Dose Justification for Asciminib in Patients With Philadelphia Chromosome-Positive Chronic Myeloid Leukemia With and Without the T315I Mutation

Supplementary Materials

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Methods

S1: Data Pooling

For the population pharmacokinetics (PopPK) analysis, PK data from patients with CML-CP/AP receiving asciminib in the dose-finding and ASCEMBL studies were pooled. The exposure-response efficacy (ERe) analysis included data from patients with CML-CP, the target population from single-agent cohorts in the dose-finding study, and from the asciminib cohort in the ASCEMBL study who had predicted PK metrics. The exposure-response safety (ERs) analysis was performed using pooled data from patients with CML-CP/AP from single-agent cohorts in the dose-finding study, and all patients from the asciminib cohort in ASCEMBL who provided at least one predicted daily AUC/C_{max}/C_{min} from the PopPK model. QT/QTc data from patients with CML or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) treated with single-agent asciminib in the dose-finding study who provided baseline QT/QTc data and at least one corresponding post-dose time-matched plasma asciminib concentration and QT/QTc record were analyzed.

S2: Software Used in the Analyses

The PopPK and ERe analyses were performed using Monolix suite 2019R2 software (Lixoft SAS, a Simulations Plus company, Paris, France), deployed on Red Hat Enterprise Linux version 7 (Red Hat, Raleigh, NC). Data preparation and other model diagnostics were performed using R 3.6.1. Simulx (from Monolix Suite 2019R2), with R3.6.1 used for simulations. Earlier versions, up to Monolix Suite 2021R2 and R 4.1.0, have also been used for the latest simulations. The ERs analysis was performed using SAS version 9.4.

S3: Exposure response analysis for efficacy

The PK/PD model was discussed in detail in our previous publication presenting "the effect of longitudinal asciminib exposure on CML disease progression, specifically on the *BCR::ABL1* levels over time, along with factors influencing the efficacy."[1] For the better understanding of the data presented in the current manuscript, we provide below a brief summary of the PK/PD model developed based on a semi-mechanistic model developed by Fassoni et al.[2] with modifications in order to add a resistant leukemic cell compartment that is necessary to describe the interplay between tumor growth (proliferating cells) (P), drug-resistant leukemic cells (R), and activation/deactivation of quiescent cells (Q). The cytotoxic drug effect was applied on the proliferating cells only.

Disease model

The model is described by the following differential equations:

$$\frac{dQ}{dt} = k_{pq} \cdot P + k_{rq} \cdot R - (k_{qp} + k_{qr}) \cdot Q$$

$$\frac{dP}{dt} = k_{qp} \cdot Q - k_{pq} \cdot P + k_{gr} \cdot (1 - \frac{P}{tot_{max}}) \cdot P - DRUG \cdot P$$

$$\frac{dR}{dt} = k_{qr} \cdot Q - k_{rq} \cdot R + k_{gr} \cdot (1 - \frac{R}{tot_{max}}) \cdot R$$

where the growth rate constant of proliferating and resistant cells is represented by k_{gr} and the maximum amount of proliferating and resistant cells able to reside within the bone marrow is denoted by tot_{max}.

$(1 - \frac{P}{tot_{max}})$ is a logistic growth model, where tot_{max} represents the carrying capacity[3]. For some of the patients who relapsed, *BCR::ABL1* levels increased by 10 to 100 times their pre-treatment levels. For this reason, tot_{max} was defined as 100 multiplied by the sum of steady-state P and R, from which follows:

$$tot_{max} = 100 \cdot (P_{t=0} + R_{t=0})$$

where P(t = 0) and R(t = 0) represented the steady-state P and R prior to treatment. Finally, DRUG (i.e., the effect of the treatment drug) represented the rate of death in proliferating cells caused by asciminib.

