Clinical Pharmacology Review	
NDA	NDA 022068 (SDN 1259, eCTD 260)
Type/Category	Supplement 027
Submission Date	9/25/2017
PDUFA	3/25/2018
Brand Name	Tasigna®
Generic name	Nilotinib
Formulation and Strength	Capsules: 50 mg, 150 mg and 200 mg
Route of Administration	Oral
Applicant	Novartis Pharmaceuticals Corp.
Proposed New Indication	Treatment of pediatric patients with: • Newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase • Ph+ CML-CP resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy
Approved Indications	Treatment of adult patients with: • Newly diagnosed Ph+ CML-CP • Ph+ CML-CP and CML-AP resistant to or intolerant to prior therapy that included imatinib
Proposed Dosing Regimen	Recommended pediatric dose: 230 mg/m^2 orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg)
Approved Dosing Regimen	Treatment of adult patients with: • Newly diagnosed Ph+ CML-CP: 300 mg orally twice daily. • Resistant or intolerant Ph+ CML-CP and CML-AP: 400 mg orally twice daily.
OCP Divisions	Division of Clinical Pharmacology V (DCPV)
OND Division	Division of Hematology Products (DHP)
OCP Primary Reviewers	Liang Li, Ph.D.
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1. EXECUTIVE SUMMARY

The key review question focuses on the appropriateness of the dose for the administration of Tasigna 230 mg/m^2 orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg), for the treatment of pediatric patients ≥ 1 years of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), or with Ph+ CML-CP resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy. The Office of Clinical Pharmacology has reviewed the information contained in this Efficacy Supplement of NDA 022068 including: 1) the primary efficacy and safety data from two registration pediatric Trials CAMN107A2120 and CAMN107A2203; 2) population pharmacokinetic (PK) analysis and exposure-response (ER) analyses for both efficacy and safety with data from these two pediatric trials. This NDA Efficacy Supplement is approvable from a clinical pharmacology perspective.

1.1.Recommendations

The key review issues with specific recommendations and comments are summarized below:

<table>
<tr><th>Review Issues</th><th>Recommendations and Comments</th></tr>
<tr><td>Evidence of effectiveness</td><td>Trials CAMN107A2120 and CAMN107A2203 provide primary evidence of effectiveness.</td></tr>
<tr><td>General Dosing instructions</td><td>The recommended dose of Tasigna for pediatric patients is 230 mg/m^2 orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg).
<table>
<tr><th>Body Surface Area (BSA)</th><th>Single Dose</th><th>Total Daily Dose</th></tr>
<tr><td>Up to 0.32 m^2</td><td>50 mg</td><td>100 mg</td></tr>
<tr><td>0.33 – 0.54 m^2</td><td>100 mg</td><td>200 mg</td></tr>
<tr><td>0.55 – 0.76 m^2</td><td>150 mg</td><td>300 mg</td></tr>
<tr><td>0.77 – 0.97 m^2</td><td>200 mg</td><td>400 mg</td></tr>
<tr><td>0.98 – 1.19 m^2</td><td>250 mg</td><td>500 mg</td></tr>
<tr><td>1.20 – 1.41 m^2</td><td>300 mg</td><td>600 mg</td></tr>
<tr><td>1.42 – 1.63 m^2</td><td>350 mg</td><td>700 mg</td></tr>
<tr><td>≥1.64 m^2</td><td>400 mg</td><td>800 mg</td></tr>
</table>
If needed, attain the desired dose by combining different strengths of Tasigna capsules. Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.

The recommended dosing regimen is effective and appears to be safe.</td></tr>
</table>

1.2.Post-Marketing Requirements and Commitments

None.

Signatures:

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Cc: DHP: RPM –N Kormanik; MO – N Richardson; MTL – A De Claro

DCPV: DDD – B Booth; DD – NA Rahman

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1.Pharmacology and Clinical Pharmacokinetics

Nilotinib is an inhibitor of the BCR-ABL kinase. Nilotinib binds to and stabilizes the inactive conformation of the kinase domain of ABL protein. Nilotinib was able to overcome imatinib resistance resulting from BCR-ABL kinase mutations. Tasigna (nilotinib) was approved for the treatment of adult patients with newly diagnosed Ph+ CML-CP, and adult patients with Ph+ CML-CP and CML-AP resistant to or intolerant to prior therapy that included imatinib. For brevity, only information related to the current submission is summarized.

Population PK analysis was conducted using PK data from pediatric patients with newly diagnosed Ph+ CML-CP and pediatric patients with resistant to or intolerant Ph+ CML-CP in the pediatric Trials CAMN107A2120 and CAMN107A2203. The population PK analysis showed that steady-state exposure of nilotinib in pediatric patients following administration of the proposed dosing regimen were within 2-fold to adult patients treated with 400 mg twice daily. Steady-state C_{min} was comparable across all age groups (pediatric patients from ages 2 to < 18 years), diseases (patients with newly diagnosed and resistant or intolerant Ph+ CML) and studies. Body surface area (BSA) correlated with nilotinib clearance and was the primary factor responsible for the PK differences between pediatrics and adults.

2.2.Dosing and Therapeutic Individualization

2.2.1. General dosing

The Applicant proposed dose of Tasigna for pediatric patients is 230 mg/m^2 orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg).

Body Surface Area (BSA)	Single Dose	Total Daily Dose
Up to 0.32 m^2	50 mg	100 mg
0.33 – 0.54 m^2	100 mg	200 mg
0.55 – 0.76 m^2	150 mg	300 mg
0.77 – 0.97 m^2	200 mg	400 mg
0.98 – 1.19 m^2	250 mg	500 mg
1.20 – 1.41 m^2	300 mg	600 mg
1.42 – 1.63 m^2	350 mg	700 mg
≥1.64 m^2	400 mg	800 mg

If needed, attain the desired dose by combining different strengths of Tasigna capsules. Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.

In general, the proposed dosing regimen is effective and appears to be safe based on efficacy and safety data in the pediatric Trials CAMN107A2120 and CAMN107A2203.

2.2.2. Therapeutic individualization

The population PK analysis in pediatric patients indicated that BSA correlated with nilotinib clearance and was the primary factor responsible for the PK differences between pediatrics and adults, which supported the proposed BSA-based dosing regimen in pediatric patient populations. No other new significant covariates were identified that had a clinically meaningful effect on the safety and efficacy of nilotinib in pediatric patient populations. Dose adjustment in specific population of pediatric patient populations should follow the current recommendations in the labeling.

2.3.Outstanding Issues

There are no outstanding issues at this time.

2.4.Summary of Labeling Recommendations

Section 2.4 "Dosage Adjustments", Section 5 "Warnings and Precautions", Section 7 "Drug Interactions", and Section 12 "Clinical Pharmacology" were revised in light of current labeling practices and new guidance document "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products - Content and Format".

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1.Overview of the Product and Regulatory Background

Tasigna received FDA approval for the treatment of adult patients with with newly diagnosed Ph+ CML-CP, and adult patients with Ph+ CML-CP and CML-AP resistant to or intolerant to prior therapy that included imatinib on 10/29/2007.

In the current submission, the Applicant submitted results of two pediatric trials:

- **Trial CAMN107A2120 (referred as 2120 hereafter):** A multi-center, open-label pharmacokinetic study of oral nilotinib in pediatric patients with newly diagnosed Ph+ CML-CP, with Ph+ CML-CP or CML-AP resistant/ intolerant to imatinib and/or dasatinib, or with refractory/relapsed Ph+ ALL;
- **Trial CAMN107A2203 (referred as 2203 hereafter)**: A multi-center, open label, non-controlled phase II study to evaluate efficacy and safety of oral nilotinib in pediatric patients with newly diagnosed Ph+ CML-CP or with Ph+ CML-CP or CML-AP resistant or intolerant to either imatinib or dasatinib.

