)	-	-
t1/2 (hr)	14.4 (28)	14.6 (40)	-	-

*Median (Min, Max)

4.1.5 Study 006-23

The Applicant conducted an open label, single-dose, randomized, single-treatment, three-sequence, three-period, single dose three-way crossover study to compare the bioavailability of DANZITEN 190 mg under fasting, fed, and modified fasting conditions after a high-fat meal (Table 17).

Table 17: Design of Study 006-23

Purpose	Relative bioavailability of DANZITEN, 95 mg under fasting, fed and modified fasting conditions
Study Design	Randomized, three-treatment, three-sequence, three-period, single dose fully replicate three-way crossover. Washout period of 10-11 days.
Study Population	36 were enrolled into the study. 30 subjects completed all three periods of the study.
Proposed Dose	In one of the groups, a single oral dose of DANZITEN 2 x 95 mg tablets was administered after subjects fasted overnight for 10 hours prior to consuming a high-fat, high calories breakfast and till 4 hours post dose. The drug was administered after 2 hours of consumption. In one of the groups, a single oral dose of DANZITEN 2 x 95 mg tablets was administered after subjects fasted overnight for 10 hours prior to consuming a high-fat, high calories breakfast 30 minutes before dosing and till 4 hours post dose. In the final group, a single oral dose of DANZITEN 2 x 95 mg tablets was administered after subjects fasted overnight for 10 hours prior to dosing and till 4 hours post dose. Meals were consumed and completed within 30 minutes. Additionally, the drugs were administered with 240 mL of water.
Instruction for Concomitant Medication (DDI Potential)	• Not to consume drugs known to prolong the QT interval • Not to consume drugs that strong CYP3A Inhibitors/Inducers • Not to consume drugs that are proton pump inhibitors (PPI) and to use H2 blockers approximately 10 hours before or 2 hours after the dose
PK Sampling Schedule	Pre-dose, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours post dose
ECG Monitoring Schedule	0, 3 to 4 (fasting), 5 to 6 (fed and modified fasting), 96 hrs post-dose

ECG Monitoring Results (Increase in QTcF)

Dose and Condition	**<0 msec**	**<10 msec**	**10-20 msec**	**20-30 msec**	**30-60 msec**	**>60 msec**
DANZITEN 190 mg fasted	15.6% (5/32)	59.4% (19/32)	18.8% (6/32)	6.3% (2/32)	0% (0/32)	0% (0/32)
DANZITEN 190 mg modified fasted (HFM)	24.2% (8/33)	51.5% (17/33)	21.2% (7/33)	3% (1/33)	0% (0/33)	0% (0/33)

	DANZITEN 190 mg fed	61.8% (21/34)	32.4% (11/34)	2.9% (1/34)	2.9% (1/34)	0% (0/34)	0% (0/34)
Safety Signals	• **DANZITEN**: Itching in lower limb (n=1), Fever (n=2), Tachycardia (n=1), Vomiting (n=2), Nausea (n=2), Headache (n=2).						

Geometric Mean PK Parameters (fed (n=33) vs fasting (n=32), high-fat meal)

Parameter (unit)	DANZITEN, 2 x 95 mg (Test, Fed, %CV))	DANZITEN 2 x 95 mg (Reference, Fasting, %CV))	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	28468 (30)	17927 (43)	1.59	145.80, 172.95
$AUC_{0-\infty}$ (h*ng/mL)	29493 (31)	18499 (41)	1.59	146.8, 173.16
Cmax (ng/mL)	1244 (29)	840 (46)	1.48	134.76, 162.91
Tmax (hr)*	4.67 (1.67, 12)	2.5 (1, 6)	-	-
t1/2 (hr)	14.7 (30)	13.5 (40)	-	-

*Median (Min, Max)

Geometric Mean PK Parameters (modified fasting (n=31) vs fasting (n=32), high-fat meal)

Parameter (unit)	DANZITEN, 2 x 95 mg (Test, Modified Fasting, %CV)	DANZITEN 2 x 95 mg (Reference, Fasting, %CV)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	29197 (26)	17927 (43)	1.63	149.25, 177.71
$AUC_{0-\infty}$ (h*ng/mL)	30561 (28)	18499 (41)	1.65	151.81, 179.76
Cmax (ng/mL)	1391 (25)	840 (46)	1.66	150.35, 182.50
Tmax (hr)*	4.67 (2.33, 12)	2.5 (1, 6)	-	-
t1/2 (hr)	16.0 (27)	13.5 (40)	-	-

*Median (Min, Max)

4.1.6 Study 007-23

The Applicant conducted an open label, single-dose, randomized, single-treatment, three-sequence, three-period, single dose three-way crossover study to compare the bioavailability of DANZITEN 142 mg under fasting, fed, and modified fasting conditions after a high-fat meal (Table 18).

Table 18: Design of Study 007-23

Purpose	Relative bioavailability of DANZITEN 142 mg under fasting, fed and modified fasting conditions
Study Design	Randomized, three-treatment, three-sequence, three-period, single dose fully replicate three-way crossover. Washout period of 10 days.
Study Population	36 were enrolled into the study. 32 subjects completed all three periods of the study.

<table>
<tr><td>Proposed Dose</td><td>In one of the groups, a single oral dose of DANZITEN 2 x 71 mg tablets was administered after subjects fasted overnight for 10 hours prior to consuming a high-fat, high calories breakfast and till 4 hours post dose. The drug was administered after 2 hours of consumption.

In one of the groups, a single oral dose of DANZITEN 2 x 71 mg tablets was administered after subjects fasted overnight for 10 hours prior to consuming a high-fat, high calories breakfast 30 minutes before dosing and till 4 hours post dose.

In the final group, a single oral dose of DANZITEN 2 x 71 mg tablets was administered after subjects fasted overnight for 10 hours prior to dosing and till 4 hours post dose.

Meals were consumed and completed within 30 minutes. Additionally, the drugs were administered with 240 mL of water.</td></tr>
<tr><td>Instruction for Concomitant Medication (DDI Potential)</td><td>• Not to consume drugs known to prolong the QT interval
• Not to consume drugs that strong CYP3A Inhibitors/Inducers
• Not to consume drugs that are proton pump inhibitors (PPI) and to use H2 blockers approximately 10 hours before or 2 hours after the dose</td></tr>
<tr><td>PK Sampling Schedule</td><td>Pre-dose, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours post dose</td></tr>
<tr><td>ECG Monitoring Schedule</td><td>0, 3 to 4 (fasting), 5 to 6 (fed and modified fasting), 96 hrs post-dose</td></tr>
<tr><td>ECG Monitoring Results (Increase in QTcF)</td><td>
<table>
<tr><th>Dose and Condition</th><th><0 msec</th><th><10 msec</th><th>10-20 msec</th><th>20-30 msec</th><th>30-60 msec</th><th>>60 msec</th></tr>
<tr><td>DANZITEN 142 mg fasted</td><td>29.4% (10/34)</td><td>41.2% (14/34)</td><td>20.6% (7/34)</td><td>8.8% (3/34)</td><td>0% (0/34)</td><td>0% (0/34)</td></tr>
<tr><td>DANZITEN 142 mg modified fasted (HFM)</td><td>21.2% (7/33)</td><td>42.4% (14/33)</td><td>33.3% (11/33)</td><td>3% (1/33)</td><td>0% (0/33)</td><td>0% (0/33)</td></tr>
<tr><td>DANZITEN 142 mg fed</td><td>61.8% (21/34)</td><td>23.5% (8/34)</td><td>11.8% (4/34)</td><td>2.9% (1/34)</td><td>0% (0/34)</td><td>0% (0/34)</td></tr>
</table>
</td></tr>
<tr><td>Safety Signals</td><td>• DANZITEN: Uneasiness (n=1), Giddiness (n=1), Generalized weakness (n=1), Headache (n=2), Heaviness in head (n=1), Dry cough (n=1).</td></tr>
</table>

Geometric Mean PK Parameters (fed vs fasting, high-fat meal, n=32)

Parameter (unit)	DANZITEN, 2 x 71 mg (Test, Fed, %CV)	DANZITEN 2 x 71 mg (Reference, Fasting, %CV)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	20582 (28)	13356 (26)	1.54	143.14, 165.91
$AUC_{0-\infty}$ (h*ng/mL)	21164 (29)	13692 (25)	1.58	143.51, 166.48
Cmax (ng/mL)	943 (16)	657 (39)	1.44	130.56, 157.88
Tmax (hr)*	4.84 (2.33, 10)	2.33 (1, 4.67)	-	-
t1/2 (hr)	13.2 (31)	13.0 (24)	-	-

*Median (Min, Max)

Geometric Mean PK Parameters (modified fasting vs fed, high-fat meal, n=32)

Parameter (unit)	DANZITEN, 2 x 71 mg (Test, Modified Fasting, %CV)	DANZITEN 2 x 71 mg (Reference, Fasting, %CV)	GMR of Test / Reference	90% Confidence Interval of Ratio
AUC_{0-t} (h*ng/mL)	21615 (27)	13356 (26)	1.62	150.33, 174.24
$AUC_{0-\infty}$ (h*ng/mL)	22165 (27)	13692 (25)	1.62	150.30, 174.35
Cmax (ng/mL)	1078 (22)	657 (39)	1.64	149.29, 180.54
Tmax (hr)*	4.67 (2.67, 8)	2.33 (1, 4.67)	-	-
t1/2 (hr)	13.6 (31)	13.0 (24)	-	-

*Median (Min, Max)

Overall, there were no cases of QTcF increase from baseline of > 30 ms or > 60 ms or absolute QTcF of greater than 500 ms with Danziten in the above listed studies. It is noted that some instances of higher incidences of QTcF increase from baseline of < 10 ms, 10-20 ms, and 20-30 ms were observed with Danziten vs. Tasigna in the studies. The risk of QTc prolongation with nilotinib has been previously characterized for Tasigna in a thorough QT study in healthy volunteers at lower concentrations and in patients at higher doses. According to the IRT review, as long as the Cmax,ss from Danziten at the highest therapeutic dose is not higher than the listed product, Tasigna, the previously characterized concentration-QT relationship can be extended to predict the QT effects of Danziten.

Details of the following 8 pilot studies conducted with pilot formulations that are not intended to be marketed are not included. According to the Applicant, the total excipient differences on a %w/w basis between the pilot formulations and the to-be-marketed formulation do not exceed (b) (4)%.