Further assumptions were made aligning with the nature of CML cells in the chronic phase and thus P, R, and Q represented the ratio of proliferating and quiescent cells to healthy cells, respectively. The growth rate constant k_{gr} was set at 28 year^{-1}, representing a doubling time of approximately 9 days.[1]

Drug effect model[1]

Power model (final PD model):

In the final ER model, the drug effect was characterized by 2 parameters, Eff_{mag} and gamma, such as

$$DRUG = Eff_{mag} * (\frac{C_{min}}{median\ C_{min}})^{gamma}$$

Regimen model (used for the 80 mg vs 40 mg model):

In an alternative model, the drug effect was estimated with a covariate effect value $beta_{ARM-Effmag}$ for each dosing regimen:

$$DRUG = Eff_{mag_{Regimen}}$$

$$log\,(Eff_{mag_{Regimen}}) = \log(Eff_{mag}) + beta_{ARM-Effmag} * ARM$$

Where ARM = 0 is for a patient following a 40 mg b.i.d. regimen, and ARM = 1 for a patient following an 80 mg q.d. regimen, and $beta_{ARM-Effmag}$ characterizes the difference between the 2 regimens.

E_{max} model (T315I model)

In an alternative model, the drug effect was estimated with an E_{max} model:

$$DRUG = E_{max} * \frac{Daily\ PK}{EC_{50} + Daily\ PK}$$

In order to follow the principle of parsimony and ensure model convergence, some parameters (k_{gr}, k_{qp}, k_{qr}) were fixed at the estimated values from the final model,[1] and number of prior TKIs was reduced to two categories, i.e. ≤2 or ≥3. Since the number of patients with CML-CP harboring the T315I mutation and treated with these dose regimens was small (N=2), these patients were excluded from this analysis.

Results

Table S1. Summary of number of events in Exposure-safety analyses of laboratory events (PK-Safety set)

Laboratory parameter abnormality		**Number of events (n/N)**		
	Study	**#Events/#Records**	**#Cycles with events /#Cycles**	**#Patients with events /#Patients**
Amylase increase (any grade)	ASCEMBL	52/2207 (2.4%)	37/1706 (2.2%)	17/151 (11.3%)
	Dose-finding study	444/6803 (6.5%)	321/3912 (8.2%)	66/198 (33.3%)
Amylase increase (grade ≥3)	ASCEMBL	1/2207 (0.0%)	1/1706 (0.1%)	1/151 (0.7%)
	Dose-finding study	23/6803 (0.3%)	22/3912 (0.6%)	14/198 (7.1%)
Lipase increase (any grade)	ASCEMBL	42/2207 (1.9%)	34/1707 (2.0%)	20/151 (13.2%)
	Dose-finding study	642/6962 (9.2%)	441/3927 (11.2%)	94/198 (47.5%)
Lipase increase (grade ≥3)	ASCEMBL	7/2207 (0.3%)	5/1707 (0.3%)	4/151 (2.6%)
	Dose-finding study	105/6962 (1.5%)	90/3927 (2.3%)	36/198 (18.2%)
Platelet decrease (grade ≥3)	ASCEMBL	153/2555 (6.0%)	74/1689 (4.4%)	30/151 (19.9%)
	Dose-finding study	318/7266 (4.4%)	115/3961 (2.9%)	29/198 (14.6%)
Neutrophil decrease absolute (grade ≥3)	ASCEMBL	98/2296 (4.3%)	71/1651 (4.3%)	26/151 (17.2%)
	Dose-finding study	291/7219 (4.0%)	152/3960 (3.8%)	34/198 (17.2%)
Hemoglobin decrease (grade ≥3)	ASCEMBL	3/2566 (0.1%)	2/1699 (0.1%)	1/151 (0.7%)
	Dose-finding study	71/7282 (1.0%)	35/3965 (0.9%)	14/198 (7.1%)
ALT increase (grade ≥2)	ASCEMBL	14/2236 (0.6%)	11/1702 (0.6%)	6/151 (4.0%)
	Dose-finding study	47/7020 (0.7%)	36/3944 (0.9%)	14/198 (7.1%)
AST increase (grade ≥2)	ASCEMBL	2/2212 (0.1%)	2/1681 (90.1%)	2/151 (1.3%)
	Dose-finding study	18/6956 (0.3%)	17/3925 (0.4%)	9/198 (4.5%)
Bilirubin increase (grade ≥2)	ASCEMBL	7/2135 (0.3%)	5/1647 (0.3%)	4/151 (2.6%)
	Dose-finding study	68/7000 (1.0%)	51/3941 (1.3%)	11/198 (5.6%)
Triglyceride increase (any grade)	ASCEMBL	714/2164 (33.0%)	574/1699 (33.8%)	96/151 (63.6%)
	Dose-finding study	2157/6620 (32.6%)	1436/3865 (37.2%)	139/198 (70.2%)