The Applicant also submitted study reports for population PK analysis, and ER analyses of safety and efficacy for nilotinib in pediatric patient populations based on data from Trials 2120 and 2203.

3.2.General Pharmacological and Pharmacokinetic Characteristics

Clinical pharmacological and PK characteristics of nilotinib have been well characterized in adult patients with newly diagnosed Ph+ CML-CP and adult patients with resistant to or intolerant Ph+ CML-CP and CML-AP. Refer to the current labeling and the clinical pharmacology review in the original NDA submission for more detailed information.

Per Applicant's population PK analysis based on 1155 nilotinib serum concentrations from 72 pediatric patient populations Trials 2120 and 2203, steady-state exposure of nilotinib in pediatric patients following administration of the proposed dosing regimen were found within 2-fold to adult patients treated with 400 mg twice daily. Steady-state C_{min} was comparable across all age groups (pediatric patients from ages 2 to < 18 years), diseases (patients with newly diagnosed and resistant or intolerant Ph+ CML) and studies. The geometric mean (%CV) of steady-state Cmin was 1110 ng/mL (107%) for the age group of 2 to <6 years, 1040 ng/mL (70%) for the age group of 6 to <12 years, and 1180 ng/mL (77%) for the age group of 12 to <18 years. The median predictions of BSA-normalized clearance (CL) was 13.8 L/h/m^2 (41%) for the age group of 2 to <6 years, 13.1 L/h/m^2 (38%) for the age group of 6 to <12 years, and 13.0 L/h/m^2 (41%) for the age group of 12 to <18 years.

3.3.Clinical Pharmacology Questions

For brevity, only questions related to the current submission are addressed below. For additional information, please refer to the clinical pharmacology review for the original NDA submission in DARRTS on July 09, 2007.

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

The proposed nilotinib dosing regimen for pediatric patient populations demonstrated sufficient efficacy with tolerable and managable safety profile in pediatric patients ≥ 1 years of age with newly diagnosed Ph+ CML-CP, or with resistant or intolerant Ph+ CML-CP in Trials 2120 and 2203.

Efficacy

The rates of major molecular response (MMR) at Cycles 3, 6 and 12, for pediatric patients with newly diagnosed Ph+ CML-CP, or with resistant or intolerant Ph+ CML-CP in Trials 2120 and 2203are listed in **Table 1**. The median (range) time of treatment with Tasigna was 13.8 (0.7 to 30.9) months. Among the 21 patients with resistant or intolerant CML who were in MMR at any time on treatment, the median (range) time to first MMR was 2.8 (0.0 - 11.3) months. For the 17 patients with newly diagnosed CML who achieved MMR, the median (range) time to first MMR was 5.6 (2.7 - 16.6) months.

Table 1: Major Molecular Response Rate Pooled from Trial 2120 and 2203.

MMR status at Cycle x		Imatinib/dasatinib resistant/intolerant Ph+ CML-CP N=44	Newly Ph+ CML-CP diagnosed N=25
Cycle 3	Response – n (%)	14 (31.8)	3 (12.0)
	95% CI for response (%)	(18.6, 47.6)	(2.5, 31.2)
	No response – n (%)	30 (68.2)	22 (88.0)
Cycle 6	Response – n (%)	15 (34.1)	13 (52.0)
	95% CI for response (%)	(20.5, 49.9)	(31.3, 72.2)
	No response – n (%)	29 (65.9)	12 (48.0)
Cycle 12	Response – n (%)	18 (40.9)	15 (60.0)
	95% CI for response (%)	(26.3, 56.8)	(38.7, 78.9)
	No response – n (%)	26 (59.1)	10 (40.0)

Source: Applicant's Summary of Clincal Efficacy in Pediatric CML, Table 3-6.

Safety

Overall, the safety profile of nilotinib in 73 pediatric patients dosed at 230 mg/m^2 BID in Trials 2120 and 2203 was consistent with the known safety profile in adult patients dosed at 400 mg BID. The majority of these AEs were manageable by dose interruption and/adjustment or additional therapy and rarely required study drug discontinuation (**Table 2**).

Table 2: Overall Summary of Adverse Events in Pediatric Paitent Populations in Trials 2120 and 2203 (Pooled Safety Population).

	Imatinib/dasatinib resistant/intolerant CML-CP		Newly diagnosed Ph+ CML-CP		All patients Ph+ CML-CP		All patients Ph+ CML-CP and ALL	
	N=44		N=25		N=69		N=73	
	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All deaths[1]	0		0		0		0	
On-treatment deaths[2]	0		0		0		0	
Adverse events	44 (100.0)	19 (43.2)	25 (100.0)	16 (64.0)	69 (100.0)	35 (50.7)	73 (100.0)	37 (50.7)
Suspected to be drug-related	38 (86.4)	16 (36.4)	22 (88.0)	16 (64.0)	60 (87.0)	32 (46.4)	62 (84.9)	32 (43.8)
SAEs	8 (18.2)	5 (11.4)	2 (8.0)	1 (4.0)	10 (14.5)	6 (8.7)	13 (17.8)	7 (9.6)
Suspected to be drug-related	3 (6.8)	2 (4.5)	2 (8.0)	1 (4.0)	5 (7.2)	3 (4.3)	5 (6.8)	3 (4.1)
AEs leading to discontinuation	5 (11.4)	2 (4.5)	4 (16.0)	4 (16.0)	9 (13.0)	6 (8.7)	10 (13.7)	6 (8.2)
Suspected to be drug-related	5 (11.4)	2 (4.5)	4 (16.0)	4 (16.0)	9 (13.0)	6 (8.7)	9 (12.3)	6 (8.2)
AEs requiring dose adjustment or interruption	24 (54.5)	14 (31.8)	17 (68.0)	15 (60.0)	41 (59.4)	29 (42.0)	43 (58.9)	30 (41.1)
Suspected to be drug-related	23 (52.3)	14 (31.8)	17 (68.0)	15 (60.0)	40 (58.0)	29 (42.0)	41 (56.2)	29 (39.7)
AEs requiring additional therapy	39 (88.6)	7 (15.9)	23 (92.0)	4 (16.0)	62 (89.9)	11 (15.9)	65 (89.0)	12 (16.4)
Suspected to be drug-related	25 (56.8)	6 (13.6)	15 (60.0)	3 (12.0)	40 (58.0)	9 (13.0)	42 (57.5)	9 (12.3)

Source: Applicant's Summary of Clincal Safety in Pediatric CML, Table 2-1.

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

Yes. The proposed dosing regimen of nilotinib 230 mg/m^2 orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg), is appropriate for pediatric patient populations based on the ER analyses for both safety and efficacy, as well as the PK comparison to adult patient populations.

Exposure-Efficacy Relationship

The ER analyses were conducted for MMR in newly diagnosed pediatric patients and resistant/intolerant pediatric patients using logistic regression models.

In the resistant/intolerant patients (**Figure 1A**), all patients with BCR-ABL/ABL ratio <0.1% at baseline had experienced MMR by 6 months. Increasing trough concentrations of nilotinib was observed to increase the probability of MMR in patients with BCR-ABL/ABL ratio 0.1 to ≤10% at baseline. The observed response rate and estimated probability of response appeared to decrease for patients with BCR-ABL/ABL ratio >10% at baseline.

