CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215358Orig1s000
215358Orig2s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology/Virology

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	New Drug Application
Application Number(s)	NDA 215358 ORIG-1 and ORIG-2
Priority or Standard	Priority
Submit Date(s)	June 24, 2021
Received Date(s)	June 24, 2021
PDUFA Goal Date	February 24, 2022
Division/Office	Division of Hematologic Malignancies I Office of Oncologic Diseases
Review Completion Date	October 29, 2021
Established Name	Asciminib
(Proposed) Trade Name	Scemblix
Pharmacologic Class	ABL/BCR-ABL1 tyrosine kinase inhibitor
Code name	ABL001
Applicant	Novartis Pharmaceuticals Corporation
Formulation(s)	Tablets: 20 mg and 40 mg
Dosing Regimen	Ph+ CML in CP previously treated with two or more TKIs: 80 mg daily or 40 mg twice daily Ph+ CML in CP with the T315I mutation: 200 mg twice daily
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with: • Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs) • Ph+ CML in CP harboring the T315I mutation
Recommendation on Regulatory Action	ORIG-1: Accelerated approval for treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs) ORIG-2: Regular approval for treatment of adult patients with Ph+ CML in CP with the T315I mutation
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with: • Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs) • Ph+ CML in CP with the T315I mutation

Table of Contents

Table of Tables

Table of Figures

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRM=Division of Risk Management

Glossary

2G	Second generation TKIs
ABL1/ABL1	*Italicized:* Abelson oncogene; non-italicized: Abelson protein
ABL2/ABL2	*Italicized:* Abelson related oncogene; non-italicized: Abelson related protein
ADME	absorption, distribution, metabolism, excretion
ADR	Adverse drug reaction
AE	adverse event
AESI	Adverse event of special interest
aGFR	Adjusted glomerular filtration rate
ALL	Acute lymphoblastic leukemia
Allo-SCT	Allogeneic stem cell transplantation
ALT	Alanine aminotransferase
AOEs	Arterial occlusive events
AP	Accelerated phase
AST	Aspartate aminotransferase
AUC	Area under curve
AUCinf	AUC from time zero to infinity
AUClast	AUC from time zero to the time of the last quantifiable concentration
AUCtau	AUC from time zero to the end of the dosing interval tau
BC	Blast crisis
BCR	Breakpoint Cluster Region
BCR-ABL	Chimeric *BCR-ABL1* oncogene
BCR-ABL	BCR-ABL1 oncoprotein with dysregulated ABL1 kinase activity
BCRP	Breast Cancer Resistance Protein
BCS	Biopharmaceutics classification system
BID	*bis in diem*/twice a day
BLA	biologics license application
BLRM	Bayesian logistic regression model
BMA	Bone marrow aspirate
BP	Blastic phase
CCyR	Complete Cytogenetic Response
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHR	Complete hematological response
CI	Confidence Interval
CI	Cumulative incidence function
Cmax	Observed maximum plasma (or serum or blood) concentration following drug administration

CMH	Cochran–Mantel–Haenszel
Cmin	Trough concentration
CL	Systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration
CL/F	Apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration
CLr	Renal clearance from plasma (or serum or blood) [volume / time]
CMC	chemistry, manufacturing, and controls
CML	Chronic Myeloid Leukemia
CML-AP	Chronic myeloid leukemia in accelerated phase
CML-BP	Chronic myeloid leukemia in blast phase
COVID-19	Coronavirus Disease of 2019
CRF	case report form
CSF	Clinical service formulation
CSR	Clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough/Cmin	Plasma concentration (measured concentration at the end of a dosing interval at steady state [taken directly before next administration]
CV	Coefficient of variation
CYP	Cytochromes P450
DDI	Drug interaction
DMC	data monitoring committee
DMPK	Drug metabolism and pharmacokinetics
EAIR	Exposure-adjusted incidence rate
EC50	Half maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EFD	Embryo-fetal development
ELN	European Leukemia Net
EMA	European Medicines Agency
EOT	End of treatment
EQ VAS	EuroQol Visual Analogue Scale
EWOC	Escalation with overdose control
FAS	Full Analysis Set
FCT	Film-coated tablet
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FIH	First in human
FMI	Final market image

GCP	good clinical practice
GGT	Gamma-glutamyltransferase
GLP	Good laboratory practice
GMR	Geometric-mean ratio
GRMP	good review management practice
HCRE	Highest clinical relevant exposure
hERG	Human ether-à-go-go-related gene
HF	High-fat (breakfast)
IC50	Half maximal inhibitory concentration
IC90	90% inhibitory concentration
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IS	International standard
Ka	Absorption rate constant
KM	Kaplan-Meier
ITT	intent to treat
MCyR	Major cytogenetic response
mCyR	Minor Cytogenetic Response
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Major molecular response
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCCN	National Comprehensive Cancer Network
NDA	new drug application
NE	Not estimable
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OS	Overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
Ph+ CML	Philadelphia chromosome-positive chronic myelogenous leukemia
PBPK	Physiologically based pharmacokinetic
PCR	Polymerase Chain Reaction
PCyR	Partial Cytogenetic response
PD	pharmacodynamics
PFS	Progression-free survival
P gp	P-glycoprotein
Ph+	Philadelphia chromosome positive
PK	pharmacokinetics
PopPK	Population PK

PRO	Patient-reported outcomes
QD	Once daily
QTcF	QT interval corrected by Fridericia's formula
RDE	Recommended dose for expansion
REMS	risk evaluation and mitigation strategy
RQ-PCR	Real time quantitative polymerase chain reaction
SAE	serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
TEAE	treatment emergent adverse event
T1/2	elimination half-life
TDD	Total daily dose
TKI	Tyrosine kinase inhibitors
Tmax	Time to reach the maximum concentration after drug administration
TTF	Time to treatment failure
UGT	Uridine 5-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
V1	Volume of central compartment, representing V1/F
V2	Volume of peripheral compartment, representing V2/F
Vz	Volume of distribution during the terminal elimination phase

1 Executive Summary

1.1. Product Introduction

Trade Name:	Scemblix®
Established Name:	Asciminib
Also Known As:	ABL-001
Therapeutic Class:	Antineoplastic
Chemical Class:	Small molecule
Pharmacologic Class:	ABL/BCR-ABL1 tyrosine kinase inhibitor
Mechanism of Action:	Inhibition of tyrosine kinase by binding to the myristoyl pocket of BCR-ABL1

Asciminib is an orally administered ABL/BCR-ABL1 tyrosine kinase inhibitor and ABL1 is a ubiquitously expressed, tightly regulated kinase. Unlike other BCR-ABL TKIs that bind to the ATP site of BCR-ABL1 protein, asciminib binds to the myristoyl pocket of BCR-ABL1 protein and mimics myristolated Gly-2 residue and stabilizes inactive conformation of the enzyme. Therefore, it is not expected to have the same off-target kinase-mediated effects seen with other ATP-competitive TKIs. Based on the binding site, asciminib is expected to have activity against point mutations that confer resistance to other ATP-competitive BCR-ABL TKIs, like T315I mutation.