Cycle: The treatment duration is divided in 28-day cycles.
ALT, alanine aminotransferase; *AST*, aspartate aminotransferase.

Figure S1. Goodness-of-fit for the population pharmacodynamic model in patients not harboring the T315I mutation, who were administered a starting dose of 40 mg b.i.d. or 80 mg q.d. Observation versus population fit (A) and individual fit (B) of asciminib plasma concentrations; normalized prediction distribution error versus time (C) and population fit (D); residual NDPE versus theoretical normal quantile (E) and frequency versus normalized prediction distribution error (F). The gray circles depict the individual asciminib plasma concentrations, the red dashed line captures the correlation between observed and predicted concentration, while the solid black line depicts the identity line (A-B). The gray circles depict the individual asciminib plasma concentrations, the red dots represent data below the limit of quantification, the red dashed line captures the correlation between predicted concentration and time or *BCR::ABL1*^{IS} levels, the black dashed lines represent reference for 2 and –2 units of NPDE (C-D). The solid dots represent NPDE at each population estimate or time point since first dose, the red lines indicate smoothing, and the solid line represents residual NPDE equals to zero (E). Frequency distribution of NPDE (F). *b.i.d.,* twice daily*; NPDE,* normalized prediction distribution error; *q.d.,* once daily.

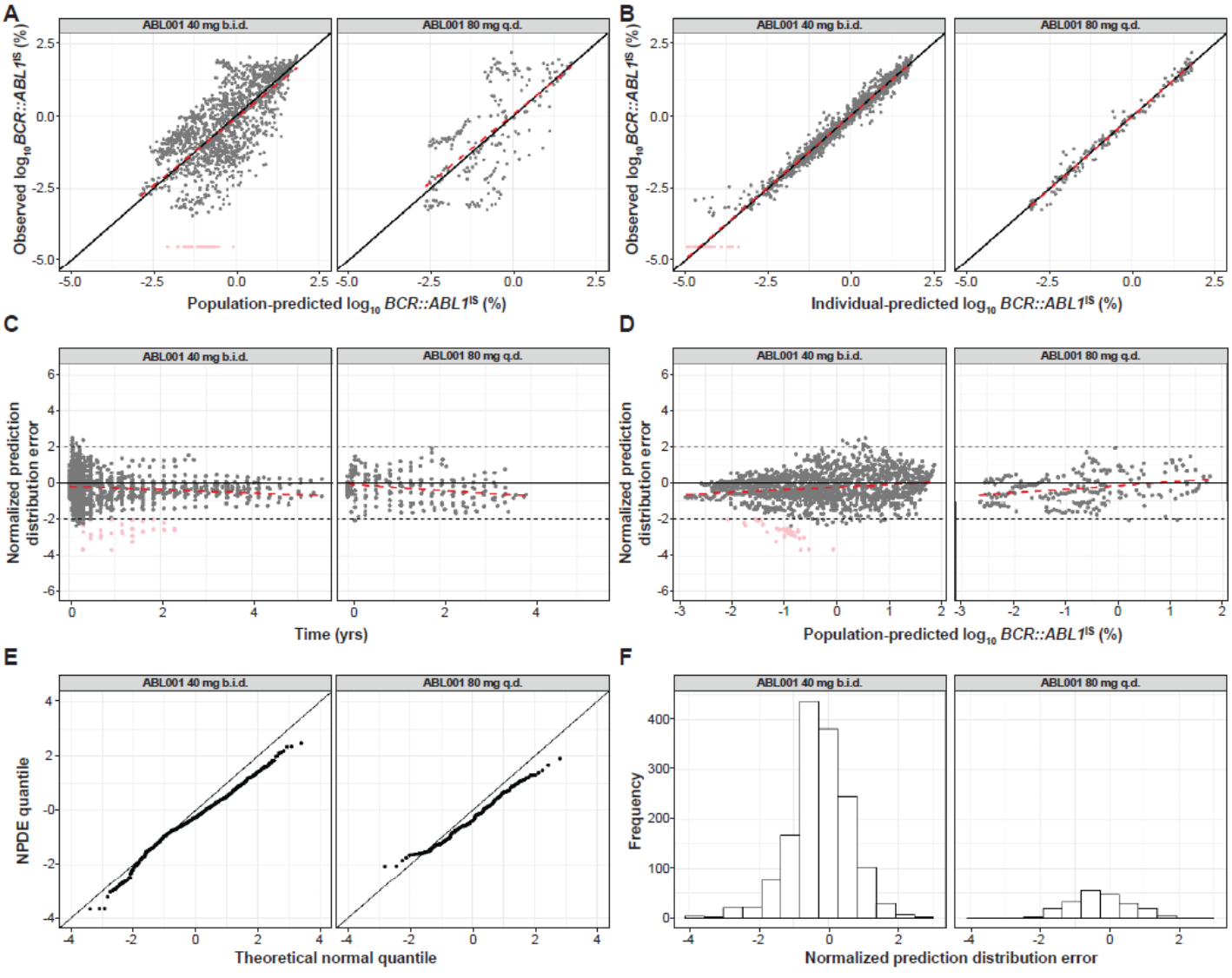
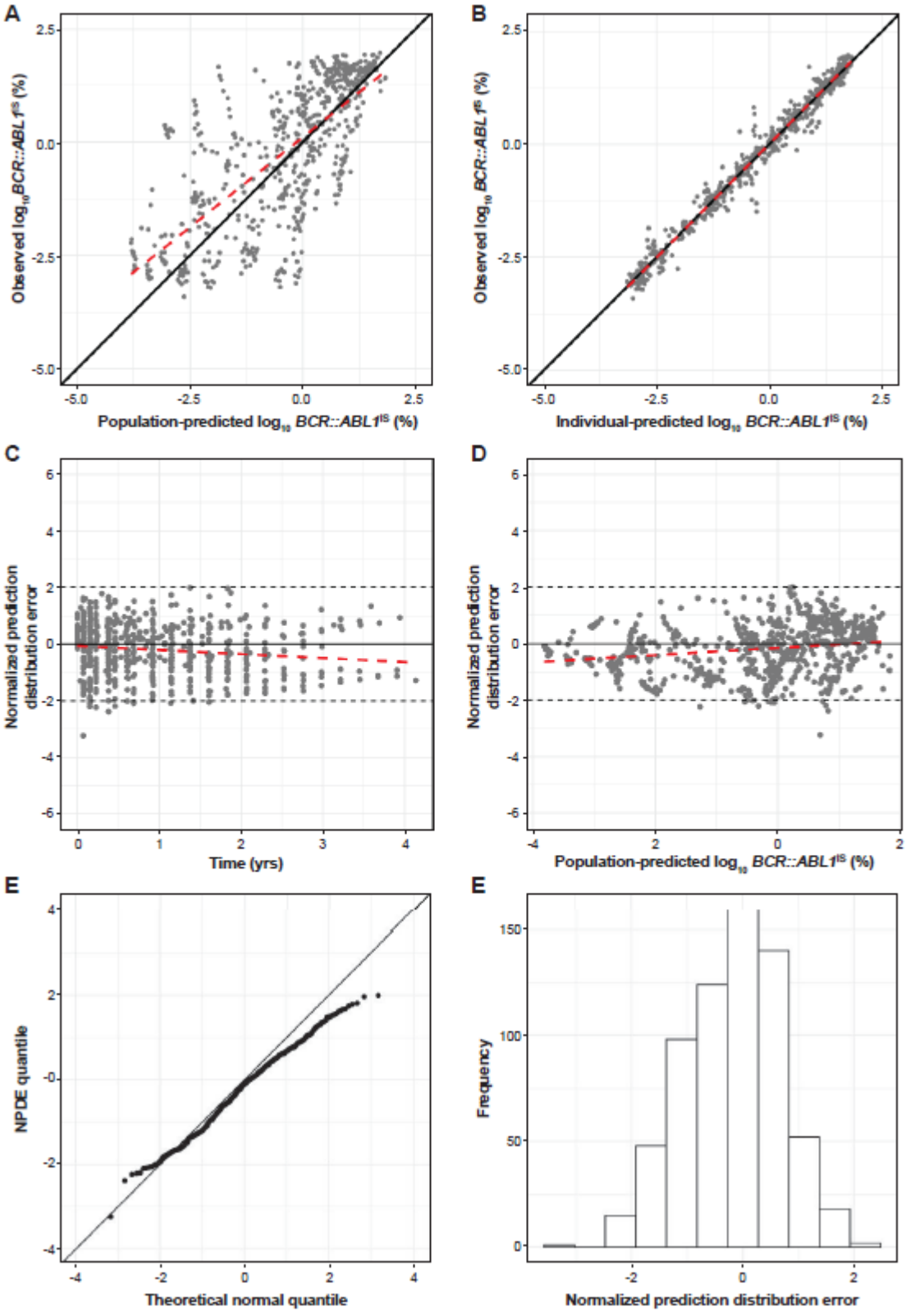