In the newly diagnosed patients (**Figure 1B**), all patients had BCR-ABL/ABL ratio >10% at baseline (median: 62.68%). The observed response rate for patients with the median observed baseline BCR-ABL/ABL ratio was 65.2% and the estimated response rate was 75.3% (90% CI: 0.40, 0.93).

However, the ER analyses results were not statistically significant or definitive, due to limited sample size (n = 66) and narrow steady-state C_{min} derived from only one dose level (280 mg/m^2).

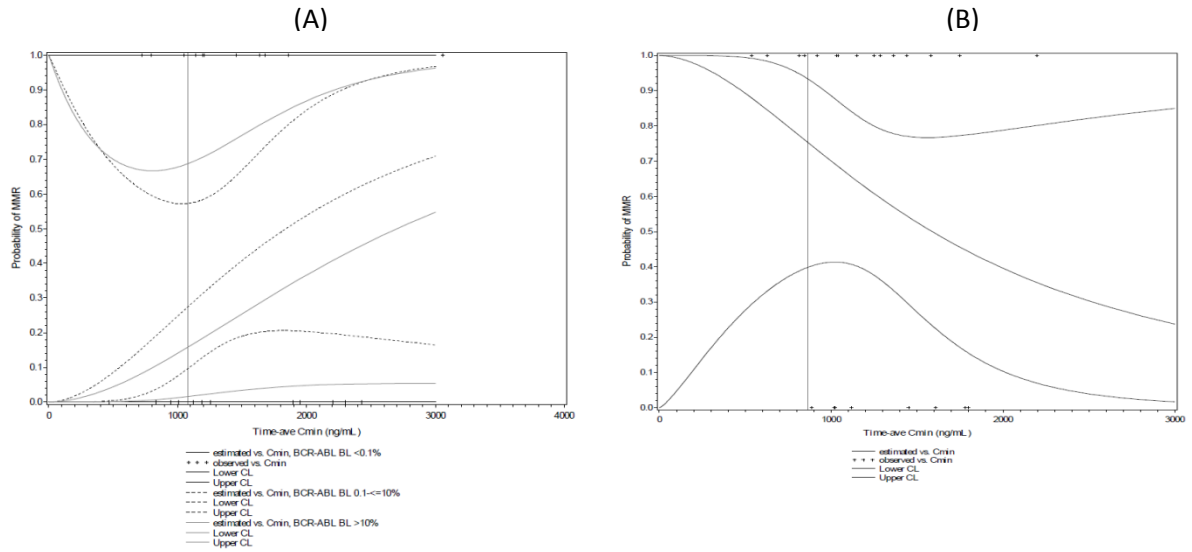

Figure 1: Logistic Regression of MMR vs. Trough Concentration in (A) Resistant/Intolerant Pediatric Patients and (B) Newly Diagnosed Pediatric Patients.

Applicant's Addendum to 2.7.2 Summary of Clinical Pharmacology in Pediatric Patients with CML Figure 4-3.

Exposure-Safety Relationship

Based on limited data from 25 newly diagnosed pediatric patients and 41 resistant/intolerant pediatric patients at only one dose level (280 mg/m^2), no significant correlation was observed between population PK model predicted AUC_{SS} and the probability of occurrence of adverse events of special interests (AESIs) (**Figure 2**), AEs leading to dose modification (**Table 3**), AST/ALT increase (**Figure 3**), or total bilirubin (**Figure 4**) was observed in both pediatric patient populations. Though a trend was noted in the resistant/intolerant pediatric patients for an increase in total bilirubin elevations (to >2xULN) with increasing AUC_{SS} (**Figure 5**), the data should be interpreted with caution given the wide range of bilirubin values observed, and the small sample size.

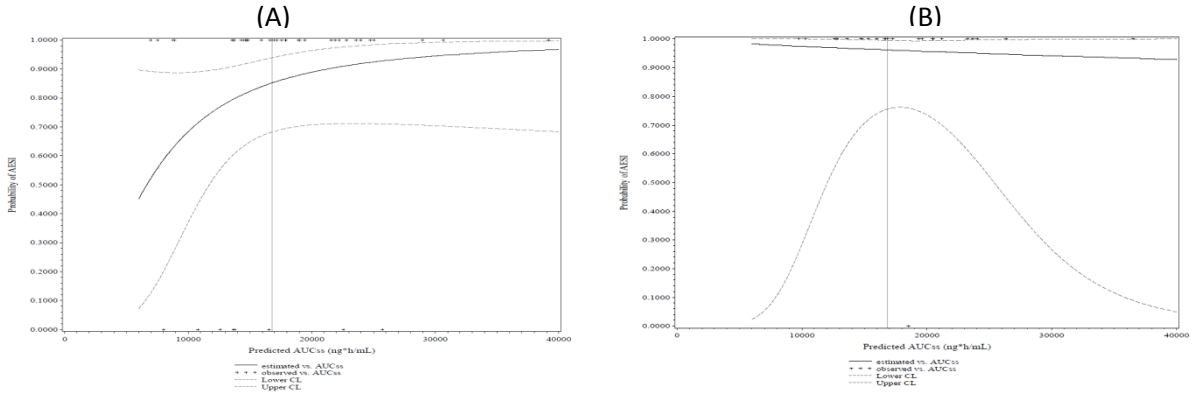

Figure 2: Logistic Regression of AESI vs PopPK Predicted AUC_{SS} in (A) Resistant/Intolerant Pediatric Patients and (B) Newly Diagnosed Pediatric Patients.

Applicant's Summary of Clinical Pharmacology in Pediatric Patients with CML Figure 3-4.

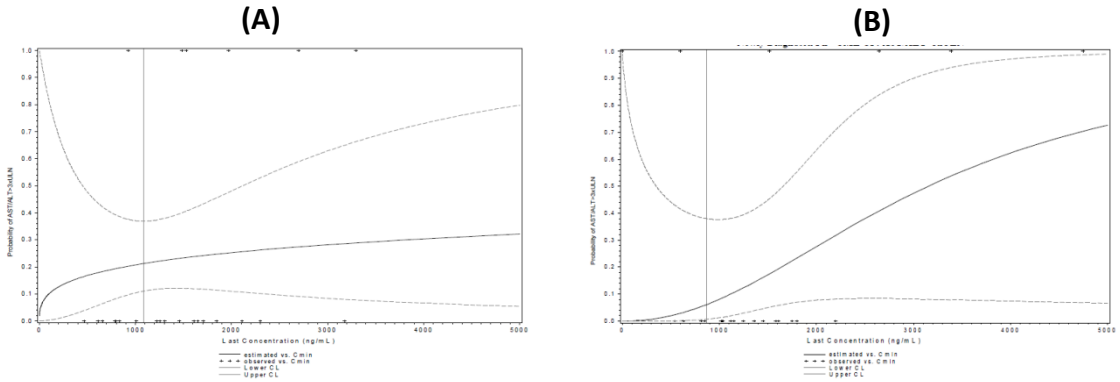

Figure 3: Logistic Regression of AST/ALT increase vs Steady-State C_{min} in (A) Resistant/Intolerant Pediatric Patients and (B) Newly Diagnosed Pediatric Patients.

Applicant's Summary of Clinical Pharmacology in Pediatric Patients with CML Figure 3-6.