Asciminib is being developed in chronic myeloid leukemia (CML) or Philadelphia-chromosome positive ALL (Ph+ ALL) patients (including those with T315I mutation) and has also been investigated in healthy volunteers. The Applicant submits a New Drug Application (NDA) with results from randomized phase 3 study CABL001A2301 (NCT03106779) to support the indication "for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs)" and phase 1 study CABL001X2101 (NCT02081378) to support the indication "for the treatment of adult patients with Ph+ CML in CP harboring the T315I mutation."

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval for asciminib for the treatment of Ph+ CML in CP previously treated with two or more TKIs (ORIG-1 application). The recommendation is based on the finding of improved major molecular response (MMR) at 24 weeks in study ASCEMBL (CABL001A2301, referred to as study A2301), and supportive evidence of improved complete cytogenetic response rate (CCyR) at 24 weeks, MMR at 48 weeks and other prespecified time points, durability of response, and subgroup analyses. The current framework for regular approval for a previously treated CP-CML indication requires a minimum of 96 weeks

for efficacy follow-up.

Study A2301 was a randomized (2:1), open-label, active controlled trial of asciminib monotherapy (n=157) versus bosutinib monotherapy (n=76). Randomization was stratified by the patients' cytogenetic response status at baseline (with or without major cytogenetic response [MCyR]). Patients with T315I or V299L mutations were excluded from the study because response would not be expected from bosutinib in patients with these mutations. The demographic and disease characteristics of the randomized patients were balanced between arms except for fewer females, fewer prior lines of TKI therapy, and more patients who discontinued their prior therapy due to intolerance as opposed to lack of efficacy in the asciminib arm. These imbalances could bias the results toward the asciminib arm.

The interim analysis of A2301 included a prespecified assessment of MMR at 24 weeks. MMR at 96 weeks is a key secondary endpoint and was not available at the time of this analysis. Other secondary endpoints include MMR at other scheduled time points, MMR by all scheduled time points, CCyR at and by all scheduled time points, time to response, duration of response, time to treatment failure, progression free survival, and overall survival.

At the time of analysis, MMR (defined as BCR-ABL1 ratio ≤0.1% on the International Scale) at 24 weeks was significantly better on the asciminib arm at 25% (95% CI: 19, 33) compared to that in the bosutinib arm at 13% (95% CI: 6.5, 23). The treatment difference in MMR rate at Week 24 was 12% (95% CI: 2.2, 22; two-sided p value of 0.029, stratified by the MCyR status at baseline).

At each scheduled time point, the MMR rate was improved in the asciminib arm, with observed improvement starting at the 12-week assessment. Median time to MMR was 12.7 weeks asciminib arm and 14.3 weeks in bosutinib arm. With a median duration of follow-up of 20 months (range: 1 day to 36 months), the median duration of response had not yet been reached for patients with MMR at any time.

Exploratory subgroup analyses were performed over demographics and baseline disease characteristics. Analyses over subgroups showed a consistent treatment effect favoring asciminib, including the imbalances in randomization (sex, number or prior TKIs, and intolerance to prior TKI), though the subgroup of those intolerant to their prior TKI only had a minor trend toward asciminib. The only subgroup analyzed that showed a risk difference less than zero (favoring bosutinib) was those with <1% BCR-ABL transcript levels at baseline; however, this subgroup was exceedingly small.

Labeling will describe the primary endpoint of MMR at 24 weeks, and important secondary endpoints of CCyR at 24 weeks. Median duration of MMR was not reached, so MMR at 48 weeks was also described.

The review team recommends regular approval for asciminib for the treatment of Ph+ CML in CP with a T315I mutation (ORIG-2 application). The recommendation for approval is based on

the finding of an acceptable rate of MMR at 24 weeks in patients with T315I mutations in study CABL001X2101 (referred to as study X2101) and supported by durability of MMR, MMR by prespecified time points, and the MMR rate in patients with or without prior ponatinib treatment. Regular approval is supported by the availability of MMR data with 96 week follow-up time.

Study X2101 was a non-randomized, open-label, dose escalation, first-in-human study of asciminib monotherapy or asciminib in combination with other TKIs (imatinib, nilotinib, or dasatinib] in patients with previously treated CML in CP or accelerated phase (AP), and a cohort of patients with CML in blast phase (BP) or Ph+ acute lymphoblastic leukemia (ALL) treated with asciminib monotherapy. This trial included dose finding in patients who had T315I mutations, and the 48 patients with CML in CP with T315I mutations treated with the recommended dose of 200 mg twice daily served as the pivotal cohort for this indication. Of these 48 patients, 3 had atypical/unknown BCR-ABL transcripts and were therefore unevaluable for efficacy.

The primary endpoint of the study was the incidence of dose limiting toxicities, and secondary efficacy endpoints included MMR by and at scheduled timepoints, duration of MMR, and time to MMR, cytogenetic response, and hematologic response

By the data cutoff, the majority of patients had reached 96 weeks of treatment or had discontinued study drug prior to 96 weeks. MMR was achieved by 24 weeks in 42% (95% CI: 28, 58) of the 45 patients treated with asciminib. MMR was achieved by 96 weeks in 49% (95% CI: 34, 64) of the 45 patients treated with asciminib. The median duration of treatment was 108 weeks (range, 2 to 215 weeks).

Of the 45 patients in the efficacy population with T315I mutations treated at 200 mg twice daily, all had received at least one prior BCR-ABL TKI; however, 26/45 (58%) had prior ponatinib treatment, and 19/45 (42%) did not have prior ponatinib treatment which is the only other TKI with activity in the T315I mutation. Of the 26 patients with prior ponatinib treatment, the cumulative MMR rate by 24 weeks was 30.8% (90% CI: 16.3%-48.7%), and the MMR rate at week 24 was 26.9% (90% CI: 13.4, 44.7). Of the 19 patients without prior ponatinib treatment, the cumulative MMR rate by 24 weeks was 57.9% (90% CI: 36.8%-77.0%), and the MMR rate at Week 24 was 52.6% (90% CI: 32.0, 72.6).

Labeling will describe the efficacy endpoint of cumulative MMR by 24 weeks and by 96 weeks and the duration of treatment.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Asciminib is an orally administered ABL/BCR-ABL1 tyrosine kinase inhibitor that binds to the myristoyl pocket of BCR-ABL1 protein, unlike other BCR-ABL TKIs that bind to the ATP site of the BCR-ABL1 fusion protein. Based on the binding site, asciminib is expected to have activity against point mutations, including T315I mutation, which confer resistance to ATP-competitive TKIs.