Figure S2. Goodness-of-fit for the population pharmacodynamic model based on AUC as PK metric in patients harboring the T315I mutation. Observation versus individual fit (A) and population fit (B) of asciminib plasma concentrations; normalized prediction distribution error versus time (C) and population fit (B); residual NPDE versus theoretical normal quantile (E) and frequency versus normalized prediction distribution error (F). The gray circles depict the individual asciminib plasma concentrations, the red dashed line captures the correlation between observed and predicted concentration, while the solid black line depicts the identity line (A-B). The gray circles depict the individual asciminib plasma concentrations, the red dots represent data below the limit of quantification, the red dashed line captures the correlation between predicted concentration and time or *BCR::ABL1*^{IS} levels, the black dashed lines represent reference for 2 and –2 units of NPDE (C-D). The solid dots represent NPDE at each population estimate or time point since first dose, the red lines indicate smoothing, and the solid line represents residual NPDE equals to zero (E). Frequency distribution of NPDE (F). *AUC*, area under the curve; *NPDE*, normalized prediction distribution error; *PK*, pharmacokinetics.


A
Observed log10 BCR::ABL1IS (%)
Population-predicted log10 BCR::ABL1IS (%)
B
Observed log10 BCR::ABL1IS (%)
Individual-predicted log10 BCR::ABL1IS (%)
C
Normalized prediction distribution error
Time (yrs)
D
Normalized prediction distribution error
Population-predicted log10 BCR::ABL1IS (%)
E
NPDE quantile
Theoretical normal quantile
E
Frequency
Normalized prediction distribution error

References

1. Combes FP, Li YF, Hoch M, Lorenzo S, Ho YY, Sy SKB. Exposure-Efficacy Analysis of Asciminib in Philadelphia Chromosome-Positive Chronic Myeloid Leukemia in Chronic Phase. *Clin Pharmacol Ther* **112(5)**, 1040–1050 (2022).
2. Fassoni, A.C., Baldow, C., Roeder, I. & Glauche, I. Reduced tyrosine kinase inhibitor dose is predicted to be as effective as standard dose in chronic myeloid leukemia: a simulation study based on phase III trial data. *Haematologica* **103**, 1825–1834 (2018).
3. Sy, S. & Derendorf, H. Pharmacometrics in bacterial infections. In *Applied Pharmacometrics. AAPS Advances in the Pharmaceutical Sciences Series*, Vol. **14** (eds. S. Schmidt & H. Derendorf) 229– 258 (Springer, New York, NY, 2014).