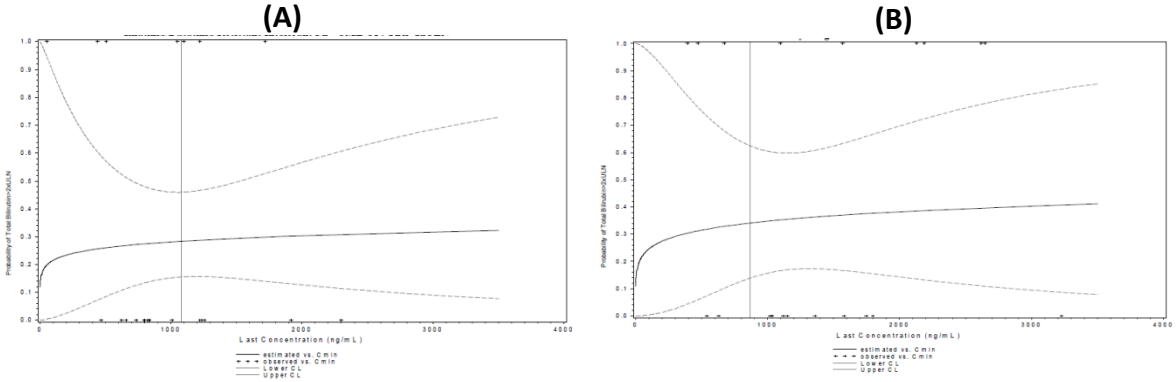

Figure 4: Logistic Regression of Total Bilirubin increase vs Steady-State C_{min} in (A) Resistant/Intolerant Pediatric Patients and (B) Newly Diagnosed Pediatric Patients.

Applicant's Summary of Clinical Pharmacology in Pediatric Patients with CML Figure 3-7.

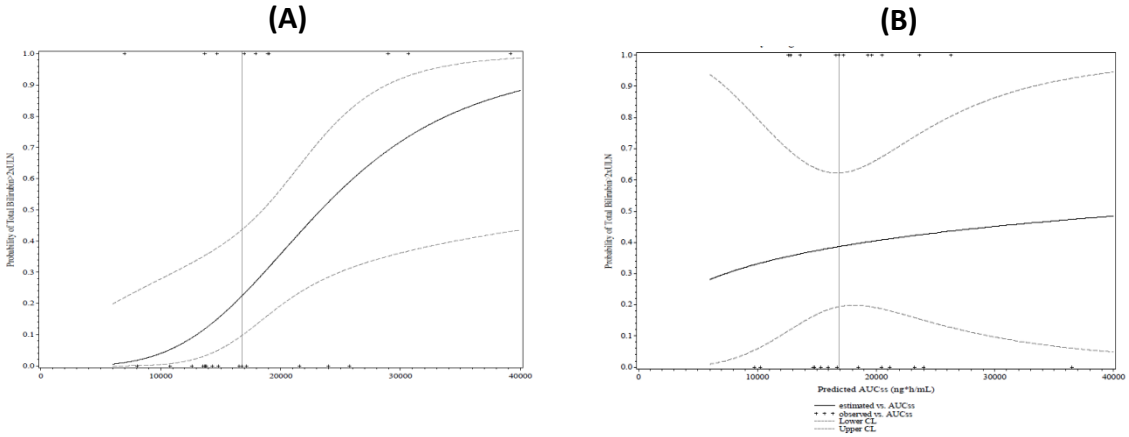

Figure 5: Logistic Regression of Total Bilirubin increase vs Popluation PK Model Predicted AUC_{SS} in (A) Resistant/Intolerant Pediatric Patients and (B) Newly Diagnosed Pediatric Patients.

Applicant's Summary of Clinical Pharmacology in Pediatric Patients with CML Figure 3-8.

Exposure values of >1800 ng/mL result in the upper limit of the CI associated with the estimated QTcF interval change from baseline exceeding 10 msec for resistant/intolerant patients, while exposure values of >1100 ng/mL resulted in the upper limit of the CI associated with the estimated QTcF interval change from baseline being greater than 10 msec among older patients in the newly diagnosed patients (**Figure 6**). No significant exposure-related changes were observed in the ECG parameters PR, QRS, and HR.These findings are consistent with the observations in adult patients and it is advised that ECG monitoring is conducted in all patients treated with nilotinib.

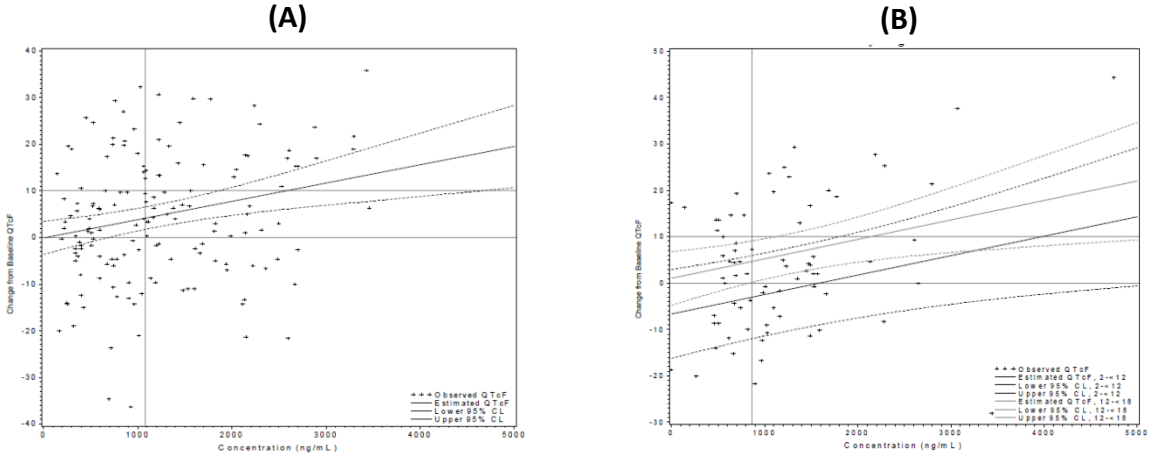

Figure 6: Logistic Regression of QTcF Change from Baseline vs. Nilotinib Concentrations in (A) Resistant/Intolerant Pediatric Patients and (B) Newly Diagnosed Pediatric Patients.

Applicant's Summary of Clinical Pharmacology in Pediatric Patients with CML Figure 3-10.

In addition, the logistic regression analyses also showed that no significant difference in the risk of onset of AEs leading to dose modification or treatment discontinuation, across dose quartiles in both pediatric patient populations (**Table 3**).

Table 3: Model Estimates from Logistic Regression Model for the Probability of AEs leading to dose modification vs. Dose Intensity in Both Pediatric Patient Populations.

				Odds Ratio 95% CI		
Cohort	Parameter	Estimate	Standard error	Estimate	Lower	Upper
Imatinib/dasatinib resistant/intolerant Ph+ CML-CP	Intercept	7.3200	28.1000		-47.8	62.5
	Log DI	-1.2200	4.6000		-10.2	7.79
	Odds Ratio Co1: increase from Q1 to Q3		0.4240	0.894	0.389	2.05
Newly diagnosed Ph+ CML-CP	Intercept	-10.3000	52.4000		-113	92.5
	Log DI	1.8900	8.6000		-15	18.7
	RCE5C	-2.2000	1.0200		-4.21	-0.192
	RCE5C					
	Odds Ratio Co2: increase from Q1 to Q3		0.5390	1.13	0.391	3.24

Source: Applicant's Summary of Clincal Pharmacology in Pediatric CML, Table 3-9.