- 033-18 [fasting and fed study (Danziten vs. Tasigna): 50mg vs. 50mg]

- 075-20 [fasting and fed study (Danziten vs. Tasigna): 2x150mg vs 2x200mg]
- 108-21 [fasting study (Danziten vs. Tasigna): 2x120mg vs 2x200mg]
- 109-21 [fasting study (Danziten vs. Tasigna): 120mg vs 200mg]
- 032-21 [fasting and fed study (Danziten): 2x120mg vs 2x200mg]
- 135-21 [fasting study (Danziten vs. Tasigna): 2x90mg vs 2x150mg]
- 136-21 [fasting study (Danziten vs. Tasigna): 2x105mg vs 2x200mg]
- 148-21 [fasting study (Danziten vs. Tasigna): 2x100mg vs 2x200mg]

4.2 Population PK and/or PD Analyses

Review Summary:

Applicant conducted a population PK (PopPK) analysis using the PK data from 14 BE/BA studies to assess the impact of potential covariates on the PK of Danziten (hereafter referred to as nilotinib tablets) and Tasigna and to predict nilotinib exposure at steady-state under various scenarios (i.e., taken as nilotinib tablets or Tasigna under different food conditions such as overnight fasting, modified fasting with low-fat meal [MF-LFM], modified fasting with high-fat meal [MF-HFM], and fed condition).

Applicant's PopPK analysis adequately described the observed PK data from the BE/BA studies and captured the food effects observed in the BE/BA studies. The simulated steady-state exposures of nilotinib tablets taken under overnight fasting, MF-LFM, MF-HFM, and fed conditions are comparable to those of Tasigna taken under overnight fasting, MF-LFM, and MF-HFM. Overall, the PopPK analysis results support a scientific bridge between nilitonib Tablet at the proposed dosage (142 mg BID and 190 mg BID with or without food) and Tasigna at the labeled dosage (300 mg BID and 400 mg BID with the recommended food condition "No food should be consumed for at least 2 hours before the dose is taken and for at least 1 hour after the dose is taken"). The results also suggest that no additional risk of QT prolongation is expected when nilotinib tablets at the proposed dosages are administered with or without food. The assessment of credibility of the PopPK approach in this submission is summarized in the table below.

Summary of Risk-Informed Credibility of PopPK analysis	
Question of interest	• Is a scientific bridge established between nilotinib tablets (the proposed drug) and Tasigna (the listed drug)? • Can the proposed drug (nilotinib tablet) be administered with food without posing an additional risk of QT prolongation?
Context of use	• To predict the steady-state PK exposures of nilotinib tablets (the proposed drug) and Tasigna under various food conditions

Model influence	Moderate
	• The PopPK analysis results were to provide supportive evidence on the establishment of scientific bridging, and to inform the labeling language regarding the food effect on PK and the risk of QT prolongation.
	  • The PopPK approach assumed that the PK of multiple-dose administration at steady state can be predicted from the PopPK model developed only based on the PK data following single-dose administration. The level of uncertainty depends on the robustness in characterization of the nonlinear PK.
	  • The data source is considered reliable as rich PK sampling was collected and food consumption was controlled in the BA/BE studies included in the PopPK dataset.

Decision consequence	Moderate • Patients may be associated with moderate risk on QT prolongation, if the decision on the food effect based on the totality of evidence is inaccurate.
Model risk	Moderate: The rating is determined based on moderate rating for both model influence and decision consequence.

4.2.1 Summary of Applicant's PopPK analysis

The objectives of PopPK analysis were (1) to develop a PopPK model for nilotinib using all available PK study data and to assess the impact of potential covariates on the PK of the proposed drug, nilotinib tablets and the listed drug, Tasigna, (2) to predict nilotinib exposure under multiple scenarios (i.e., nilotinib tablets or Tasigna, under different food conditions and therapeutic dosing regimens) and summarize the distribution of key exposure metrics, and (3) to compare the steady-state PK following an overnight fasted dosing of nilotinib tablet and Tasigna at high and low therapeutic doses. The PK data

from the following bioavailability (BA)/bioequivalence (BE) studies were used for the PopPK analysis:

Study Number[a]	Study Design, Objective, Population	Number of Subjects	Dose and Regimen	Prandial State
033-18	Three-way cross-over; Relative BA; Healthy male subjects	18	50 mg tablet nilotinib tartarate vs 50 mg capsule Tasigna®, single dose	Fasted or fed*
075-20	Three-way cross-over; Relative BA; Healthy male subjects	30	300 mg (2 x 150 mg) tablets nilotinib tartarate vs 400 mg (2 x 200 mg) capsules Tasigna®, single dose	Fasted, fed*, Modified fasted*
032-21	Three-way cross-over; Relative BA; Healthy male subjects	30	240 mg (2 x 120 mg) tablets nilotinib tartarate vs 400 mg (2 x 200 mg) capsules Tasigna®, single dose	Fasted, fed*, Modified fasted*
108-21	Two-way cross-over; Relative BA; Healthy male subjects	16	240 mg (2 x 120 mg) tablets nilotinib tartarate vs 400 mg (2 x 200 mg) capsules Tasigna®, single dose	Fasted
109-21	Two-way cross-over; Relative BA; Healthy male subjects	16	120 mg tablet nilotinib tartarate vs 200 mg capsule Tasigna®, single dose	Fasted
135-21	Two-way cross-over; Relative BA; Healthy male subjects	16	180 mg (2 x 90 mg) tablets nilotinib tartarate vs 300 mg (2 x 150 mg) capsules Tasigna®, single dose	Fasted

Study Number[a]	Study Design, Objective, Population	Number of Subjects	Dose and Regimen	Prandial State
136-21	Two-way cross-over; Relative BA; Healthy male subjects	14	210 mg (2 x 105 mg) tablets nilotinib tartarate vs 400 mg (2 x 200 mg) capsules Tasigna®, single dose	Fasted
148-21	Two-way cross-over; Relative BA; Healthy male subjects	14	200 mg (2 x 100 mg) tablets nilotinib tartarate vs 400 mg (2 x 200 mg) capsules Tasigna®, single dose	Fasted
010-22	Two-way cross-over; Relative BA; Healthy male subjects	96	190 mg (2x 95 mg) tablets nilotinib tartarate vs 400 mg (2 x 200 mg) capsules Tasigna®, single dose	Fasted
011-22	Three-way cross-over; Relative BA; Healthy male subjects	36	190 mg (2x 95 mg) tablets nilotinib tartarate vs 400 mg (2 x 200 mg) capsules Tasigna®, single dose	Fed*, modified fasted*
128-22	Two-treatment, two-period, two-sequence, crossover, fasted oral relative bioavailability study in healthy male and females	90	I: Test product, 142 mg (2×71 mg Nilotinib Tablets); Fasted II: Reference product, 300 mg (2×150 mg Tasigna® capsules); Fasted	Fasted
006-23	Three-treatment, three-period, three-sequence, three-way crossover oral food-effect study in healthy male and females	36	I: Test product, 190 mg (2×95 mg Nilotinib Tablets); Fasted II: Test product, 190 mg (2×95 mg Nilotinib Tablets); Modified fasted III: Test product, 190 mg (2×95 mg Nilotinib Tablets); Fed	Fasted or Fed* or modified fasted*
007-23	Three-treatment, three-period, three-sequence, three-way crossover oral food-effect study in healthy male and females	36	I: Test product, 142 mg (2×71 mg Nilotinib Tablets); Fasted II: Test product, 142 mg (2×71 mg Nilotinib Tablets); Modified fasted III: Test product, 142 mg (2×71 mg Nilotinib Tablets); Fed	Fasted or Fed* or modified fasted*
052-23	Two-treatment, two-period, two-sequence, crossover, oral relative	90	I: Test product, 190 mg (2×95 mg Nilotinib Tablets); Modified fasted low-fat meal	Modified fasted (low fat meal)[$]

Reviewer comments: Data sources is adequate. All the studies are from BE/BA studies with intense PK samplings and tightly controlled food consumption.

Methods

Base model: The initial model was developed using the PK data under fasted conditions from 10 clinical BA/BE studies (033-18, 075-20, 032-21, 108-21, 109-21, 135-21, 136-21, 148-21, 010- 22, 011-22). The base model was 2-compartment model with a zero-order absorption with a lag-time. The differences by formulation (nilotinib tablets vs Tasigna) were quantified both on relative bioavailability (F1) and duration of zero-order absorption (D1). Non-linear PK was described by including a dose effect on F1 using a power relationship as the following equations:

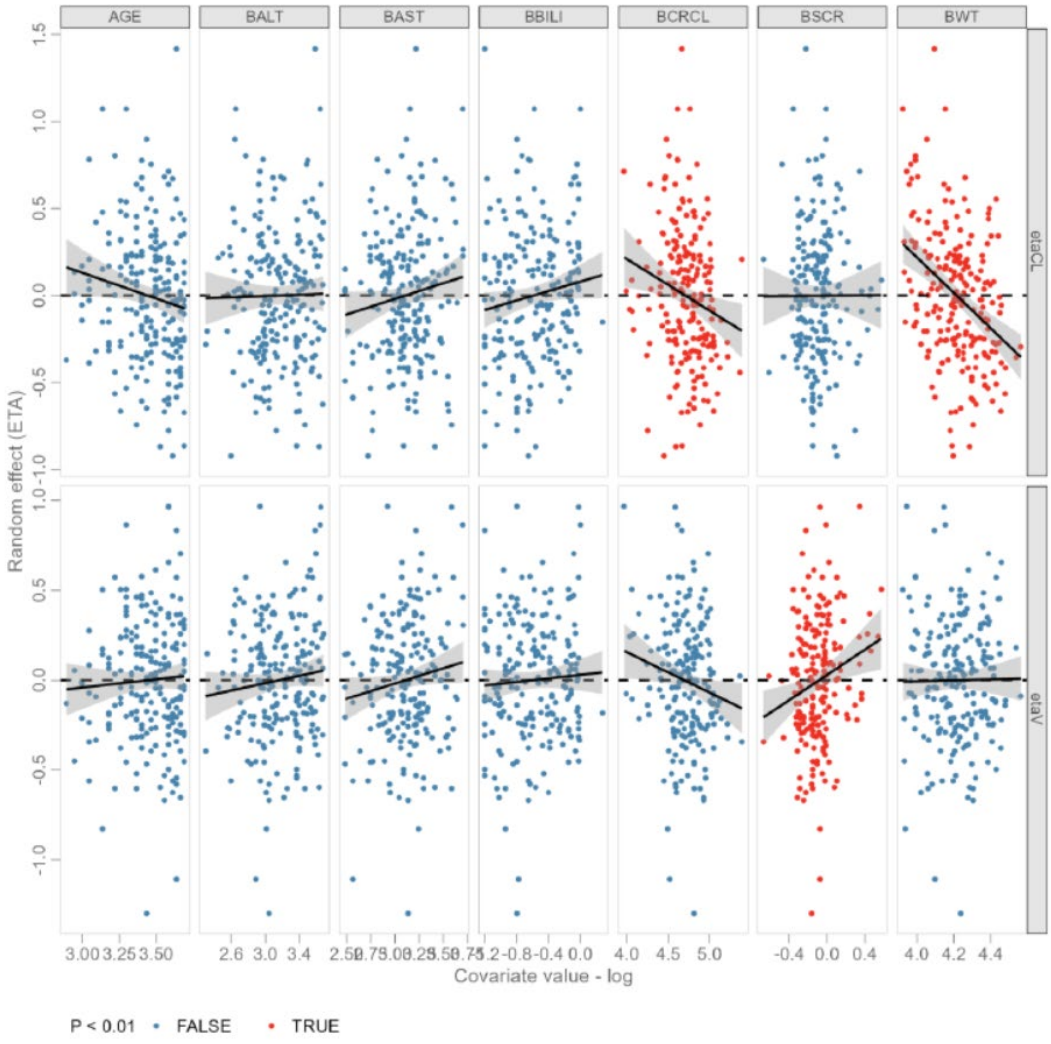
- For Tasigna
  - $F1$ (T$asigna$) = 1 × ($DOSE/$400)^θ10
- For nilotinib tablets,
  - when dose ≤ 200 mg: $F1$ (nilotinib tablet) = 1 × (1 + θ6) × ($DOSE/$200)^θ10
  - when dose > 200 mg: $F1$ (nilotinib tablet) = 1 × (1 + θ6)

  (θ6 and θ10 are the parameter names to be estimated by PopPK analysis)

The increase in nilotinib concentrations observed at approximately 12 and 24 hours after the dose was described by introducing additional doses via a secondary depot compartment. The interindividual variability (IIV) was estimated for CL and V1. Including IIV was not supported on lag time, D1, Q or V2, resulting in large residual standard of error (RSE) and model instability. A combined (additive and proportional) error model was used to describe the residual variability. Inter-occasional variability (IOV) on V1 were included as it provided the largest decrease in objective function values (OFV) while maintaining overall model stability.