This risk benefit assessment of asciminib considers the following factors: patients with chronic myeloid leukemia (CML) who are refractory to or intolerant of approved TKIs have a poor prognosis and limited treatment options; the usual course of CML is response to initial therapy followed by eventual relapse and retreatment with another TKI and eventual progression of disease and death; the only curative treatment is stem cell transplantation (SCT), but not all patients have donors and many have comorbidities that preclude SCT; patients with T315I mutations are resistant to all available TKIs except ponatinib; and the clinical activity of asciminib must be weighed against the toxicities of therapy.

The recommendation for accelerated approval for asciminib for the treatment of Ph+ CML in CP previously treated with two or more TKIs is based on the results of a randomized controlled trial evaluating asciminib versus bosutinib, study ASCEMBL (CABL001A2301, referred to as study A2301). Supportive efficacy and safety information in this population is provided from the first-in-human dose escalation study CABL001X2101 (referred to as study X2101) with total daily doses ranging from 20 mg to 400 mg, either daily or divided twice daily. Study X2101 also include dose finding and efficacy information in patients with T315I mutations which confers resistance to most other TKIs. The cohort of patients with T315I mutations treated at the recommended dose of 200 mg twice daily supports the recommendation of regular approval for this population.

Study A2301 was a randomized (2:1), open-label, active controlled trial of asciminib monotherapy (n=157) versus bosutinib monotherapy (n=76). Randomization was stratified by the patients' cytogenetic response status at baseline (with or without major cytogenetic response [MCyR]). Patients with T315I or V299L mutations were excluded from the study because response would not be expected from bosutinib in patients with these mutations. The primary endpoint was MMR at 24 weeks with key secondary endpoint of MMR at 96 weeks. MMR at 24 weeks was significantly better on the asciminib arm at 25% (95% CI: 19, 33)

compared to that in the bosutinib arm at 13% (95% CI: 6.5, 23). The treatment difference in MMR rate at Week 24 was 12% (95% CI: 2.2, 22; two-sided p value of 0.029, stratified by the MCyR status at baseline). The 96-week MMR timepoint was not reached at the time of this interim analysis.

In the randomized study, patients with previously treated CML in CP were treated with either asciminib at 40 mg twice daily or bosutinib at 500 mg daily. The exposure in the asciminib arm was longer than the bosutinib arm due to more discontinuations in the bosutinib arm due to lack of efficacy or dose modifications for toxicity. The overall rate of serious adverse events was lower the in asciminib arm, though the safety profile differed between the two agents and should be considered when choosing the appropriate treatment for a patient based on underlying comorbities. Serious adverse reactions occurred in 15% of patients who received asciminib with the most common occurrence of pyrexia, congestive cardiac failure, thrombocytopenia, and urinary tract infection. Two patients had a fatal adverse reaction, one each for mesenteric artery thrombosis and ischemic stroke. The most common adverse reactions of any grade excluding laboratory related events were upper respiratory tract infections and musculoskeletal pain with most common select laboratory abnormalities were cytopenias (platelet, neutrophil, and hemoglobin), and increased triglycerides, creatine kinase, and ALT. Overall, the safety profile observed in the randomized study is reasonable for this patient population, and is managed primarily by dose modifications.

Study X2101 was a non-randomized, open-label, dose escalation, first-in-human study of asciminib monotherapy or asciminib in combination with other TKIs in patients with previously treated CML in CP or accelerated phase (AP). Due to a higher half maximal inhibitory concentration (IC50) in CML cells with T315I mutation at 12 to 13-fold higher than wild type cell, the dose in patients with T315I mutations was escalated determined to be 200 mg twice daily. The efficacy population to support the approval of asciminib for patients with T315I mutations included 45 patients with CML in CP with T315I mutations treated with the recommended dose of 200 mg twice daily. The efficacy endpoints of the study included MMR by and at scheduled timepoints and duration of MMR. Cumulative MMR was achieved by 24 weeks in 42% (95% CI: 28, 58) of the 45 patients treated with asciminib. MMR was achieved by 96 weeks in 49% (95% CI: 34, 64). The median duration of treatment was 108 weeks (range, 2 to 215 weeks).

In 48 patients with T315I mutations treated at 200 mg twice daily asciminib, the occurrence of adverse reactions and serious adverse reactions appeared higher than those treated at 40 mg twice daily. However, the overall pattern of adverse reactions was similar. Serious adverse reactions occurred in 23% of patients who received asciminib in this cohort with the most common events of abdominal pain, vomiting, and pneumonia. The most common adverse reactions of any grade excluding laboratory

abnormalities were musculoskeletal pain, fatigue, nausea, rash, and diarrhea, with common select laboratory abnormalities of increased ALT, lipase, triglycerides and cytopenias (hemoglobin, neutrophil, lymphocyte, and platelets). Given the lack of treatment options in patients with T315I mutations, the safety profile is acceptable for this patient population and is largely managed by dose modification. Given that the only other TKI that has activity in patients with T315I mutation is ponatinib with a boxed warning for arterial occlusive events and other significant adverse reactions, additional treatment options in this population is needed.

Study X2101 also included patients treated at 80 mg once daily. Only 17 patients were treated at this dose; however, exposure, safety, and preliminary efficacy in this dosing regimen appeared similar to patients treated with 40 mg twice daily. Population PK models further supported the approval of this dosing regimen in patients with previously treated CML in CP.

The safety of asciminib was further described in relevant warnings and precautions, with the occurrence of specified adverse reactions evaluated in the overall safety population from both studies treated at doses of asciminib as monotherapy from 10 mg to 200 mg twice daily. Warnings and precautions include myelosuppression, pancreatic toxicity, hypertension, hypersensitivity, cardiovascular toxicity, and embryo-fetal toxicity.