PK

Following the administration of 230 mg/m^2 BID, the geometric mean ratios of steady-state PK $AUC_{0-\tau}$ and CL/F of nilotinib in the pediatric patients aged 1 to <10 years and 10 - <18 years to that observed in adlult patients administered 400 mg BID was 0.86 for $AUC_{0-\tau}$ and 1.3 for CL/F (**Table 4**). This small difference in exposure is not expected to have a significant impact on efficacy and safety in pediatric patient populations compared to adults.

Table 4: Summary of Geometric Mean Ratio of Steady-State PK Parameters in Pediatric Population Compared to Adult Population with 90% CI by Age Group.

					Age Group Comparison		
						90% CI	
PK Parameter (unit)	Age group	N[1]	Adjusted Geo-mean	Comparison	Geo-mean Ratio	Lower	Upper
AUCss (ng*h/mL)	Adult	17	17102.856				
	Group 1: Age 1 year to < 10 years	7	15129.182	Group 1 / Adult	0.885	0.683	1.145
	Group 2: Age ≥ 10 years to < 18 years	7	14383.076	Group 2 / Adult	0.841	0.650	1.089
	All pediatric	14	14751.413	All pediatric / Adult	0.863	0.701	1.061
CL/F (BSA adjusted) (L/h/m^2)	Adult	17	12.033				
	Group 1: Age 1 year to < 10 years	7	15.356	Group 1 / Adult	1.276	0.971	1.677
	Group 2: Age ≥ 10 years to < 18 years	7	15.922	Group 2 / Adult	1.323	1.007	1.739
	All pediatric	14	15.637	All pediatric / Adult	1.300	1.044	1.618

ANOVA = analysis of variance ; AUCss = AUCtau for bid dose at steady state; BSA = body surface area; CI = confidence interval; CL/F = apparent systemic clearance; Geo-mean = geometric mean; PK = pharmacokinetic
All pediatric patients: 1 year to <18 years
Adult: patients from study AMN107A2101 whose PK data are used as reference.
ANOVA model of the log-transformed PK parameters. Included in the model was age group as main effect.
Results were back transformed to get adjusted geometric mean, geometric mean ratio and 90% CI.
[1] number of subjects with evaluable PK data.

Source: Applicant's Summary of Clincal Pharmacology in Pediatric CML, Table 2-3.

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

No. The population PK model based on concentrations from 72 pediatric patients identified that BSA was a significant covariate on CL and volumes of distribution, which supported the BSA-based dosing regimen in pediatric patient populations. Refer to **Section 4.3** for more information. No dose adjustment is recommended for specific pediatric populations after adjusting the dose regimen by BSA.

4. APPENDICES

4.1.Summary of Bioanalytical Method Validation and Performance

Serum samples from two pediatric trials were analyzed for the concentrations of nilotinib via a validated liquid-liquid extraction followed by evaporation to dryness and analysis of the reconstituted samples by LC-MS/MS using ESI, which was developed by (b) (4). The bioanalytical method was adequately validated according to the FDA guideline for bioanalytical method validation with a calibration range of 2.50 ng/mL to 5000 ng/mL for nilotinib, and demonstrated long-term storage stability at -15°C for serum samples in the current trial. **Table 5** is a summary of bioanalytical report and corresponding bioanalytical method performance for both pediatric trials.

Table 5: Summary of Bioanalytical Methods for Nilotinib in Trial 2120 and 2203.

Trial No.	Matrix	Bioanalytical Report	Bioanalytical method performance
2120 & 2203	Serum	13BAS0249 ((b) (4))	Method: LC-MS/MS using ESI Lower limit of quantification: 2.50 ng/mL Calibration Range: 2.50 to 5000 ng/mL Intra-assay Precision (%CV): 3.1% to 6.6% Inter-assay Precision (%CV): 2.1% to 7.0% Intra-assay Accuracy: 96.6% to 102.0% Inter-assay Accuracy: 88.8% to 113.6% Bench Top Stability: 6 hours at RT Long-term Stability: 96 hours at room temperature, 8 months at ≤ -15°C Free thaw stability: 3 freeze-thaw cycles at ≤ -15°C

4.2.Clinical PK and/or PD Assessments

PK Assessment

The PK of nilotinib was characterized by non-compartmental analysis (NCA) based on intensive PK data from Trials 2120 and 2203 in pediatric patients with newly diagnosed Ph+ CML-CP, or with resistant/ intolerant Ph+ CML-CP.

Trial 2120

The full PK profiles of nilotinib in pediatric patients following a single 230 mg/m^2 dose on Cycle 1 Day 1 and at steady state are shown in **Figure 7**. Although nilotinib tended to decline faster in age group of 10 to < 18 years than in age group of 1 to <10 years (**Figure 7A**), the steady-state concentrations appeared to be generally comparable between age group of 1 to <10 years and age group of 10 to < 18 years (**Figure 7B**).

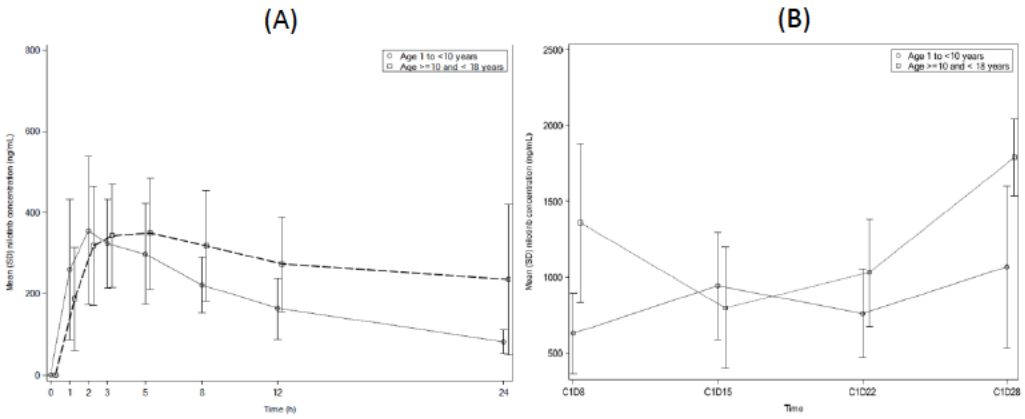

Figure 7: Arithmetic Mean (SD) Serum Concentration-Time Profiles for Nilotinib (A) on Cycle 1 Day 1 and (B) at Steady State.

Source: Applicant's Clinical Stduy Report 2120, Figure 11-1 and 11-3.

The geometric means of C_{max}, T_{max}, AUC_{last}, and $AUC_{0\text{-}12h}$ in pediatric patients after first dose on Cycle 1 Day 1 and at steady state are presented in **Table 6** and **Table 7**, respectively. The geometric mean of $AUC_{0\text{-}12h}$ tended to be higher in age group of 10 to < 18 years than in age group of 1 to <10 years (3393 vs. 2796 ng·h/mL). However, no marked difference was observed between two age groups with regard to the steady-state PK exposure and CL of nilotinib. Parameters pertinent to the terminal phase (AUC_{inf}, $T_{1/2}$, V_d/F, and CL/F) were unable to be reliably estimated due to the short sampling scheme after the single dose.

Table 6: Summary of Nilotinib NCA PK Parameters on Cycle 1 Day 1 by Age Group in Trial 2120.