Covariate analysis: The following covariates were graphically evaluated based on η-covariate plots for CL and V: body weight, age, sex, creatinine clearance, total bilirubin, ALT, AST, test/reference formulation, formulation lot number, nilotinib dose. Body weight and creatinine clearance were the only two covariates showing a statistically significant trend against CL (**Figure 4**). Therefore, using the base model, body weight and creatinine clearance were formally evaluated in the stepwise covariate analysis, which identified body weight as the significant covariate on CL. The correlation between CL and V1 was addressed by inclusion of an omega block between the two parameters.

Figure 4. η – covariate plot in the base popPK model



Source: Applicant's PopPK analysis report, Figure 31 on page 114.

Final model: The final model was further updated by including all data available across the 13 studies, which included the PK data of nilotinib tablet under fed or MF-HFM conditions and those of Tasigna under MF-HFM. The final PK analysis dataset included 25472 PK observations from 412 subjects including 39 female subjects. Individual effects of food on F1 were quantified by formulation (nilotinib tablet vs. Tasigna) and dose level. Sex was tested on CL and a separate F1 was estimated in female participants receiving nilotinib tablets under fasted conditions.

Updated model with the date from study 052-23: The model was further updated by including the data from Study 052-23 that evaluated the influence of modified fasted with high fat meal (MF-LFM) conditions for both nilotinib tablets (190 mg dose) and Tasigna (400 mg dose).

Results

The final updated PK analysis dataset included 30089 PK observations from 502 subjects. The observations below the low limit of quantification (BLQ) (n=1311, 4.4%) after the first dose were excluded from the analysis. In the PopPK population, all subjects (n= 502, 100%) were Asian and healthy volunteers. Majority of patients were male (n = 433, 86.3%). The summary statistics of continuous covariates of the PK dataset is presented in Table 19.

Table 19: Summary of covariates in the final PopPK analysis population

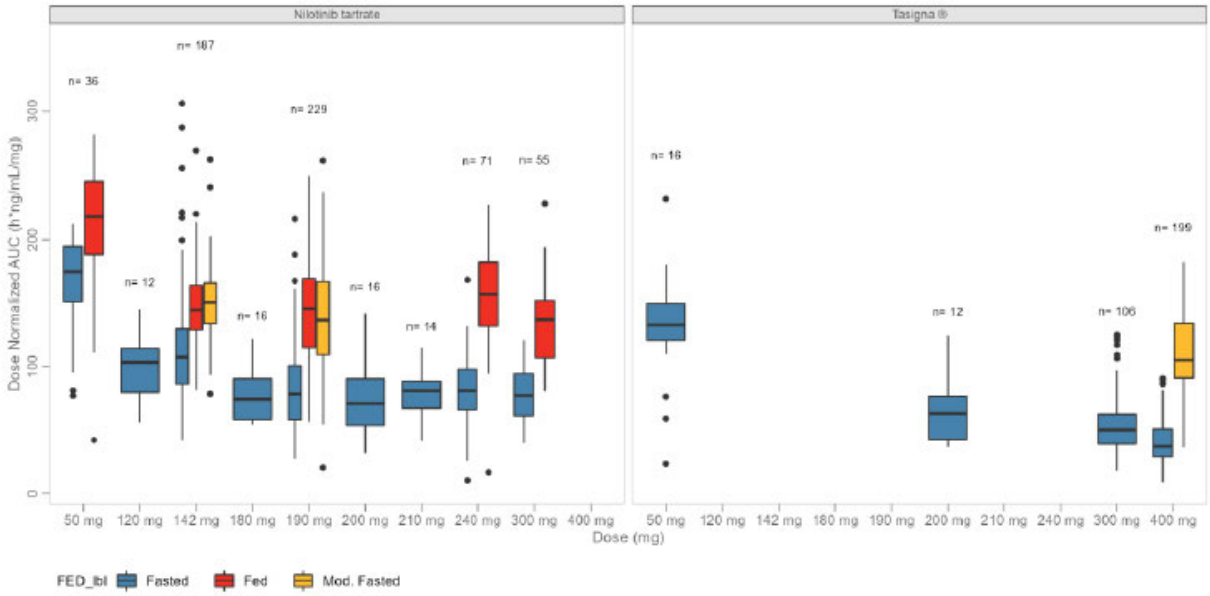
	N	Mean (SD)	Median (min – MAX)
Age (years)	502	31.6 (5.38)	32.0 (18.0 - 42.0)
Baseline Body Weight (kg)	502	67.2 (9.44)	67.0 (45.8 - 95.8)
Baseline Body Height (cm)	502	165 (7.48)	166 (140 - 184)
Baseline Body Mass Index (kg/m²)	501	24.6 (2.92)	24.6 (18.6 - 29.9)
Baseline Alanine aminotransferase (U/L)	502	22.8 (8.31)	21.0 (6.39 - 41.8)
Baseline Aspartate aminotransferase (U/L)	502	20.2 (7.14)	19.2 (0.780 - 42.3)
Baseline Creatinine (µmol/L)	495	0.856 (0.157)	0.840 (0.500 - 1.78)
Baseline Bilirubin (mg/dL)	501	0.571 (0.214)	0.510 (0.170 - 1.32)
Baseline Creatinine clearance (mL/min)	495	119 (24.5)	116 (54.2 - 220)

Source: Adapted from Applicant's PopPK analysis report, Table 13 on page 59.

Reviewer's comment: There are sufficient number of subjects providing PK data under different food conditions. PK data were collected from 407, 176, 129, and 90 subjects under fasted, fed, MF-HFM, and MF-LFM respectively

The dose normalized AUC by dose and food status (**Table 20**) shows non-linearity in the dose below 200 mg for nilotinib tablet and all dose levels for Tasigna (50 to 400 mg). The exposures increase under fed or modified fasted conditions as compared to fasted conditions at same dose levels, however, food effect is more pronounced at higher dose (e.g., 190 mg, 240 mg) compared to lower dose (e.g., 50 mg).

Table 20: Dose-normalized AUC for nilotinib tablet (left panel) and Tasigna (right panel) by dose, and food condition



Source: Applicant's PopPK analysis report, Figure 3 on page 35.

A 2-compartment model with linear elimination and zero order absorption with lag-time was found to best describe nilotinib PK data. The estimates for structural parameters, covariate effect parameters, and random effect parameters from the final PopPK model are presented in **Table 21**, **Table 22** and **Table 23**, respectively. The goodness of fit (GOF) plots and the prediction corrected visual predictive check (pcVPC) plots are shown in **Figure 5, Figure 6, Figure 7, Figure 8, and Figure 9**. The final PopPK model was further updated by including the data from Study 052-23 that evaluated effects of MF-LFM on the bioavailability (F1) of the two products relative to their reference BA under fasted conditions. The effects on absorption parameters such as D1 and lag-time were also estimated. The parameter estimates from the updated PopPK analysis are presented in **Table 21**. The summary of the key PK characteristics quantified by the updated PopPK analysis is following:

- Dose dependent absorption was characterized by including a dose effect on F1, which resulted in higher relative bioavailability (BA) at decreasing doses. For Tasigna, PK exposure was less than dose proportional within the dose range available (50 to 400 mg), whereas, for nilotinib Tablets, PK was found to remain dose proportional at doses greater than 200 mg.
- Formulation effects (nilotinib tablets vs. Tasigna) were included on both F1 and D1. Nilotinib tablets was found to have 99.2% increase in F1 at 200 mg as compared to Tasigna 400 mg, and faster rate of absorption with a 43.2% reduction in D1.
- In the presence of food, the rate of absorption was slower with a delayed lag-time for both nilotinib tablet and Tasigna. However, food was found to increase relative BA in a dose-dependent fashion with larger impact at increasing doses. The followings are summary of the PopPK estimated food effect on relative BA (F1) from the updated model:
    - Fed vs. overnight fasting
        - The BA increases by 46.7% for nilotinib tablets 142 mg

        - The BA increases by 60.4% for nilotinib tablets 190 mg
    - MF-HFM vs. overnight fasting
        - The BA increases by 57.1% for nilotinib tablets 142 mg
        - The BA increases by 59.0% for nilotinib tablets 190 mg
        - The BA increases by 179% for Tasigna 400 mg
    - MF-LFM vs. overnight fasting
        - The BA increases by 29.4% for nilotinib tablets 190 mg
        - The BA increases by 51.2% for Tasigna 400 mg
- Body weight and sex were found to have statistically significant effects on nilotinib CL. Female participants receiving nilotinib tablets under fasted conditions were found to have an 11.1% increase in relative BA as compared to male participants receiving nilotinib tablets under fasted conditions. No differences between male and female were observed under fasted conditions for Tasigna or under fed conditions for both nilotinib tablets and Tasigna.
- For describing the increase in concentrations observed at approximately 12 and 24 hours after dose, the fraction of the dose being absorbed via the secondary depot was 11% of the relative BA, and the absorption process was described by a first-order rate with lag-time.