The FDA approach toward approval in CML in CP the R/I population is to grant accelerated approval when at least 24 weeks of efficacy and safety data is available. For conversion to regular approval, the FDA requires 96-weeks (2 years) of efficacy and safety information. Follow up to the later timepoint is required only from the study-drug treatment arm in the case of an active-controlled study to demonstrate benefit with use of the study drug. In this submission, the Applicant provided efficacy and safety information from study A2301 to 48 weeks; however, approximately 30% had not reached the 96-week evaluation. Therefore, the data from A2301 supports accelerated approval in patients with CML in CP in patients treated with at least 2 prior TKIs. The study includes a key secondary endpoint for MMR at 96 weeks, and a PMR will be issued to obtain this information. For the treatment of patients with T315I mutations, the majority of patients (~90%) have reached the 96-week evaluation. The durability of MMR responses and safety in this population supports regular approval for this indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CML is a clonal myeloproliferative disease driven by the BCR-ABL1 fusion product from the translocation of t(9; 22) known as the Philadelphia chromosome (Ph) • The overall life expectancy in patients with CML in CP is approaching normal with treatment; however, patients with resistance or intolerance to available therapies are at higher risk of progressive disease and have worse prognosis • Approximately 9110 new cases of CML could be diagnosed and about 1,220 people could die of the malignancy in the US during 2021 • T315I mutation confers resistance to most available BCR-ABL TKIs. T315I mutations are more common in patients previously treated with BCR-ABL TKIs	CML in chronic phase is a rare, but serious and life-threatening disease.
Current Treatment Options	• Five BCR-ABL TKIs are approved for the treatment of CML in CP (imatinib, dasatinib, nilotinib, bosutinib, and ponatinib). • Patients with newly-diagnosed CML-CP may be treated with imatinib, dasatinib, nilotinib, and bosutinib. • Treatment of relapsed CMP-CP is limited to second generation BCR-ABL TKIs (dasatinib, nilotinib, and bosutinib) • Ponatinib is approved for patients with CML-CP previously treated with two or more prior TKIs or those with T315I-positive CML. • Treatment options for patients with CML-CP previously treated with 2 or more TKIs is very limited and patients may have cross resistance to other TKIs. • Ponatinib is the only available treatment for CML-CP patients with T315I mutation, and has a known risk of arterial	There is a need for effective therapies for patients with CML in CP who are resistant or intolerant to prior TKI treatment. More effective and safer therapies are needed for patients with T315I mutations.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	occlusive events. There is a need for development of more effective and safer treatment regimens in these patient populations.	
Benefit	• Study ASCEMBL (CABL001A2301) was a randomized (2:1), open-label, active controlled trial of asciminib monotherapy (n=157) versus bosutinib monotherapy (n=76), stratified by was stratified by cytogenetic response status at baseline (with or without MCyR). The primary endpoint was MMR at 24 weeks. MMR at 24 weeks on the asciminib arm was 25% (95% CI: 19, 33) compared to that in the bosutinib arm of 13% (95% CI: 6.5, 23). The treatment difference in MMR rate at Week 24 was 12% (95% CI: 2.2, 22; two-sided p value of 0.029, stratified by the MCyR status at baseline). Median time to MMR was 12.7 weeks asciminib arm and 14.3 weeks in bosutinib arm. With a median duration of follow-up of 20 months (range: 1 day to 36 months), the median duration of response had not yet been reached for patients with MMR at any time. • Study CABL001X2101 was a non-randomized, open-label, dose escalation, first-in-human study of asciminib monotherapy or asciminib in combination with other TKIs (imatinib, nilotinib, or dasatinib] in patients with previously treated CML in CP or accelerated phase (AP). The efficacy population included 45 patients with CML in CP with T315I mutations treated with the recommended dose of 200 mg twice daily. The efficacy endpoints of the study included MMR by and at scheduled timepoints and duration of MMR.	The endpoint of MMR at 24 weeks and the cumulative MMR by 24 weeks support effectiveness in patients with CML in CP who have received at least 2 prior TKIs Asciminib shows a statistically significant and clinically meaningful improvement in MMR at 24 weeks compared to bosutinib treatment in this population. The magnitude and duration of major molecular response are clinically meaningful. The cumulative MMR rate by 24 and 96 weeks supports effectiveness of asciminib treatment in patients with T315I mutations with or without prior ponatinib treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Cumulative MMR was achieved by 24 weeks in 42% (95% CI: 28, 58) of the 45 patients treated with asciminib. MMR was achieved by 96 weeks in 49% (95% CI: 34, 64) The median duration of treatment was 108 weeks (range, 2 to 215 weeks).	
Risk and Risk Management	• In the randomized study of patients with previously treated CML in CP, patients were treated with 40 mg twice daily asciminib or 500 mg daily bosutinib. • In 156 patients, the most common (≥ 20%) adverse reactions were upper respiratory tract infections and musculoskeletal pain. The most common select laboratory abnormalities that worsened from baseline in ≥ 20% of patients were platelet count decreased, triglycerides increased, neutrophil count decreased, hemoglobin decreased, creatine kinase increased, and ALT increased. • Serious adverse reactions occurred in 15% of patients who received asciminib. Serious adverse reactions in ≥ 1% included pyrexia (1.9%), cardiac failure congestive (1.3%), thrombocytopenia (1.3%), and urinary tract infection (1.3%). Two patients (1.3%) had a fatal adverse reaction, one each for mesenteric artery thrombosis and ischemic stroke. • The recommended dose for patients with T315I mutations is 200 mg twice daily. • In 48 patients with T315I mutations, the most common (≥ 20%) adverse reactions were musculoskeletal pain, fatigue, nausea, rash, and diarrhea. The most common select laboratory abnormalities that worsened from baseline in ≥	The safety profile of asciminib treatment at 40 mg twice daily for patients with CML in CP after at least 2 prior TKIs is tolerable and manageable. Long-term safety information is needed in this population since asciminib is intended for prolonged use and there may be potential for cumulative toxicity. The safety profile of asciminib treatment at 200 mg twice daily for patients with T315I mutations is acceptable over a median of approximately 2 years of treatment. Risks overall at either dose are sufficiently addressed through warnings and precautions in the United States Prescribing Information.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	20% of patients ALT increased, lipase increased, triglycerides increased, hemoglobin decreased, neutrophil count decreased, lymphocyte count decreased, phosphate decreased, AST increased, amylase increased, platelet count decreased, and bilirubin increased. • Serious adverse reactions occurred in 23% of patients who received asciminib. Serious adverse reactions in > 1% included abdominal pain (4.2%), vomiting (4.2%), pneumonia (4.2%), musculoskeletal pain (2.1%), headache (2.1%), hemorrhage (2.1%), constipation (2.1%), arrhythmia (2.1%), and pleural effusion (2.1%).	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as			
			x	Patient reported outcome (PRO)	Sections 8.1.2, 8.2.6
			□	Observer reported outcome (ObsRO)	Not applicable
			□	Clinician reported outcome (ClinRO)	Not applicable
			□	Performance outcome (PerfO)	Not applicable
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			Not applicable
	□	Patient-focused drug development or other stakeholder meeting summary reports			Not applicable
	□	Observational survey studies designed to capture patient experience data			Not applicable
	□	Natural history studies			Not applicable

	□	Patient preference studies (e.g., submitted studies or scientific publications)	Not applicable
	□	Other: (Please specify)	Not applicable
□	Patient experience data that was not submitted in the application, but was considered in this review.		