Age Group	Statistics	Cmax (ng/mL)	Tmax (h)	AUClast (ng*h/mL)	AUC0-12h (ng*h/mL)
Group 1: Age 1 year to < 10 years	n[1]	7	7	7	7
	Mean (SD)	433.286 (163.1050)	N/A	4397.063 (1500.786)	2932.341 (917.1243)
	CV% mean	37.6	N/A	34.1	31.3
	Geo-mean	405.111	N/A	4160.969	2795.782
	CV% geo-mean	42.5	N/A	38.5	35.7
	Median	407.000	2.000	4374.288	2895.676
	[Min; Max]	[222.00; 669.00]	[1.02; 7.08]	[2116.92; 6820.32]	[1490.13; 4098.21]
Group 2: Age ≥ 10 years to < 18 years	n[1]	7	7	7	7
	Mean (SD)	422.857 (140.8314)	N/A	6313.115 (3193.430)	3531.036 (1141.116)
	CV% mean	33.3	N/A	50.6	32.3
	Geo-mean	402.715	N/A	5707.368	3393.206
	CV% geo-mean	35.2	N/A	51.2	30.4
	Median	397.000	3.000	5704.000	3331.763
	[Min; Max]	[231.00; 636.00]	[2.00; 7.88]	[2759.76; 12625.46]	[2316.18; 5754.96]

Age Group	Statistics	Cmax (ng/mL)	Tmax (h)	AUClast (ng*h/mL)	AUC0-12h (ng*h/mL)
All pediatric patients	n[1]	14	14	14	14
	Mean (SD)	428.071 (146.4978)	N/A	5355.089 (2595.136)	3231.689 (1041.969)
	CV% mean	34.2	N/A	48.5	32.2
	Geo-mean	403.911	N/A	4873.211	3080.043
	CV% geo-mean	37.3	N/A	46.8	33.5
	Median	402.000	2.525	4727.179	3087.408
	[Min; Max]	[222.00; 669.00]	[1.02; 7.88]	[2116.92; 12625.46]	[1490.13; 5754.96]

AUC = area under the curve; CL/F = apparent systemic clearance; CV% = coefficient of variation (%) = SD/mean*100; Geo-mean = geometric mean; CV% Geo-mean = sqrt ((exp (variance for log transformed data)-1))*100; Last = 24 hrs; PAS = PK analysis set; PK = pharmacokinetic; SD = standard deviation; Tmax = time to reach maximum serum concentration
[1] = number of patients with corresponding PK parameter available.
Source: Table 14.2-1.1

Source: Applicant's Clinical Stduy Report 2120, Table 11-5.

Table 7: Summary of Nilotinib NCA PK Parameters at Steady State by Age Group in Trial 2120.

Age Group	Statistics	AUCss (ng*h/mL)	CL/F (BSA adjusted) (L/h/m^2)	Cmin (ng/mL)
Group 1: Age 1 year to < 10 years	n[1]	7	7	7
	Mean (SD)	16036.175 (6017.8590)	16.231 (5.4766)	842.262 (270.1217)
	CV% mean	37.5	33.7	32.1
	Geo-mean	15129.182	15.356	804.791
	CV% geo-mean	38.0	38.7	33.7
	Median	14420.130	16.127	877.000
	[Min; Max]	[9032.53; 26984.92]	[7.94; 22.99]	[549.00; 1236.67]
Group 2: Age ≥ 10 years to < 18 years	n[1]	7	7	7
	Mean (SD)	15006.959 (4413.9681)	16.928 (7.1759)	1091.917 (221.7097)
	CV% mean	29.4	42.4	20.3
	Geo-mean	14383.076	15.922	1072.850
	CV% geo-mean	33.6	37.0	20.5
	Median	14046.393	16.533	1055.667
	[Min; Max]	[7943.94; 19807.20]	[11.72; 32.11]	[835.67; 1435.00]
All pediatric patients	n[1]	14	14	14
	Mean (SD)	15521.567 (5098.2195)	16.579 (6.1433)	967.089 (270.4515)
	CV% mean	32.8	37.1	28.0
	Geo-mean	14751.413	15.637	929.204
	CV% geo-mean	34.5	36.3	30.9
	Median	14268.403	16.330	979.792
	[Min; Max]	[7943.94; 26984.92]	[7.94; 32.11]	[549.00; 1435.00]

AUC = area under the curve; AUCss = AUCtau for bid dose at steady state; CL/F = apparent systemic clearance; Cmin = lowest trough concentration observed as the average value of the evaluable Ctrough from C1D8, C1D15, C1D22 and C1D28; CV% = coefficient of variation (%) = SD/mean*100; Geo-mean = geometric mean; CV% Geo-mean = sqrt ((exp (variance for log transformed data)-1))*100; PAS = PK analysis set; PK = pharmacokinetic; SD = standard deviation.
[1] number of patients with corresponding PK parameter available
All pediatric patients:1 year to < 18 years
Source: Table 14.2-1.2

Source: Applicant's Clinical Stduy Report 2120, Table 11-6.

Trial 2203

Nilotinib concentrations achieved steady state approximately on Cycle 1 Day 8, based on sparse trough concentrations from 25 pediatric patients with newly diagnosed CML-CP (**Figure 8A**) and 30 patients with resistant or intolerant CMP-CP (**Figure 8B**).

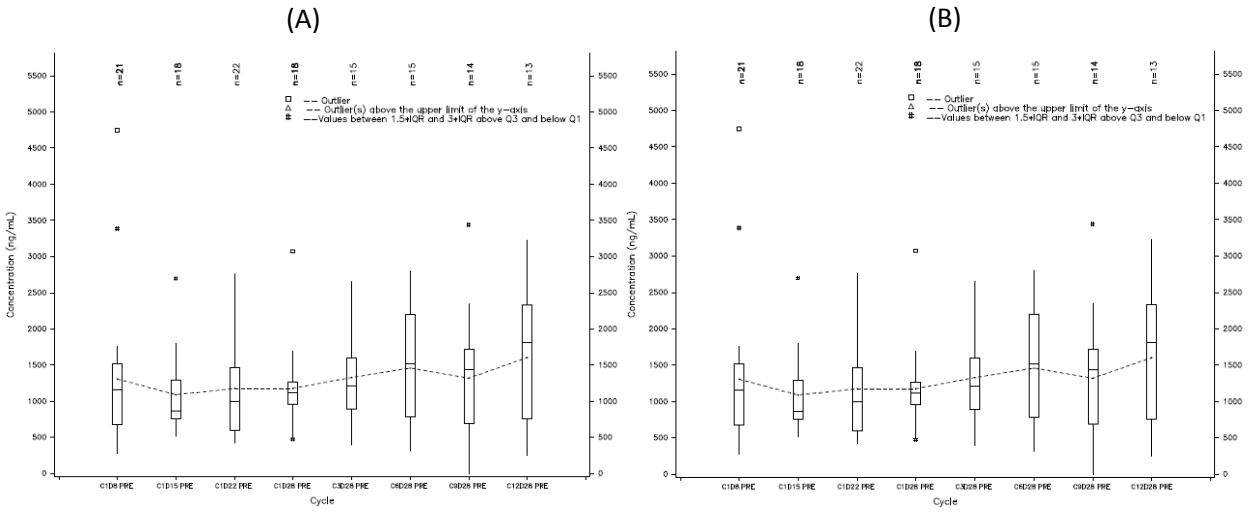

Figure 8: Box-plots of Trough Nilotinib Concentration Over Time in Patients with (A) Newly Diagnosed Ph+ CML-CP and (B) resistant or intolerant Ph+ CML-CP.

Source: Applicant's Clinical Stduy Report 2203, Figures 11-9 and 11-10.