Table 21: PopPK model estimates for structural parameters

	Applicant's final model	**Applicant's updated PopPK analysis**	**Reviewer's sensitivity analysis**
Data	13 BA/BE studies	13 BA/BE studies + Study 052-23	6 BA/BE studies using TBM formulation
Parameters	Estimate (%RSE)	Estimate (%RSE)	Estimate (%RSE)
Clearance (CL) (L/h)	34.5 (2.85%)	34.3 (3.18%)	34.9 (4.9)
Central volume (V1) (L)	557 (2.66%)	551 (2.71%)	563 (4.2)
Absorption lag (ALAG1) (h)	0.0988 (14.8%)	0.0866 (21%)	0.105 (29.9)
Inter-compartmental clearance (Q)	4.54 (16.6%)	5.56 (19.1%)	4.63 (36.5)
Peripheral volume (V2) (L)	223 (8.78%)	217 (6.74%)	200 (9.1)
Duration of absorption (D1) (h)	2.32 (1.63%)	2.41 (1.61%)	2.43 (2.2)
Absorption from secondary depot (1/h)	0.140 (5.46%)	0.141 (6.16%)	0.128 (11.9)
Fraction re-absorbed from secondary depot (proportional)	-0.888 (0.656%)	-0.890 (0.681%)	-0.892 (0.8)
Absorption lag re-absorbed from secondary depot (h)	5.35 (6.24%)	4.72 (5.58%)	4.35 (6.6)

Source: Reviewer's analysis and Applicant's analysis resutls from Applicant's PopPK analysis report, Table 9 on page 47-48, Table 14 on page 63-64.

Table 22: PopPK model estimates for covariate effect parameters

	Applicant's final model	**Applicant's PopPK analysis**	**Reviewer's sensitivity analysis**
Parameters	Estimate (%RSE)	Estimate (%RSE)	Estimate (%RSE)
Formulation (nilotinib Tablets) effect on F1 (proportional)	0.988 (3.84%)	0.992 (3.84%)	1.06 (5%)
Dose effect on F1 (power)	-0.701 (6.79%)	-0.698 (6.79%)	-0.755 (24.4%)
Formulation (nilotinib Tablets) effect on D1 (proportional)	-0.423 (3.21%)	-0.432 (3.03%)	-0.503 (4.5%)
Bodyweight covariate effect on CL (power)	-0.727 (13.4%)	-0.670 (14.0%)	-0.637 (18.8%)
Food (**MF-HFM**) effect on F1 for Tasigna (proportional)	1.81 (7.19%)	1.79 (7.15%)	1.79 (10.4%)
Food (**Fed**) effect on F1 for nilotinib Tablets (proportional)			
at 50 mg	0.166 (33.9%)	0.155 (36.1%)	-
at 142 mg	0.484 (11.4%)	0.467 (11.6%)	0.436 (12.7%)
at 190 mg	0.617 (13.1%)	0.604 (13.2%)	0.554 (16.3%)
at 240 mg	0.748 (10.0%)	0.733 (10.0%)	-
at 300 mg	0.614 (12.0%)	0.610 (12.0%)	-
Food (**MF-HFM**) effect on F1 at 142 mg nilotinib tablets (proportional)	0.585 (10.1%)	0.571 (10.1%)	0.536 (11.1%)
Food (**MF-HFM**) effect on F1 at 190 mg nilotinib tablets (proportional)	0.603 (12.0%)	0.590 (12.0%)	0.541 (15.6%)
Food effect on D1 for Tasigna (proportional)	0.746 (9.71%)	0.706 (9.48%)	0.815 (8.4%)
Food effect on D1 for nilotinib Tablets (proportional)	2.91 (3.58%)	2.95 (3.80%)	3.45 (6.6%)
Food effect on ALAG1 for Tasigna (proportional)	7.79 (17.1%)	9.10 (23.4%)	7.26 (33.9%)
Food effect on ALAG1 for nilotinib Tablets (proportional)	2.98 (20.5%)	3.62 (26.7%)	2.86 (39.2%)
Food effect on V1 (proportional)	-0.248 (11.8%)	-0.286 (10.3%)	-0.328 (12.3%)
Food effect on Q (proportional)	2.07 (22.8%)	2.42 (25.5%)	4.11 (54.7%)
Sex (female) covariate effect on CL (proportional)	-0.227 (16.2%)	-0.266 (11.4%)	-0.275 (11.6%)
Sex (female*) covariate effect on F1 (proportional)	0.116 (36.8%)	0.111 (38.3%)	0.0877 (49.8%)
Food (**MF -LFM**) effect on F1 for Tasigna (proportional)	-	0.512 (16.4%)	0.496 (20.4%)
Food (**MF -LFM**) effect on F1 for Nilotinib (proportional)	-	0.294 (20.6%)	0.232 (31.6%)
Food (**MF-LFM**) effect on D1 for Nilotinib (proportional)	-	0.948 (7.20%)	1.23 (8.4%)
Food (**MF-LFM**) effect on ALAG1 for Tasigna (proportional)	-	3.25 (27.5%)	2.57 (40.9%)

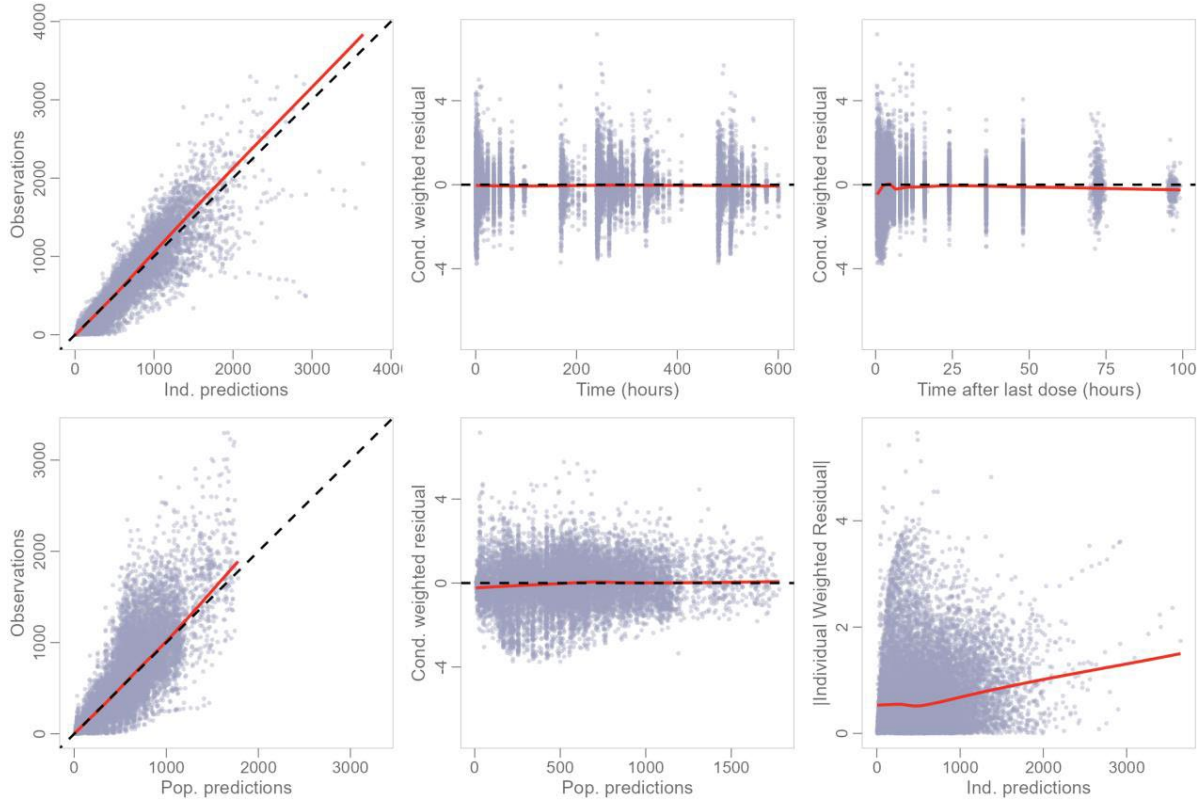
Source: Reviewer's sensitivity analysis and Applicant's analysis were adapted from Applicant's PopPK analysis report, Table 9 on page 47-48, Table 14 on page 63-64.

Table 23: PopPK model parameter estimates for random effects

	Applicant's final model	**Applicant's PopPK analysis**	**Reviewer's sensitivity analysis**
	Estimate (%RSE)	Estimate (%RSE)	Estimate (%RSE)
Between Subject Variability			
CL	0.108 (8.89%)	0.108 (10.8%)	0.108 (8.1)
Correlation CL – V1	0.0628 (12.7%)	0.0621 (0	0.0609 (0.0078)
V1	0.144 (9.30%)	0.146 (14.6%)	0.143 (8.4)
Inter-Occasion Variability			
V1	0.157 (8.52%)	0.157 (15.8%)	0.145 (9.2%)
Residual Error			
Exponential Error	0.230 (2.87%)	0.232 (2.45%)	0.239 (3.6%)
Additive Error (ng/mL)	36.6 (2.87%)	37.1 (6.22%)	36.9 (9.8%)

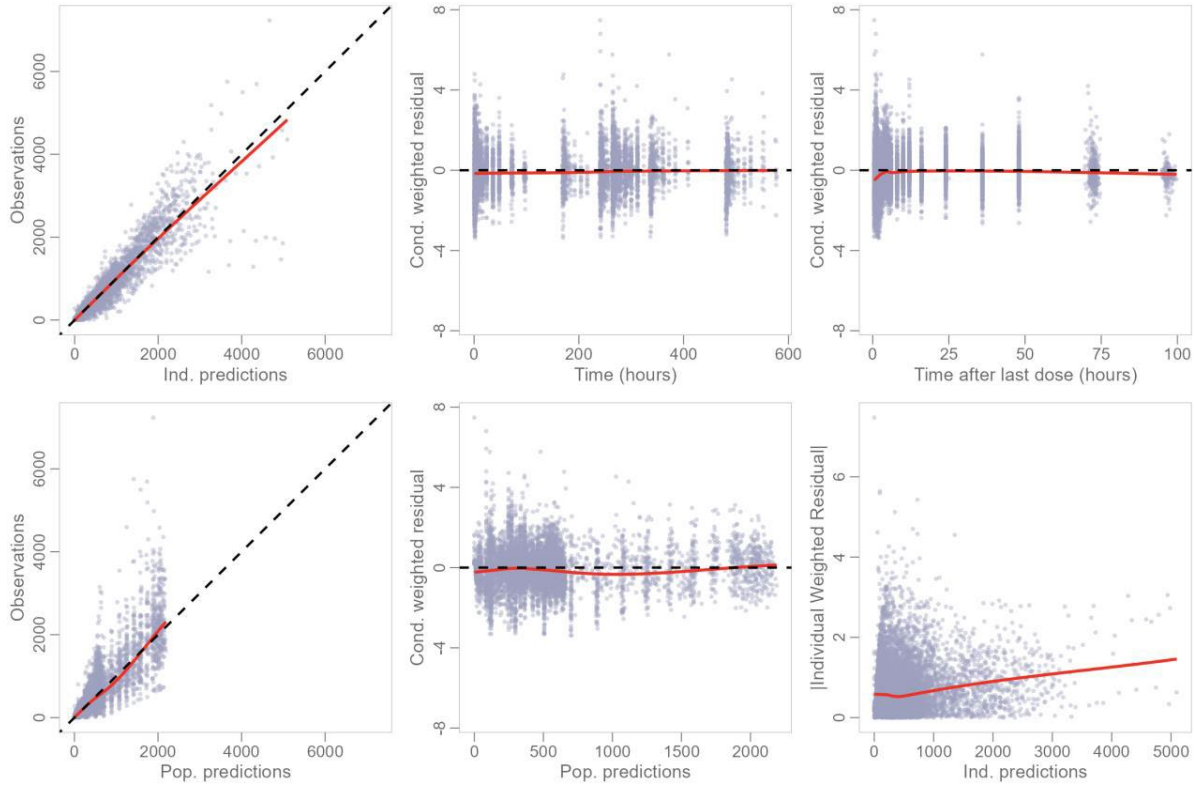
Source: Reviewer's sensitivity analysis and Applicant's analysis were adapted from Applicant's PopPK analysis report, Table 9 on page 47-48, Table 14 on page 63-64.