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Chronic Myeloid Leukemia (CML) is a clonal malignant myeloproliferative disease characterized by the presence of the BCR-ABL1 fusion product generated because of the t (9; 22) Philadelphia chromosome (Ph) (Jabbour and Kantarjian 2018). CML is a disease mainly affecting adult patients with an average age at diagnosis of 65 years. Approximately 9110 new cases of CML could be diagnosed and about 1,220 people could die of the malignancy in the US during 2021 (Siegel et al 2021).

The natural history of CML is characterized by a triphasic course: chronic phase (CP), accelerated phase (AP) and blast phase (BP). Most patients with CML are diagnosed in a chronic phase (CP) of the disease, which is characterized by overproduction of immature myeloid cells and mature granulocytes in the spleen, bone marrow, and peripheral blood. If untreated, the disease would progress through a period of increasing instability known as accelerated phase (AP), to terminal transformation to an acute leukemic-like illness or so-called blast phase (BP) (Apperley 2015). Based on the experience with tyrosine kinase inhibitors (TKIs), the best approach to avoid advanced CML (CML-AP/-BP) is preventing progression and keeping patients in the well-controlled chronic phase.

The prognosis of CML has changed during the past two decades from a disease with an overall survival of only 5-7 years to one in which patients responding to TKI treatment can expect a near to normal life expectancy (Hochhaus et al 2017). However, some patients do not respond to the treatment (primary resistance), lose their response (secondary resistance), or experience tolerability issues. The detection of mutations in BCR-ABL1, in particular T315I mutation the most frequently identified BCR-ABL1 mutation, is associated with a greater likelihood of resistance to TKI treatment and consequent disease progression (Soverini et al 2005, Miller et al 2014). T315I mutation is clinically relevant as it confers a high-level of cross-resistance to most of the available TKIs indicated for CML-CP including imatinib and all second generation (2G)-TKIs (dasatinib, nilotinib and bosutinib).

The risk of progressing from CML-CP to advanced CML, AP or BP, increases with subsequent lines of treatment (Soverini et al 2016). Biologically, it is believed that the increased BCR-ABL1 expression and its functional reactivation, associated with resistance, are responsible for the enhanced genomic instability and abrogated differentiation of hematopoietic stem/progenitor cells that are intrinsic features of blast crisis (Skorski 2012). Patients harboring the T315I mutation have worse outcomes in terms of overall survival (OS) and progression-free survival (PFS), and they have a higher risk of progression to accelerated and blast phases when compared to patients not harboring the T315I mutation (Soverini et al 2014, Cortes et al 2018). The prognosis of

patients progressing to CML-BP is dismal with expected median overall and failure-free survivals of 12 and 5 months, respectively (Jain et al 2017). Therefore, it is very important to reach optimal disease control to prevent disease progression in patients with CML-CP.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that CML is a serious disease and it has a substantial risk of mortality if it progresses to accelerated or blast phases. The presence of T315I mutation confers shorter OS and PFS. There are few treatment options for CML-CP patients, especially if they had failure with 2 or more TKIs or if they have T315I mutation.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Management of CML has evolved over time with improvements in treatment and diagnostic technologies. BCR-ABL1 tyrosine kinase inhibition has become the gold standard of care in CML. Since the advent of the first TKI, imatinib in 2001, the 10-year survival rates have improved from approximately 20% to around 85-90%; since then, targeted therapy with TKIs have become the gold standard treatment for CML (Jabbour and Kantarjian 2018).

Treatment options for newly diagnosed patients with CML-CP include imatinib (first TKI approved in 2001) or second generation (2G) TKIs (dasatinib, nilotinib, bosutinib). Patients with CML-CP resistant or intolerant to treatment with imatinib or 2G-TKIs in first line may be alternatively treated with 2G-TKI. Most patients who have failed at least two prior TKIs will have failed at least on one or two 2G TKIs. Ponatinib, a third generation (3G)-TKI, is an alternative option in these cases unless cardiovascular risk factors preclude its use (Hochhaus et al 2020, NCCN Guidelines v2.2021, Cortes et al 2018). For patients with resistance to prior TKIs, allogeneic stem cell transplantation (allo-SCT) may be used. However, allo-SCT carries a high risk of morbidity and mortality; it represents an option for patients with good performance status, normal organ functions, and for whom an appropriate donor is available (Hochhaus et al 2017, NCCN Guidelines v2.2021).

Despite available therapies that have broadened treatment choices and improved patient outcomes, there remain several challenges in the management of CML. The choice and sequencing of TKIs remains controversial with the complexity of safety and tolerability considerations in the context of a long-term therapy (Mauro et al 2013, Cortes and Kantarjian 2016). For these reasons, it is considered that patients with CML-CP who experience treatment failure represent a population with a high-unmet need requiring therapies with potent anti-leukemic activity to control the disease while providing favorable safety and tolerability.

For patients with CML-CP harboring BCR-ABL1 T315I mutation, at present ponatinib is the only available targeted therapy, but it is associated with a significant incidence of arteriothrombotic events that may make therapy unsustainable for some patients, occasionally even in the setting of an adequate response. For patients having resistance/intolerance to ponatinib or for those patients ineligible to ponatinib, the only remaining options include allo-SCT, best supportive care, or other chemotherapies that do not specifically target this mutation. All these options carry a significant adverse event safety profile with very poor treatment outcomes (Boddu et al 2018). For these reasons, new and efficacious treatment options targeting the T315I mutation with an improved safety profile are needed for this subset of CML patients.
Currently approved TKIs for Ph+ CML patients with resistance or intolerance to prior therapy, with details on the magnitude of their treatment effect and important safety issues are summarized in

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication.