The average nilotinib trough PK concentrations at all sampling time points were generally comparable between two pediatric patient populations in Trial 2203 (**Table 8**).

Table 8: Summary of Nilotinib NCA PK Parameters at Steady State by Age Group in Trial 2120.

Statistics	Imatinib/dasatinib resistant/intolerant Concentration (ng/mL) N=32	Newly Diagnosed Concentration (ng/mL) N=25	All Patients Concentration (ng/mL) N=57
n	30	25	55
Mean (SD)	1513.8 (570.55)	1405.5 (697.07)	1464.6 (627.49)
CV% mean	37.689	49.596	42.844
Geo-mean	1407.89	1274.30	1345.51
CV% geo-mean	41.667	46.208	43.663
Median (Q2)	1533.5	1248.7	1361.3
[Q1; Q3]	(1196, 1750)	(1019 ;1609)	(1032, 1750)
[Min; Max]	(577, 3178)	(539 ;3390)	(539, 3390)

Source: Applicant's Clinical Stduy Report 2203, Table 11-22.

4.3.Population PK Anlaysis

The population PK model of nilotinib was developed with 1155 concentrations from a total of 107 patients, including 14 pediatric patients in Trial 2120, 58 pediatric patients in Trial 2203, 17 adult patients in Trial 2101 with at least one PK concentration for a 400 mg twice daily regimen, and 18 adult patients in Trial 2303 with at least one PK concentration for a 400 mg twice daily regimen. The structural PK model developed in adult patients based on data from Trial 2101 (n = 493) was adopted in this analysis. This was a two-compartment model, with an absorption lag time (ALAG1, h) followed by a zero-order absorption of duration (D_1, h), and with elimination described by a first-order process. The parameter estimates from the adult population PK model (**Table 9**) were used as a starting point for the current population PK analysis.

Table 9: Parameter Estimates from the Adult Population PK Model.

Parameter name in NONMEM	Parameter Description	Unit	Estimate	RSE (%)	SE
	Parameters related to structural model				
THETA(1)	θ_{CL} in TVCL	L/h	12.8	9.3	
THETA(2)	TVV1	L	56.0	22.5	
THETA(4)	Q	L/h	103	8.7	
THETA(5)	TVV2	L	247	10.2	
THETA(6)	Duration of 0-order absorption, D1	H	3.02	0.2	
THETA(7)	Absorption lag, ALAG1	H	0.746	0.7	
	Parameters related to covariates				
THETA(3)	θ_{Dose} in TVF1		1.65	17.8	
THETA(10)	TVF1 for Dose=50 mg, evening dose, female		1 (fixed)	NA	
THETA(11)	θ_{MD} in TVF1		0.649	6.4	
THETA(12)	θ_{Male} in TVF1		0.835	5.0	
THETA(13)	$\theta_{CL,BIL}$ in TVCL		-0.117	26.9	
	Parameters related to intersubject variability				
OMEGA(1,1)	SD(η_{CL}), CV	%	27.4	22.8	
OMEGA(2,2)	SD(η_{V1}), CV	%	128.9	17.2	
OMEGA(3,3)	SD(η_{F1}), CV	%	62.0	11.4	
OMEGA(4,4)	SD(η_{V2}), CV	%	72.2	11.7	
OMEGA(2,1)	Correlation(η_{V1},η_{CL})		-0.104		0.488
OMEGA(3,1)	Correlation(η_{F1}, ,η_{CL})		0.431		0.189
OMEGA(3,2)	Correlation(η_{F1},η_{V1})		0.165		0.275
	Parameters related to residual error variability				
THETA(8)	Proportional residual error, σ_1	%	33.3	3.3	
THETA(9)	Additive residual error, σ_2	ng/mL	62.9	13.5	

Source: Applicant's Population PK Report, Table 4-1.

The final pediatric population PK model was developed based on the same model structure in adult patients with two time-varying covariates, BSA and total bilirubin, included in the final model. BSA was correlated with apparent CL and volumes of distribution; total bilirubin was correlated with apparent CL. The other tested covariates, such as age, ALT, AST, indication, race, and sex, were not found statistically significant ($p < 0.01$) on PK parameters. The parameter estimates of the final model are presented in **Table 10.** The goodness-of-fit plots (**Figure 9**) and the visual predictive check (VPC) plots (**Figure 10**) showed that the model described the data well.

Table 10: Parameter Estimates from the Final Pediatric Population PK Model.

Parameter	Parameter Description	Unit	Estimate	RSE[1] (%)	95% CI		Shrinkage[2] (%)
Parameters related to structural model							
exp(THETA(1))	TVCL at normalized BIL= 0.5	L/h	24.4	4.4	22.4	26.6	
exp(THETA(2))	TVV1 at BSA=1.73 m^2	L	87.1	28.8	50.1	152	
exp(THETA(3))	TVQ at BSA=1.73 m^2	L/h	333	10.9	269	413	
exp(THETA(4))	TVV2 at BSA=1.73 m^2	L	603	12.6	472	771	
exp(THETA(5))	Duration of 0-order absorption, D1	h	3.87	2.6	3.68	4.08	
THETA(6)	Absorption lag, ALAG1	h	0.7	NA	NA	NA	
Parameters related to covariates							
THETA(7)	Exponent for BSA for clearances		0.678	21.3	0.395	0.962	
THETA(8)	Exponent for BSA for volumes		0.565	42.8	0.0906	1.04	
THETA(9)	Exponent for normalized total bilirubin		-0.221	20.5	-0.31	-0.133	
Parameters related to intersubject variability							
OMEGA(1,1)	SD(η_{CL}), CV	%	35.9	8.6	29.8	41.9	5.6
OMEGA(2,2)	SD(η_{V1}), CV	%	95.1	22	54.1	136	48.3
OMEGA(3,3)	SD(η_{Q}), CV	%	40	34.7	12.8	67.2	54.6
OMEGA(4,4)	SD(η_{V2}), CV	%	75.6	22.7	42	109	24.6
Parameters related to residual error variability							
SIGMA(1,1)	Proportional residual error, σ_1	%	37	3.2	34.7	39.4	7.2
SIGMA(2,2)	Additive residual error, σ_2	ng/mL	32.1	36.4	9.23	55	7.2

[1] For parameters with exp(), relative standard error (RSE) is reported as 100% × sqrt[exp(SE**2)-1], where SE comes directly from NONMEM output; otherwise, RSE is reported as 100% × SE/|estimate|.

[2] Shrinkages labeled as "ETAshrink(%)" in NONMEM for parameters related to OMEGA are computed as 100% × (1-SD(η_{est}/sqrt(OMEGA))), where η_{est} is the estimated η. Shrinkages labeled as "EPSshrink(%)" in NONMEM for parameters related to SIGMA are computed in NONMEM as 100% × (1-SD((conc-F)/sqrt($\sigma_1^2F^2+\sigma_2^2$))), where conc is the observed concentration.

Source: Applicant's Population PK Report, Table 5-9.