Figure 5. GOF plots for the final PopPK model for the PK data of nilotinib tablets



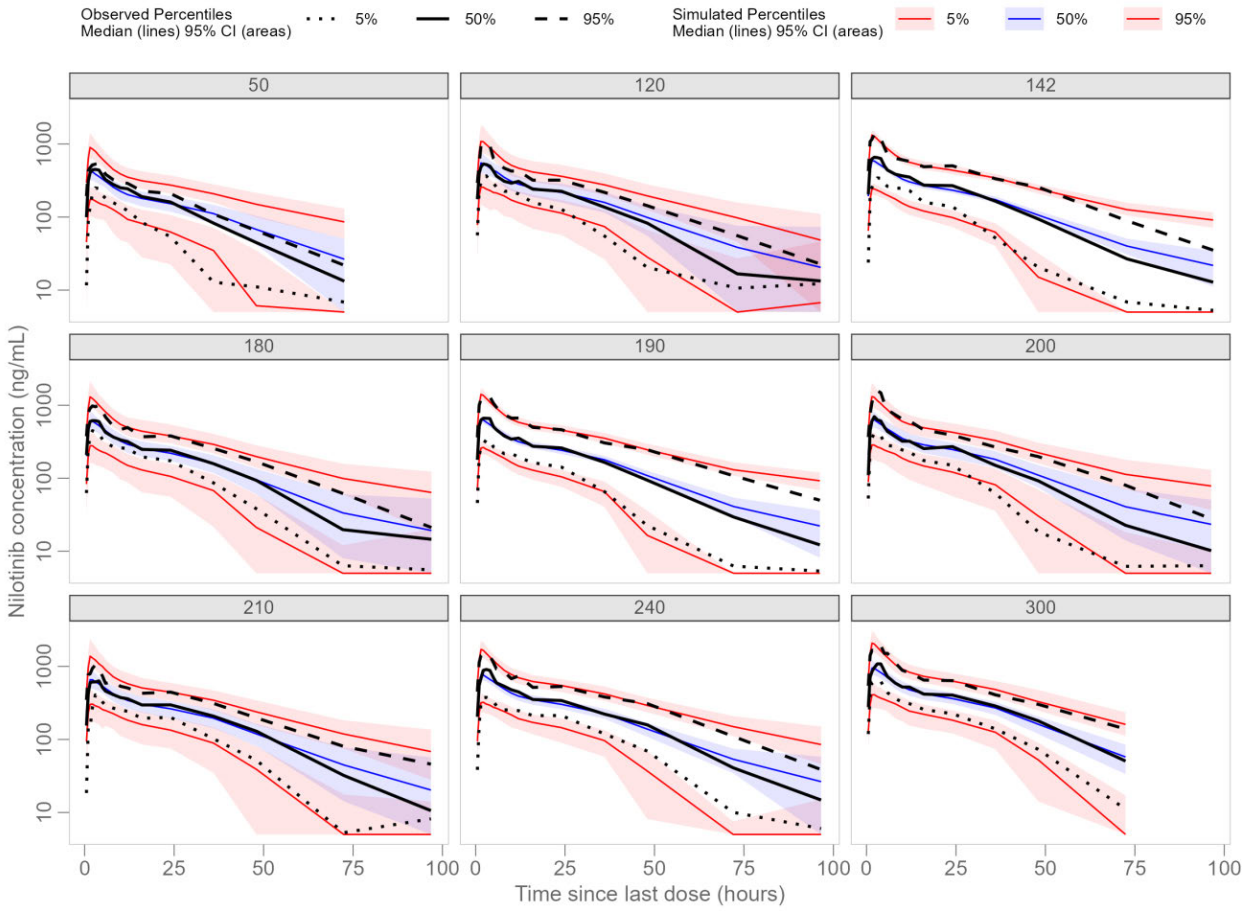
Source: Applicant's PopPK analysis report, Figure 6 on page 44.

Figure 6. GOF plots for the final PopPK model for the PK data of Tasigna



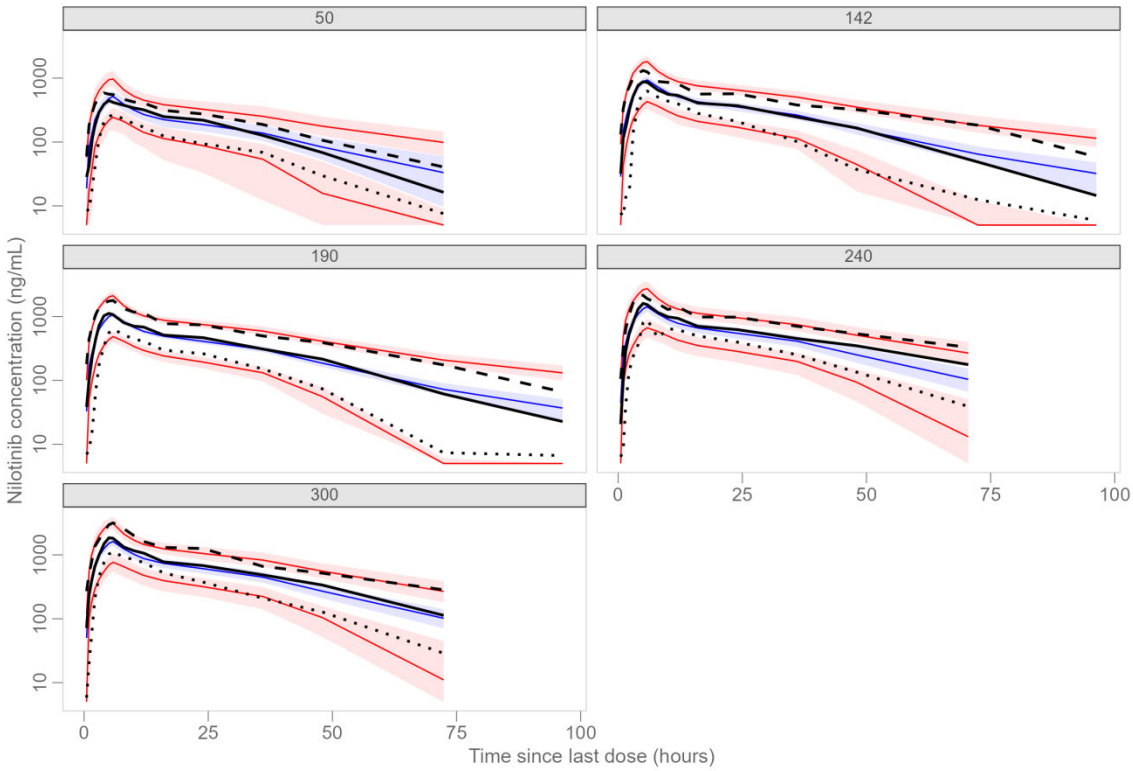
Source: Applicant's PopPK analysis report, Figure 7 on page 45.

Figure 7. pcVPC for the final PopPK model: nilotinib tablets under overnight fasting stratified by dose level



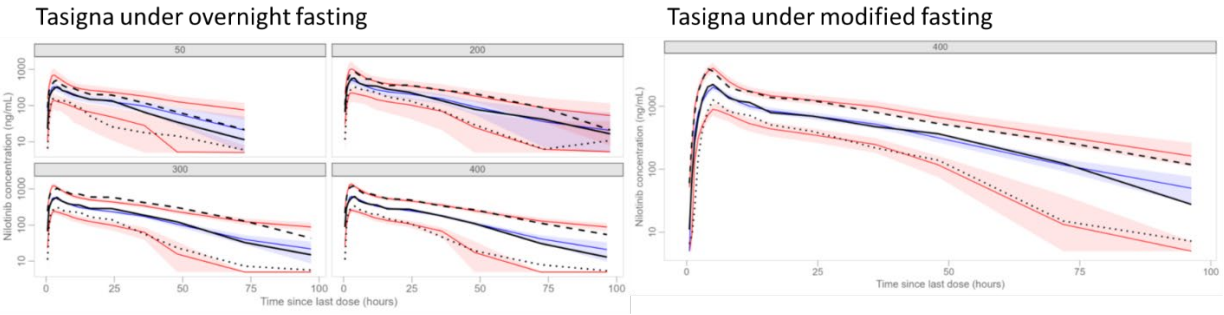
Source: Applicant's PopPK analysis report, Figure 9 on page 49.

Figure 8. pcVPC for the final PopPK model: nilotinib tablets under Fed or MF-HFM condition stratified by dose level



Source: Applicant's PopPK analysis report, Figure 10 on page 50.

Figure 9. pcVPC for the final PopPK model: Tasigna under overnight fasting (left) and MF-HFM (right) stratified by dose level



Source: Applicant's PopPK analysis report, Figure 11 and Figure 12 on page 51-52.

4.2.2 Reviewer's Assessment on PopPK analysis

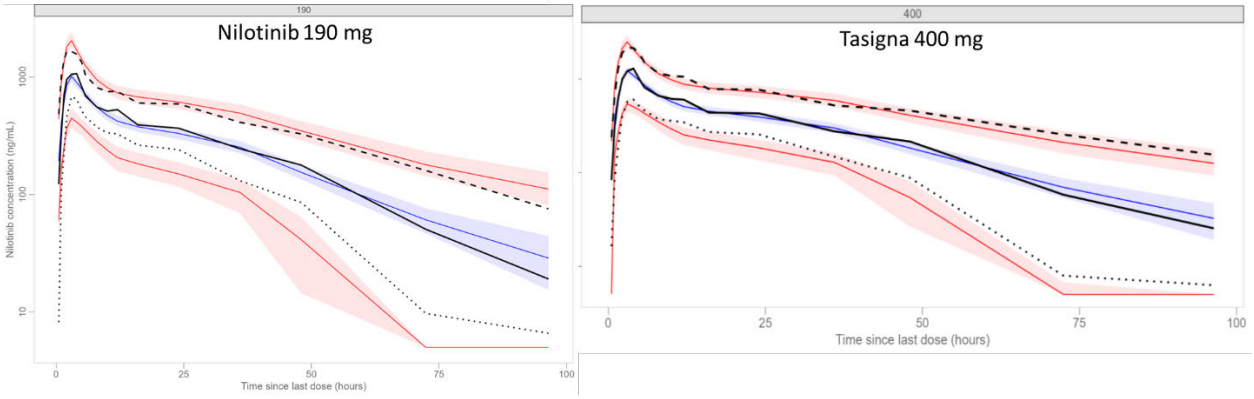
The PopPK analysis was adequately conducted and is acceptable to be used to predict the PK profiles for nilotinib at steady state under different food conditions. The final PopPK model reasonably describes the nilotinib PK for both formulations (nilotinib tablets and Tasigna) under overnight fasting, MF-HFM, and MF-LFM across the dose levels. The PopPK model also generally captures the observed PK data under fed condition for nilotinib tablets. The parameters were estimated with acceptable precision (RSE <35%). The η-shrinkage was low (<5%). Goodness of fit (GOF) plots stratified by formulation do not show obvious bias along the time, or concentration levels. The pcVPC plots stratified by dose level, food

condition, and formulation show that the model captures the central tendency and the variability of the observed PK data.