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Drug (dosage) Relevant indication for CML	Study Number of prior TKIs-CP CML	Primary efficacy analysis results	Warnings and precautions	Most common ADRs of any grade at an incidence ≥ 20%*
Nilotinib (400 mg BID) Adult patients with CP and AP Ph+ CML with resistance or intolerance to prior therapy including imatinib	Phase II, open-label, uncontrolled, multicenter trial 1 prior TKI (100% imatinib) (imatinib-resistant or intolerant CML)	Unconfirmed MCyR (minimum follow-up of 6 months) (N=232): 40% (95% CI: 33, 46)	QT prolongation, sudden death, myelosuppression, cardiac and arterial vascular occlusive events, pancreatitis and elevated serum lipase, hepatotoxicity, electrolyte abnormalities, tumor lysis syndrome, hemorrhage, fluid retention, effects on growth and development in pediatric patients, reversible posterior, embryo-Fetal Toxicity, treatment discontinuation.	60-Month Analysis: Rash, pruritus, nausea, diarrhea, constipation, vomiting, headache, fatigue, pyrexia, arthralgia, pain in extremity, cough, nasopharyngitis
Dasatinib (100 mg QD) Adult patients with CP, AP, or myeloid or lymphoid BP Ph+ CML with resistance or intolerance to prior therapy including imatinib	Phase III, randomized, open-label trial 1 prior TKI (100% imatinib)	MCyR at 6 Months 100 mg or 140 mg QD (N=247): 51.8% (95% CI: 45.4-58.2) 50 mg or 70 mg BID (N=251): 49% (95% CI: 42.7-55.4)	Myelosuppression and bleeding events, fluid retention, cardiac dysfunction, pulmonary arterial hypertension, QT prolongation, severe dermatologic reactions, tumor lysis syndrome, embryo-fetal toxicity, effects on growth and development in pediatric patients	84 months follow-up: Fluid retention, headache, diarrhea, fatigue, dyspnea, musculoskeletal pain
Bosutinib (500 mg QD) Adult patients with CP, AP, and BP Ph+ CML with resistance or intolerance to prior therapy.	Phase 1/2, single-arm, open-label, multicenter trial 1 prior TKI (imatinib only) ≥2 TKIs (imatinib and at least 1 additional TKI)	MCyR at 24 weeks (1 prior TKI; imatinib only; N=266): 33.8% (95% CI: 28.2, 39.9) MCyR by 24 weeks (≥2 TKIs; N=108): 26.9% (95% CI: 18.8-36.2)	Gastrointestinal toxicity, myelosuppression, hepatic toxicity, cardiac failure, fluid retention, renal toxicity, embryo-fetal toxicity	48 Months follow-up: Diarrhea, nausea, abdominal pain, rash, thrombocytopenia, vomiting, anemia, fatigue, pyrexia, cough, headache, ALT increased, edema

Drug (dosage) Relevant indication for CML	Study Number of prior TKIs-CP CML	Primary efficacy analysis results	Warnings and precautions	Most common ADRs of any grade at an incidence ≥ 20%*
Ponatinib (Starting dose is 45 mg QD orally, with a reduction to 15 mg QD upon achievement of ≤1% BCR-ABL1IS) Chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors. T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL.	PACE: starting dose of 45 mg orally QD) Phase 2, single-arm, open-label, international, multicenter study N=449 1 prior TKI (32; 7%) 2 prior TKIs (155; 35%) ≥3 prior TKIs (262; 58%)	MCyR (6 months minimum follow-up for all patients): Overall Resistant or Intolerant CP-CML (N=267): 54% (95% CI: 48, 60) Patients without T315I (N=203): 49% (95% CI: 42-56) Patients with T315I (N=64): 70% (95% CI: 58-81)	Arterial occlusive events (AOEs), venous thromboembolic events, heart failure, hepatotoxicity, hypertension, pancreatitis, neuropathy, ocular toxicity, hemorrhage, fluid retention, cardiac arrhythmias, myelosuppression, tumor Lysis syndrome, reversible posterior leukoencephalopathy syndrome, impaired wound healing and gastrointestinal perforation, embryo-fetal toxicity	ADRs in PACE (60 months of follow-up): Rash and related conditions, arthralgia, abdominal pain, fatigue, constipation, headache, dry skin, fluid retention and edema, hepatic dysfunction, hypertension, pyrexia, nausea, hemorrhage, pancreatitis/lipase elevation, Arterial occlusive events (AOEs), diarrhea, vomiting, and myalgia
	OPTIC (NCT02467270, EUDRACT: 2014-001617-12): 45 mg QD with reduction to 15 mg (45 mg=94; 30 mg=94; 15 mg=94) Starting dose 45 mg (N=94): 1 prior TKI (1; 1%) 2 prior TKIs (43; 46%) ≥3 prior TKIs (50; 53%)	≤1% BCR-ABL1^{IS} at 12 months: Overall = 42% (95% CI: 32, 53) Patients with T315I mutation = 42% (95% CI: 22, 63) Patients without T315I mutation - 42% (95% CI: 30, 55).		ADRs in OPTIC (median duration of exposure 1 year): Rash and related conditions, hypertension, arthralgia, hyperlipidemia, hepatic dysfunction, pancreatitis, and abdominal pain

*ADRs in Ph+ CML-CP patients with resistance or intolerance to prior therapy; MCyR = major cytogenetic response
Sources: Nilotinib: Tasigna USPI (Oct 2007), Tasigna USPI (Dec 2020), Tasigna SmPc (30 Mar 2020)
Dasatinib: ClinicalTrials.gov (NCT00123474), Sprycel USPI (21 Dec 2018), Sprycel SmPC (28 Apr 2020)
Bosutinib: Bosulif USPI (Sep 2012), Bosulif USPI (Jun 2020), Bosulif SmPC (Dec 2019)
Ponatinib: Iclusig USPI (Dec 2012), Iclusig USPI (Dec 2020), Iclusig SmPC (Oct 2019)

The FDA's Assessment:
FDA agrees with the Applicant's assessment that CML-CP previously treated with 2 or more TKIs and CML-CP with T315I mutation are life-threatening diseases. Treatment options for patients with CML-CP previously treated with 2 or more TKIs is limited and patients may have cross resistance to other TKIs. Ponatinib is the only available treatment for CML-CP patients with T315I mutation, and has a known risk of arterial occlusive events. There is a need for development of other effective and safe treatment regimens in these patient populations.

FDA agrees with the Applicant's assessment of efficacy and safety of currently approved TKIs for Ph+ CML patients with resistance or intolerance to prior therapy based on the prescribing information for the approved TKIs and the published literature.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Asciminib (ABL001) is not approved in the US and not marketed in any other country.

The FDA's Assessment:
FDA confirms the Applicant's assessment.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Asciminib is a new chemical entity and has been in clinical development as an investigational drug for Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) (b) (4) The clinical development of asciminib was initiated by Novartis under the Investigational New Drug (IND) 119,257 submitted to FDA on 17-Dec-2013 with the compound code ABL001. The "Study May Proceed" letter was issued by the Agency on 16-Jan-2014. A summary of key interactions with the FDA regarding asciminib development is provided in Table 2.