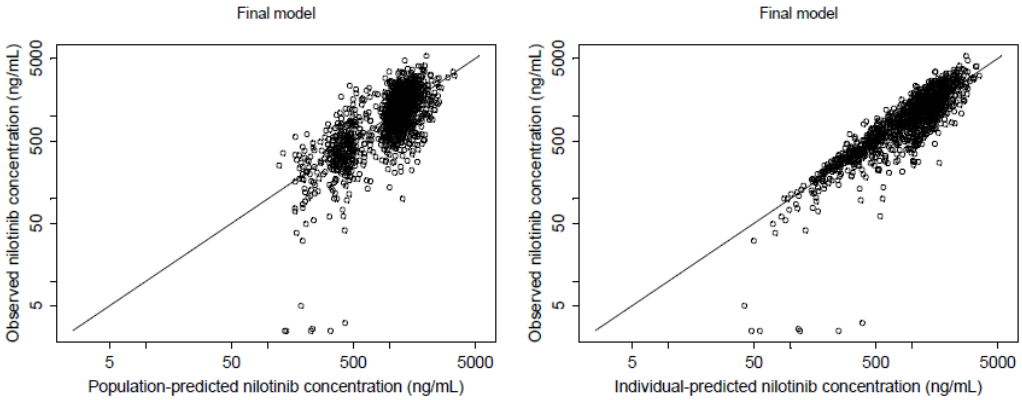

Figure 9: Goodness of Fit for Final Model based on All Data.

Source: Figure 59 from Applicant's Population PK and PK-PD Analysis Report No. 1072889.

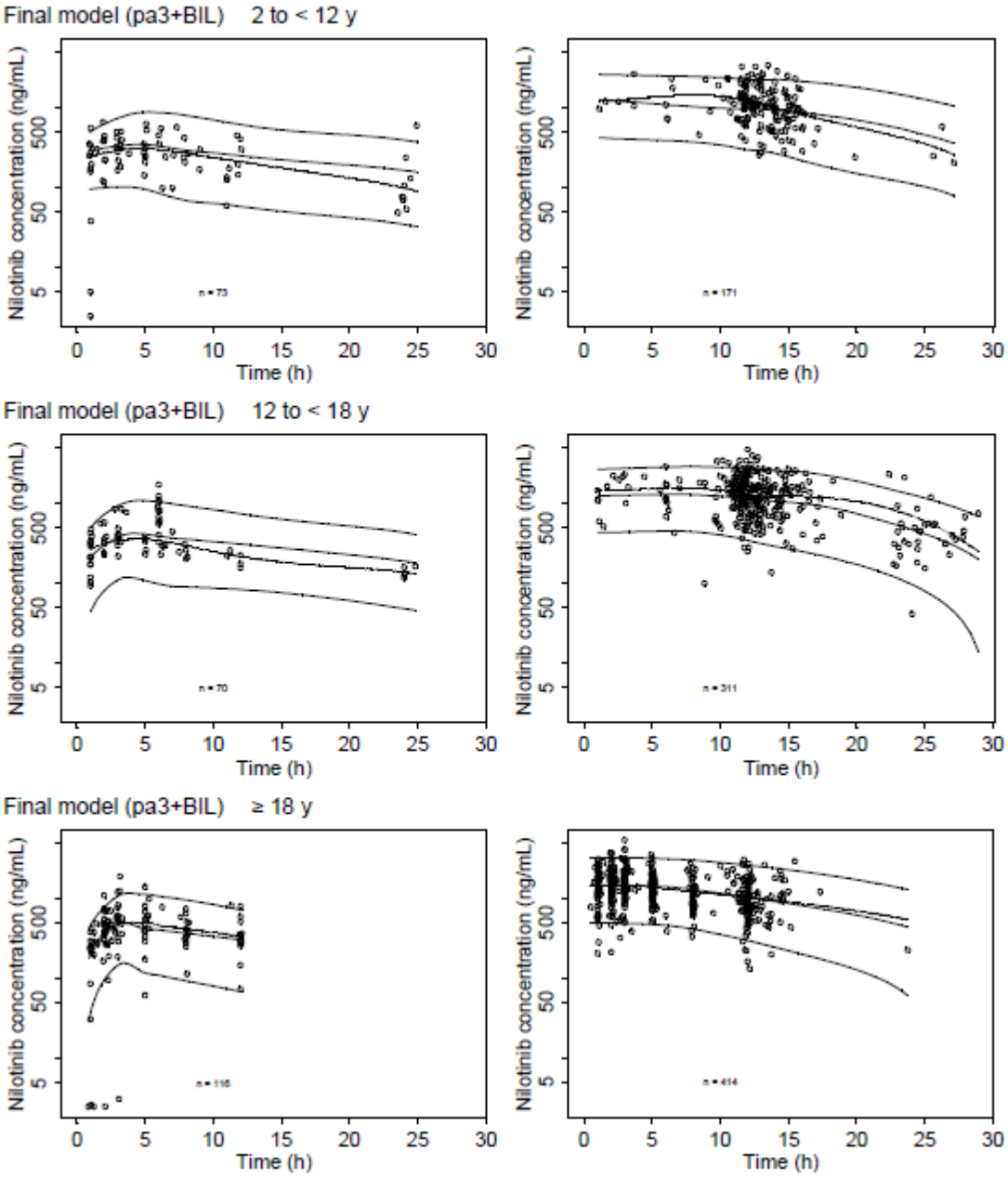

Figure 10: Visual Predictive Checks for Final Model Stratified by Age Groups (Top, Middle, and Bottom Panels), by 1st Dose (Left Panel), and by Multiple Doses (Right Panel).

Source: Applicant's Population PK Analysis, Figure 5-3.

The sensitivity analysis by refitting the data only from ages < 18 years showed that the PK parameter estimates were comparable to those in the final model. The sensitivity analysis also showed that the PK exposure in pediatric patients dosed at 230 mg/m^2 twice daily was comparable to that of the reference population of adult patients dosed at 400 mg twice daily (**Table 11**).

Table 11: Geometric Mean Ratios of Steady-State AUCs and 90% Confidence Intervals for Each Age Group of Pediatric Patients to Adult Patients based on the Final Model and the Refitted Model without Data from Adult Patients.

Ages (y)	Median age at baseline (y)	Median BSA at baseline (m^2)	Dose[1] (mg)	Median normalized bilirubin at steady state	Final nilotinib model (N=107)		Model for 2 to <18 y (N=72)	
					Estimate of ratio	90% CI	Estimate of ratio	90% CI
2 to <12	10.1	0.98	250	0.75	0.939	[0.811,1.09]	0.928	[0.766,1.13]
12 to <18	15.3	1.54	350	0.86	0.992	[0.953,1.03]	0.992	[0.941,1.04]
≥18 reference	52	1.82	400	0.80				

[1] mg dose is 400 bid for ages ≥ 18 y and 230 × BSA bid rounded to nearest 50 mg not to exceed a single dose of 400 mg for ages 2 to less than 18 y. For example, the calculated dose for 2 to less than 12 years of age was 0.98 x 230 = 225.4 mg, which was rounded to an actual dose of 250 mg.

Ratios and confidence intervals are computed at median values for BSA and normalized bilirubin.
Note that while the refitted model based on ages 2 to less than 18 excludes adults, the refitted model as well as the final model compute adult AUC based on BSA and bilirubin typical for an adult.

Source: Applicant's Population PK Analysis, Figure 5-14.

Reviewer's comments: *Reviewer's independent analysis indicated that the results were consistent to the Applicant's analysis and the nilotinib AUC at steady state were comparable across adult patients at the proposed fixed dose regimen and pediatric patients with different ages at the proposed BSA-based dose regimen. Therefore, the proposed dose regimen of 230 mg/m^2 twice daily was deemed to be acceptable. Reviewers agree with the Applicant's conclusion that no dose adjustment is recommended for specific populations in pediatric patients, since no significant covariate is expected to affect nilotinib exposure, efficacy or safety in the proposed indications.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LIANG LI
02/27/2018

OLANREWAJU OKUSANYA
03/05/2018
I concur