The reviewer conducted a sensitivity analysis by fitting the Applicant's PK model to the subset of the data from the studies that used the TBM formulation (010-22, 006-23, 007-23, 128-22, 052-23, and 011-22). Generally, the parameter estimates for structural PK parameters, covariate effects, and food effects were consistent between the sensitivity analysis and the updated model (**Table 21**, **Table 22**, and **Table 23**). GOF plots stratified by food condition and formulation (nilotinib tablet vs. Tasigna) did not show any obvious model misspecification. The summary of the reviewer's assessment is following:

- **Nonlinear PK**: The nonlinear PK was adequately captured by parametrizing the dose dependent relative BA (F1) following single dose administration of nilotinib tablets and Tasigna, supported by GOF and pcVPC stratified by dose level. The PopPK model was developed based on single-dose PK data. The previously reviewed PopPK model for nilotinib (given as Tasigna) as well as the current model supports linear elimination from the central compartment. Therefore, the PopPK model is acceptable to predict the PK profiles following multiple doses (i.e., BID).
- **Formulation effects**: The model estimated relative BA (199.2%) of nilotinib tablets to Tasigna is consistent with AUC equivalence between nilotinib tablet 190 mg and Tasigna 400 mg.
- **Food effect**: The GOF plots and pcVPC stratified by food condition did not indicate obvious bias. The magnitudes of food effect are in line with those reported in the BA/BE studies as following:
    - Fed: The AUC_{inf} of nilotinib 140 mg and 190 mg in fed condition were 55% (Study 007-23) and 60% (Study 006-23) higher than those taken under overnight fasting. The popPK estimated 47% and 60% increase in BA for 140 mg and 190 mg, respectively.
    - MF-HFM: The AUC_{inf} of nilotinib tablet 140 mg and 190 mg with MF-HFM were 61.9% (Study 007-23) and 61.3% (Study 006-23) higher than that taken under overnight fasting. The PopPK estimated 57% and 59 % increase in BA for 140 mg and 190 mg, respectively.
    - MF-LFM: Study 005-23 is the only study that evaluated the effect of MF-LFM on PK of nilotinib tablet and Tasinga. The model diagnostics for the updated model shows the consistent model performance in describing the food effect of MF-LFM on nilotinib tablets and Tasigna (**Figure 10**).

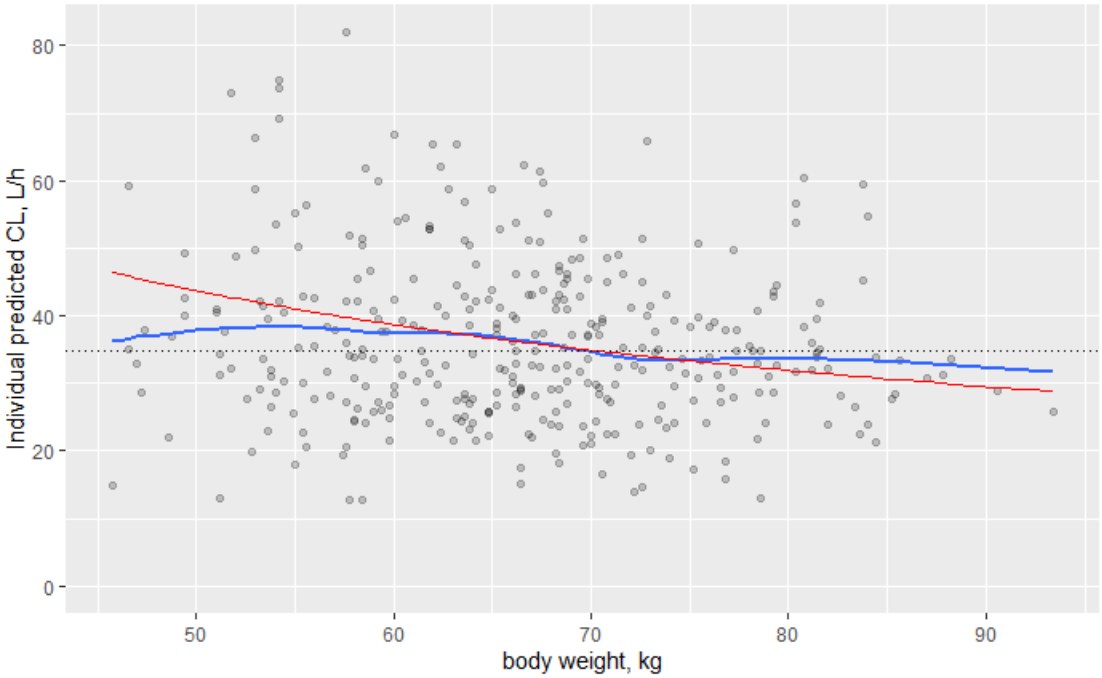
Figure 10. pcVPC for the updated model: nilotinib tablets and Tasinga under MF-LFM condition



Source: Applicant's PopPK analysis report, Figure 16 and Figure 17 on page 62-63.

- **Covariate effect**: The PopPK analysis estimated the power for the body weight effect to be -0.67, which suggests an association between the increasing body weight and the decreasing drug clearance. It is noted that the direction of the body weight effect (negative power) may not be physiologically plausible and should be cautiously interpreted. This relationship between the η for CL and body weight (**Table 22**) was identified in the base model without covariate adjustment. Upon inclusion of body weight as covariate, the final model did not show obvious trend in the relationship between η for CL and body weight. The reviewer examined the relationship between the individual-predicted CL (derived by the empiric bayes estimates) and body weight. The similar trend of increasing weight and decreasing CL was observed (blue loess trend line in **Figure 11**), however, the slope is flatter compared to population predicted CL for given body weight (derived by the power estimate for weight effect) (red line in **Figure 11**). Taken together, the magnitude of body weight effect is not considered to be of clinically significance.

Figure 11. Individual predicted CL vs. Body weight (Reviewer's sensitivity model)



Source: Reviewer's analysis. Black dotted line represents the typical value of CL (34.9L/h) for 70 kg body weight. Blue line represents loess smooth line. Red line represents the population predicted CL for respective body weight (formula = 34.9 (L/h) x (body weight/70)$^{-0.67}$).

4.2.3 PopPK simulation

Applicant conducted PopPK simulations to predict and compare the PK of nilotinib tablet and Tasigna at steady state using the final model. A dataset of healthy subjects (n = 50 or 30 with 50% male) was randomly sampled from the analysis dataset for the simulations. The doses of 190 mg and 142 mg of nilotinib tablets given as BID were simulated and compared to the doses of 400 mg and 300 mg of Tasigna. For each sample size, 100 study replicates were simulated to estimate the probability of

bioequivalence (BE) between the two formulations in a steady state BE study setting. In this review, the simulations with 50 subjects are presented. The simulation with 30 subjects showed similar results.

In the studies 010-22 and 128-22 that compared the BA of nilotinib tablet and Tasgina under overnight fasting condition, nilotinib tablets showed higher Cmax (19% for 190 mg and 18% for 142 mg) compared to 400 mg and 300 mg of Tasigna, respectively. The PopPK simulation shows that AUCss, Cmax,ss and Cmin,ss are comparable between 190 mg BID and 140 mg BID of nilotinib tablet and 400 mg BID and 300 mg BID of Tasigna (**Table 24**), which suggests that the higher Cmax with nilotinib tablets at steady state is less pronounced as single dose Cmax.

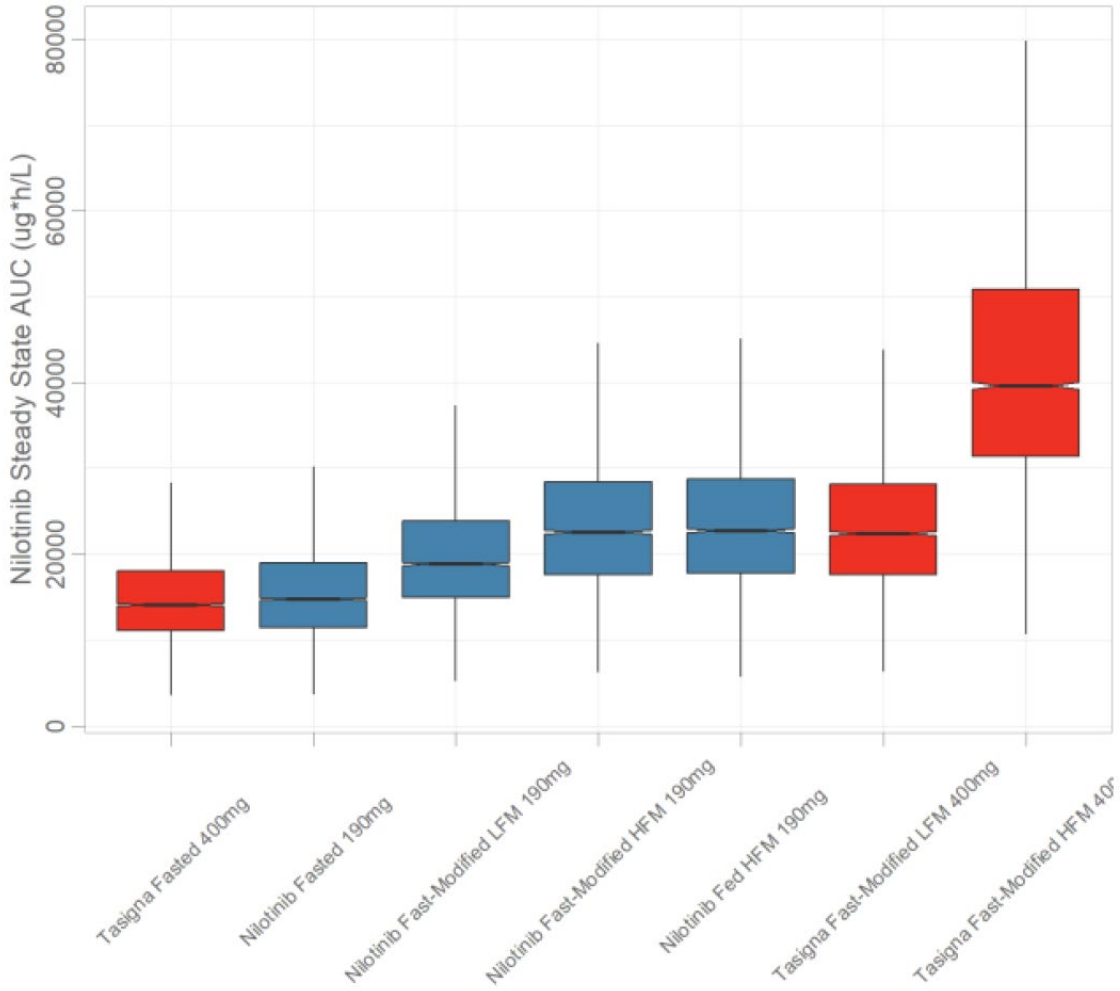
Table 24: Geometric Mean Ratio (GMR) of PK exposures of nilotinib tablets vs. Tasigna under overnight fasting