Table 2: Key interaction with FDA from the development of asciminib

Date	Purpose of Key interactions
20-Oct-2016	Type B EOP2/Pre-Phase 3 meeting to discuss Study CABL001A2301 for NDA submission
27-Feb-2017	Orphan drug designation granted for treatment of chronic myelogenous leukemia
18-Oct-2017	Type C CMC meeting on starting materials for the synthesis of ABL001 Hydrochloride drug substance

Date	Purpose of Key interactions
07-Aug-2018	Special Protocol Assessment for a 2-year carcinogenicity study in rats
22 Jan 2020	Type F FDARA meeting to discuss the proposed initial Pediatric Study Plan (iPSP) and Proposed Pediatric Study Plan (PPSR)
25-Feb-2020	Type C CMC meeting to discuss a new dissolution method
28 July 2020	Type C meeting to discuss the overall NDA submission strategy and dossier
24-Aug-2020	Fast Track Designation granted for patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs) and patients with Ph+ CML in CP harboring the T315I mutation
16-Sep-2020	Agreed iPSP Agreement received for the treatment of Pediatric Ph+ CML-CP, previously treated with one or more TKIs
10-Nov-2020	Type B Pre-NDA meeting to share top-line results of Study CABL001A2301 and Study CABL001X2101 and discuss proposed NDA submission strategy for the two proposed indications
07-Jan-2021	Proprietary name request conditionally approved
02-Feb-2021	Breakthrough Therapy Designation granted for the treatment of adult patients with Ph+ CML in CP, previously treated with two or more TKIs
02-Feb-2021	Breakthrough Therapy Designation granted for the treatment of adult patients with Ph+ CML in CP harboring the T315I mutation

The FDA's Assessment:

FDA agrees with the Applicant's presentation of development of asciminib in CML.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI inspection was requested for the Applicant, and the results were no action indicated. Clinical site inspections were not requested because no site substantively contributed to the efficacy with the highest enrolling US site including 5 patients in the pivotal cohorts (any arm of A2301 and T315I treated at 200 mg bid in X2101) and the highest enrolling ex-US site including 13 patients in pivotal cohorts.

4.2. Product Quality

The to-be-marketed asciminib drug product will be provided as film-coated tablets containing 20 mg or 40 mg of asciminib per tablet with the following excipients: colloidal silicon dioxide, croscarmellose sodium, ferric oxide, hydroxypropyl cellulose, lactose monohydrate, lecithin, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

Per the Applicant, initial clinical studies were performed using an immediate release capsule. Later clinical studies used the immediate release film coated tablet and with a change in the drug substance manufacturing process. No dose adjustments were needed with the change in formulation, and the final formulation was used in the pivotal clinical studies.

CMC did not conduct manufacturing site inspections because FDA has recently inspected the current manufacturing sites and found them to be adequate. The Applicant's responses to the requests raised about product quality were found adequate.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable. T315I mutation testing was performed by local laboratory and confirmed by central testing using Sanger sequencing. Mutation testing is part of standard clinical practice, and due to the lack of effectiveness and/or safety concerns with the other BCR-ABL TKIs in patients with T315I mutations, a companion diagnostic was not requested. However, FDA requested detailed information on the central testing for T315I mutations used in the clinical trials to evaluate the minimum performance of the assay.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The FDA recognizes that multiple code names for asciminib were used in the NDA submission: ABL001, XB-97-FZ10, NVP-ABL001-AAA, NVP-CME911(-NX-3), and NVP-ABL001.

The molecular basis of chronic myeloid leukemia (CML) is a reciprocal translocation between chromosomes 9 and 22, leading to the formation of an oncogenic *BCR (Breakpoint cluster region gene)-ABL (Abelson related oncogene)* gene fusion.[1] *ABL1* is a proto-oncogene encoding a nonreceptor tyrosine kinase with diverse roles in cytoskeleton re-modelling and the DNA damage response.[2] When fused to BCR, the tyrosine kinase activity of ABL1 becomes constitutively activated, leading to the aberrant activation of numerous downstream signaling pathways that converge to promote cell growth and survival.[3]

The allosteric inhibitory activity of asciminib is a result of its ability to bind to a pocket on the kinase domain that is normally occupied by ABL1's myristoylated N-terminus, a motif that serves as a negative regulatory element and is lost upon the fusion of ABL1 to BCR. The binding affinity of asciminib to ABL1 myristoyl pocket, expressed as K_D (dissociation constant) values, was in the range of approximately 0.5-1 nM across various methodologies. A comparable K_D value was obtained in the binding assay for the T315I mutant form of ABL1. In enzymatic assays, asciminb inhibited the kinase activity of ABL1. The mean IC_{50} values of tyrosine phosphorylation inhibition were in a low nanomolar range (0.5-2.6 nM).[8] At concentrations up to 10 μM, asciminib did not inhibit the activity of a panel of 335 protein kinases. The major metabolites M44 and M29.5 inhibited the enzymatic activity of ABL1 kinase with IC_{50} values of 5 and 6.6 nM, respectively, indicating less pharmacodynamic activity of the metabolites than asciminib.

Asciminib inhibited the proliferation of BCR-ABL expressing cancer cell lines with a higher potency (IC_{50} range of 1-24 nM) than cell lines that do not express BCR-ABL (IC_{50} range of 2-30 μM). Because asciminib does not bind to the ATP-pocket of BCR-ABL, it is anticipated that it will be active against BCR-ABL containing mutations in the ATP-binding site. Thus, the anti-tumor activity of asciminib was assessed in BaF3 cells harboring wild type BCR-ABL or BaF3 cells bearing a BCR-ABL construct engineered to contain clinically observed point mutations.

[1] Goldman Semin Hematol 47(4): 302-311, 2010.
[2] Colicelli, Sci Signal 3: 1-27, 2010.
[3] O'Hare et al., Clin Cancer Res 17: 212-221, 2010.

These mutations included T315I, E255K, E255V, Y253H, F359V, Q252H, G250H and E459K. Asciminib had comparable effects on growth inhibition in BaF3 cells expressing wild type or mutant BCR-ABL forms, with an IC_{50} value of 0.6 nM in the wild type-BCR-ABL cells and in the 0.7-11 nM range for mutant forms. The IC_{50} value against T315I-containing cells was 7.6 nM (12 to 13-fold higher than wild type). Researchers reported two distinct patterns of resistance mutations in the BCR-ABL1 kinase fusion protein following treatment with asciminib in Luc-Ba/F3 cells[4,5]. While asciminib inhibited mutants resistant to nilotinib type tyrosine kinase inhibitors (such as T315I), mutants in the myristoyl pocket, such as V468F, P465S, and A337V, were resistant to asciminib.