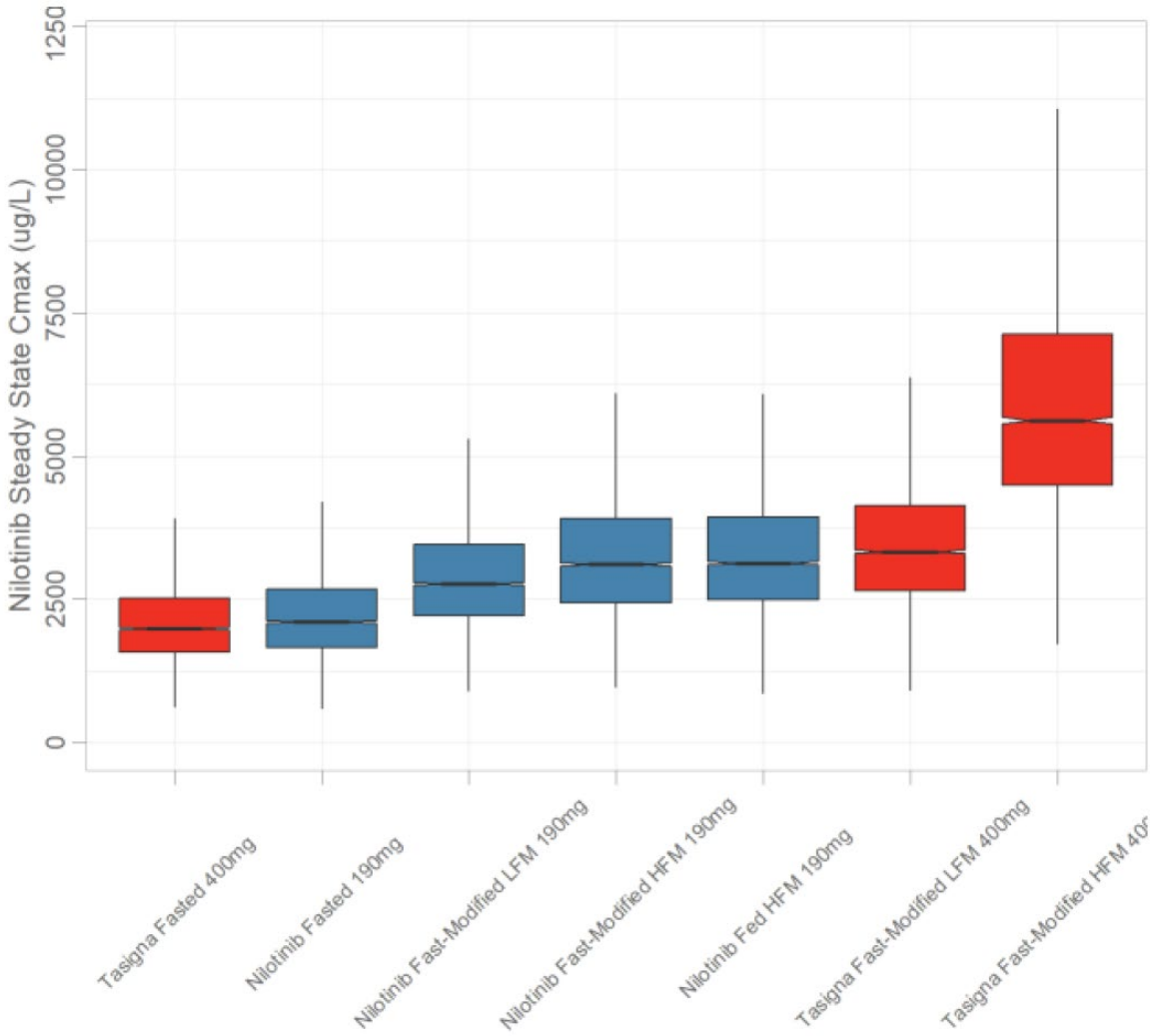
Single dose (Observed in 010-22, n = 92) Nilotinib tablets 190 mg / Tasinga 400 mg		**Steady state, BID dosing** (PopPK simulated, n = 50) Nilotinib tablets 190 mg / Tasinga 400 mg	
	GMR [90% CI]		GMR [90% CI]
Cmax (ng/mL)	1.19 [1.11, 1.28]	Cmax,ss (ng/mL)	1.06 [0.97,1.2]
AUCinf (ng*h/mL)	1.03 [0.98, 1.09]	AUCss (ng*h/mL)	1.04 [0.949,1.17]
-	-	Cmin,ss (ng/mL)	1.02 [0.89,1.18]
Single dose (Observed in 128-22, n = 87) Nilotinib tablets 142 mg / Tasinga 300 mg		**Steady state, BID dosing** (PopPK simulated, n = 50) Nilotinib tablets 142 mg / Tasinga 300 mg	
	GMR [90% CI]		GMR [90% CI]
Cmax (ng/mL)	1.18 [1.10, 1.26]	Cmax,ss (ng/mL)	1.06 [0.97,1.17]
AUCinf (ng*h/mL)	0.99 [0.93, 1.05]	AUCss (ng*h/mL)	1.03 [0.95,1.13]
-	-	Cmin,ss (ng/mL)	1 [0.888,1.15]

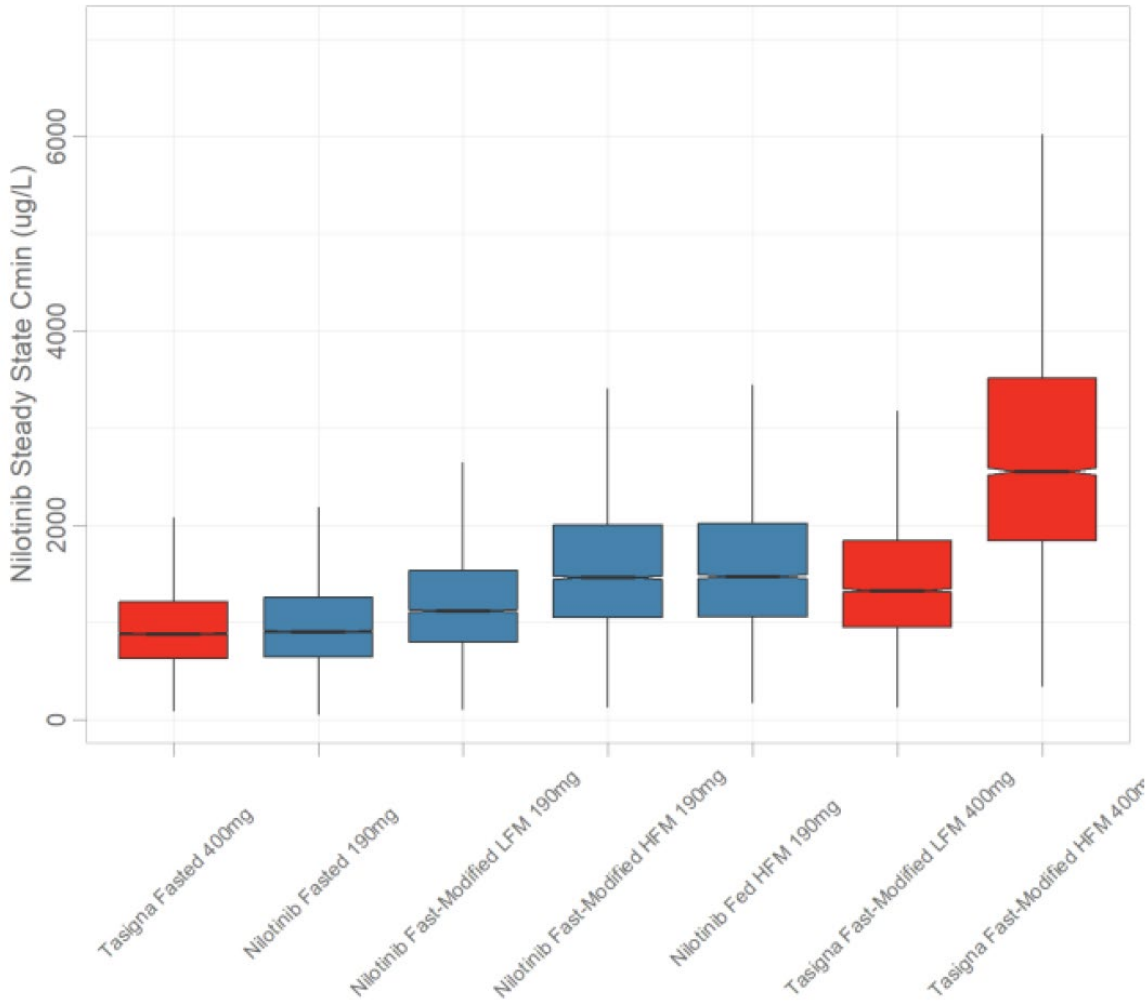
Source: Adapted from Summary of Clinical Pharmacology Studies, Table 2.7.2-1, and Table 2.7.2-5, and Applicant's PopPK analysis report, Table 10.

Figure 12 shows the simulated AUC, Cmax, Cmin at steady state when the nilotinib tablets 190 mg and Tasinga 400 mg are administered as BID regimen under different food conditions. Food increases PK exposures of nilotinib tablet as well as Tasigna. The magnitude of food effects is smaller with nilotinib tablets compared to with Tasigna. The PK exposures of nilotinib tablets taken under MF-LFM, MF-HFM, and fed condition are similar to those of Tasigna taken under MF-LFM and significantly lower than when Tasigna under MF-HFM.

Figure 12. Boxplots of the simulated steady state exposures (AUCss, Cmax,ss, Cmin,ss) for 190 mg Nilotinib Tablets and 400 mg Tasigna Under Fasted, MF-LFM, MF-HFM and Fed Conditions




Nilotinib Steady State Cmax (ug/L)
0
2500
5000
7500
10000
12500
Tasigna Fasted 400mg
Nilotinib Fasted 190mg
Nilotinib Fast-Modified LFM 190mg
Nilotinib Fast-Modified HFM 190mg
Nilotinib Fed HFM 190mg
Tasigna Fast-Modified LFM 400mg
Tasigna Fast-Modified HFM 40



Source: Applicant's PopPK analysis report, Figure 52 on page 300. The box represents the interquartile interval, the black line corresponds to the median. The upper whisker extends to the largest value no further than 1.5x IQR from the hinge. The lower whiskers extend to the smallest value at most 1.5xIQR of the hinge. Boxplots are color coded by product, red for Tasigna and blue for Danziten. Abbreviations: IQR = interquartile range.

4.3 Summary of Bioanalytical Method Validation and Performance

Nilotinib in human plasma was analyzed by tandem mass spectrometry. The assay validation parameters are as indicated in Table 25.

Table 25: Summary of the bioanalytical method validation and in-study performance for measurement of nilotinib for method MS-19-019-03

Bioanalytical method validation report name, amendments, and hyperlinks	Analysis of nilotinib in human plasma using high performance LC-MS/MS Bioanalytical Method MS-19-019-03
Method description	• MS-19-019-03: High Performance LC-MS/MS Liquid-Liquid extraction

Materials used for standard calibration curve and concentration	• Nilotinib: High Performance LC-MS/MS (biological matrix: human plasma K2- EDTA) • Nilotinib-D6: High Performance LC-MS/MS (biological matrix: human plasma K2-EDTA)		
Validated assay range	• 5.007 to 2503.554 ng/mL		
Material used for quality controls (QCs) and concentration	• Nilotinib: High Performance LC-MS/MS (biological matrix: human plasma K2- EDTA) • Nilotinib-D6: High Performance LC-MS/MS (biological matrix: human plasma K2-EDTA) • QC concentrations: 5.020 ng/mL (LLOQ), 14.696 ng/mL (LQC), 1185.121 ng/mL (MQC), 1911.486 ng/mL (HQC), and 6254.863 ng/mL (DQC)		
Source and lot of reagents	• Nilotinib, (b) (4), Batch (b) (4)/S-NB-032/a (Retest date: 29JUL22) • Nilotinib-D6, (b) (4), Batch (b) (4)/D-494 (Retest date: 29JUL22) • Human plasma K2-EDTA, (b) (4)		
Regression model and weighting	Linear regression model (weighted $1/X^2$)		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	10	Yes
	Cumulative % accuracy from LLOQ to ULOQ	97.01% to 103.39%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	0.67% to 2.69%	Yes
Performance of QCs during accuracy and precision runs	Cumulative % accuracy in QCs QCs for Nilotinib: LLOQ, LQC, MQC, HQC, DQC	98.20% to 109.89% (intra-run) 99.18% to 105.09% (inter- run)	Yes
	Inter-batch %CV QCs for Nilotinib: LLOQ, LQC, MQC, HQC, DQC	0.61% to 2.99% (intra-run) 2.11% to 4.72% (inter- run)	Yes
Selectivity & matrix effect	Selectivity: No significant interference in the screened lots of biological matrix for Nilotinib and Nilotinib D6. Matrix effect: No suppression or enhancement noted in the 8 blank matrix lots (%CV <15).		Yes
Interference & specificity	OTC medications interference: No significant baseline interference was detected at the retention times of Nilotinib or IS.		Yes
Hemolysis effect	Hemolysis effect was analyzed as part of selectivity and matrix effect with a hemolyzed matrix used (2 of 8 matrix lots). No interference, suppression, or enhancement noted with hemolyzed matrix.		Yes

Lipemic effect	Lipemic effect was analyzed as part of selectivity and matrix effect with a lipemic matrix used (2 of 8 matrix lots). No interference, suppression, or enhancement noted with lipemic matrix.	Yes
Dilution linearity & hook effect	6254.863 ng/mL diluted 5-fold % Accuracy: 99.03% Precision (%CV): 2.29%	Yes
Bench-top/process stability	Bench-top stability: 23 hours and 04 minutes at room temperature. Reinjection/Process stability: 1 Day 03 hours at 5 ± 3 °C	Yes
Freeze-Thaw stability	06 cycles at -70 ± 15 °C	Yes
Long-term storage	105 days 23 hours at -20 ± 5°C and -70 ± 15°C	Yes
Carry over	No significant carryover observed for Nilotinib and Nilotinib D6.	
Method Performance in Study 011-22 (Report Number: BAR-011-22-02)		
Assay passing rate	0 of 43 runs were rejected (100% passing rate).	Yes
Standard curve performance	Cumulative % Accuracy range: 94.61% to 105.19% Cumulative precision (%CV): 1.66% to 3.95%	Yes
QC performance	Cumulative % Accuracy range: 99.17% to 104.25% Cumulative precision (%CV): 1.72% to 5.48%	Yes
Method reproducibility	Incurred sample reanalysis was performed on 232 samples and 99.14% of the sample results met acceptance criteria.	Yes
Study sample analysis/ stability	Short term stock solution stability of Nilotinib and Nilotinib-D6 was established for 20 days and 26 minutes at room temperature during validation activities. Long term stock solution stability of Nilotinib and Nilotinib-D6 was established for 08 days, 23 hours and 20 minutes at 2-8°C during validation activities.	Yes
Standard calibration curve performance during accuracy and precision runs	The calibration standards consisted of 10 concentrations and ranged from 5.014 ng/mL to 2494.656 ng/mL.	Yes
Method Performance in Study 010-22 (Report Number: BAR-010-22-02)		
Assay passing rate	1 of 58 runs were rejected (98.3% passing rate).	Yes
Standard curve performance	Cumulative % Accuracy range: 97.85% to 102.76% Cumulative precision (%CV): 1.60% to 13.46%	Yes
QC performance	Cumulative % Accuracy range: 99.16% to 103.32% Cumulative precision (%CV): 4.13% to 9.50%	Yes
Method reproducibility	Incurred sample reanalysis was performed on 410 samples and 96.34% of the sample results met acceptance criteria.	Yes

Study sample analysis/ stability	Short term stock solution stability of Nilotinib and Nilotinib-D6 was established for 20 days and 26 minutes at room temperature during validation activities. Long term stock solution stability of Nilotinib and Nilotinib-D6 was established for 08 days, 23 hours and 20 minutes at 2-8°C during validation activities.	Yes
Standard calibration curve performance during accuracy and precision runs	The calibration standards consisted of 10 concentrations and ranged from 5.025 ng/mL to 2498.640 ng/mL.	Yes
Method Performance in Study 006-23 (Report Number: BAR-006-23-01)		
Assay passing rate	4 of 44 runs were rejected (90.9% passing rate).	Yes
Standard curve performance	Cumulative % Accuracy range: 93.69% to 103.43% Cumulative precision (%CV): 0.88% to 2.10%	Yes
QC performance	Cumulative % Accuracy range: 92.91% to 99.78% Cumulative precision (%CV): 2.88% to 7.81%	Yes
Method reproducibility	Incurred sample reanalysis was performed on 0 samples.	Yes
Study sample analysis/ stability	Short term stock solution stability of Nilotinib and Nilotinib-D6 was established for 20 days and 26 minutes at room temperature during validation activities. Long term stock solution stability of Nilotinib and Nilotinib-D6 was established for 08 days, 23 hours and 20 minutes at 2-8°C during validation activities.	Yes
Standard calibration curve performance during accuracy and precision runs	The calibration standards consisted of 10 concentrations and ranged from 5.009 ng/mL to 2500.739 ng/mL.	Yes
Method Performance in Study 007-23 (Report Number: BAR-007-23-01)		
Assay passing rate	0 of 36 runs were rejected (100% passing rate).	Yes
Standard curve performance	Cumulative % Accuracy range: 97.75% to 101.72% Cumulative precision (%CV): 1.06% to 1.97%	Yes
QC performance	Cumulative % Accuracy range: 92.89% to 98.89% Cumulative precision (%CV): 2.11% to 4.31%	Yes
Method reproducibility	Incurred sample reanalysis was not performed.	Yes
Study sample analysis/ stability	Short term stock solution stability of Nilotinib and Nilotinib-D6 was established for 20 days and 26 minutes at room temperature during validation activities.	Yes

	Long term stock solution stability of Nilotinib and Nilotinib-D6 was established for 08 days, 23 hours and 20 minutes at 2-8°C during validation activities.	
Standard calibration curve performance during accuracy and precision runs	The calibration standards consisted of 10 concentrations and ranged from 5.025 ng/mL to 2500.739 ng/mL.	Yes
Method Performance in Study 052-23 (Report Number: BAR-052-23-01)		
Assay passing rate	1 of 59 runs were rejected (98.3% passing rate).	Yes
Standard curve performance	Cumulative % Accuracy range: 97.69% to 103.01% Cumulative precision (%CV): 0.96% to 1.71%	Yes
QC performance	Cumulative % Accuracy range: 96.81% to 102.89% Cumulative precision (%CV): 1.16% to 4.04%	Yes
Method reproducibility	Incurred sample reanalysis was performed on 294 samples and 93.20% of the sample results met acceptance criteria.	Yes
Study sample analysis/ stability	Short term stock solution stability of Nilotinib and Nilotinib-D6 was established for 20 days and 26 minutes at room temperature during validation activities. Long term stock solution stability of Nilotinib and Nilotinib-D6 was established for 08 days, 23 hours and 20 minutes at 2-8°C during validation activities.	Yes
Standard calibration curve performance during accuracy and precision runs	The calibration standards consisted of 10 concentrations and ranged from 5.009 ng/mL to 2501.653 ng/mL.	Yes
Method Performance in Study 128-22 (Report Number: BAR-128-22-01)		
Assay passing rate	0 of 58 runs were rejected (100% passing rate).	Yes
Standard curve performance	Cumulative % Accuracy range: 94.97% to 103.71% Cumulative precision (%CV): 1.12% to 2.76%	Yes
QC performance	Cumulative % Accuracy range: 97.83% to 100.85% Cumulative precision (%CV): 1.71% to 3.94%	Yes
Method reproducibility	Incurred sample reanalysis was performed on 384 samples and 96.61% of the sample results met acceptance criteria.	Yes
Study sample analysis/ stability	Short term stock solution stability of Nilotinib and Nilotinib-D6 was established for 20 days and 26 minutes at room temperature during validation activities. Long term stock solution stability of Nilotinib and Nilotinib-D6 was established for 08 days, 23 hours and 20 minutes at 2-8°C during validation activities.	Yes

Standard calibration curve performance during accuracy and precision runs	The calibration standards consisted of 8 concentrations and ranged from 5.009 ng/mL to 2501.744 ng/mL.	Yes

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/s/

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