The PK/PD profile of asciminib was assessed in murine xenograft studies using patient-derived CML cell lines (e.g. KCL-22 cell). Asciminib demonstrated inhibitory effects on cellular proliferation as well as dose-dependent suppression of pSTAT (62-99%) following single oral doses at 3-30 mg/kg. The systemic exposures to asciminib were dose-dependent with a short elimination half-life in mice (<4 hours). In this model, tumor regression was 56%, 88% and 92% at doses of 7.5, 15 and 30 mg/kg (twice daily x 7), respectively. In the same study, nilotinib at 7.5 mg/kg twice daily resulted in a tumor regression of 82%. The same treatment schedule of asciminib (3-30 mg/kg) resulted in dose-dependent inhibition of tumor growth in mice with a KCL-22 xenograft harboring a T315I mutant. At 30 mg/kg twice daily, asciminib resulted in a tumor regression of 56% in the T315I tumor model, approximately one-half the anti-tumor effect of that in the wild type model. In contrast, nilotinib was relatively ineffective in the T315I mutant xenograft model. An enhanced anti-tumor effect of the combination of asciminib and nilotinib was demonstrated in KCL-22 xenograft model, with the combination treatment resulting in durable tumor regression. Furthermore, study results indicated that asciminib treatment delayed resistance to nilotinib treatment in this model; a reciprocate effect was observed for nilotinib treatment of asciminib-resistant tumors.

In secondary pharmacology studies, asciminib resulted in inhibition of 5-lipoxygenase, vesicular monoamine transporter VMAT2, and the serotonin 5HT2B receptor, with IC_{50} values of 3.3 µM, 3.5 µM and 5.1 µM, respectively. Cardiovascular effects (e.g. increased heart rate and decreased systolic and arterial pressure) were observed in safety pharmacology assessments in dogs; no QTc prolongation was noted.

The absorption and oral bioavailability of asciminib were formulation dependent with higher bioavailability for the (b) (4) formulation than the HCl salt formulation. Comparable protein binding (>94%) was observed across species. There was no or little distribution of asciminib to the central nervous system (CNS). Penetration to the reproductive organs and placenta occurred; asciminib crossed the placenta in rats and rabbits in the embryo-fetal

development studies. The metabolism of asciminib involved the oxidative opening of the pyrrolidine ring to form the carboxylic acid metabolites. There are no unique human metabolites. Excretion occurred almost exclusively through the fecal route with minor renal excretion in all species tested.

The safety of asciminib was assessed in general toxicology (dogs, rats and monkeys up to 4, 26 and 39 weeks, respectively), genotoxicity (in vitro and in rats), and reproductive and developmental toxicology (rats and rabbits) studies. Toxicology studies of 3 months duration are generally sufficient; the reason 6-9 month studies were conducted is unclear. Safety pharmacology assessments were incorporated into the general toxicology studies and asciminib did not induce adverse effects on the cardiovascular, respiratory, or central nervous systems. The general toxicology studies identified toxicities in the hematopoietic system, liver, kidney, adrenal gland, gastro-intestinal (GI) tract, and pancreas (dog only). Asciminib treatment consistently suppressed erythroid parameters including red blood cell (RBC) count, hemoglobin (HGB), and hematocrit (Hct) in rats (≥ 90 mg/m^2), dogs (1200 mg/m^2/day), and monkeys (≥ 360 mg/m^2). Increased white blood cell counts (total and neutrophils, lymphocytes, monocytes, and large unstained cells) observed in the 26-week rat study and 13-week monkey study were likely related to multi-organ inflammation. Decreased platelet counts were observed in the 4-week study in dogs, and occasionally, prolonged aPTT was observed.

The suppression of RBC mass was associated with regenerative reponses, including increased absolute reticulocytes, mean corpuscular volume (MCV), and histopathological findings in the spleen (extramedullary hematopoiesis, pigment deposits) and bone marrow (hypercellularity, pigment deposits). These findings suggest that asciminib induced a shortened RBC life span with a higher turnover rate and regenerative anemia. Additionally, increased fibrinogen, total bilirubin (mainly indirect bilirubin) and cholesterol, as well as decreased potassium concentration were reported.

The pancreatic effects of asciminib in dogs included >36-fold increases in serum lipase and amylase at 60 mg/kg/day compared to the control and microscopic findings of dose-related degeneration and/or necrosis of acinar cells, accompanied by fibrosis (atrophy) with increasing dose. These adverse effects were only partially reversible at 60 mg/kg/day.

Hepatobiliary toxicity included elevated liver enzymes (mainly ALT), serum bile acid (4-week rat study), and bilirubin, and histopathological findings of centrilobular hepatocyte hypertrophy, slight bile duct hyperplasia, and increased individual hepatocyte necrosis in rats and reversible diffuse hepatocellular hypertrophy in monkeys. In addition to gastrointestinal clinical signs (fecal changes, emesis/vomitus, excessive salivation) observed in the studies,

minimal mucosal hypertrophy/hyperplasia in the duodenum was reported in the 4-week rat study. In the 13-week study in monkeys, increases in BUN and creatinine were observed with no remarkable urinalysis findings but with occasional tubular epithelium hypertrophy. These findings may have resulted from dehydration and disturbed electrolyte levels (pre-renal azotemia). The adrenal gland findings (hypertrophy, decreased vacuolation) may be indicative of stress. Although there were no avert findings in cardiovascular function or anatomical toxicity of the heart in the general toxicology studies, it is note-worthy that asciminib induced cardiovascular malformations in the embryo-fetal developmental studies in rats and rabbits. Cardiovascular toxicities have been observed in patients and information has been added to the prescribing information.

In a combined male and female fertility and early embryonic development study in rats, animals were administered asciminib doses of 10, 50, or 200 mg/kg/day orally. Male animals were dosed once daily for at least 28 days prior to mating, during the 2-week mating period, and until terminal necropsy (Days 63-67). Female animals were dosed once daily for the 2-week premating period, during the 2-week mating period, and through gestation day (GD) 6. Decreased mean spermatozoa count and percent motility were observed at 200 mg/kg/day. While there were no effects on fertility indices or conception rates, a decreased mean number of live embryos was observed at 200 mg/kg/day and was attributed to a lower number of implantations and an increased number of early resorptions. The AUC exposure at 200 mg/kg is approximately 19-fold, 13-fold, or 2-fold higher than those achieved in patients at the 40 mg twice daily, 80 mg once daily, or 200 mg twice daily doses, respectively.

In the embryo-fetal development studies, administration of asciminib to pregnant rats (25, 150, and 600 mg/kg/day) and rabbits (15, 50, and 300 mg/kg/day) during the period organogenesis caused adverse developmental outcomes in the absence of maternal toxicities. The highest doses used in both the rat and rabbit studies were not tolerated and resulted in the early termination of these groups and no complete embryo-fetal examinations in the dams. In the rat study, increases in fetal weights at 25 and 150 mg/kg/day were observed, which may be related to an increased rate of ossification and/or increased fetal growth. Malformations were evident at 150 mg/kg and included cleft palate, anasarca (edema), and cardiac abnormalities. Additional fetal findings included urinary tract and skeletal variations, observed primarily at 150 mg/kg/day. At the dose of 25 mg/kg/day, the area under the curve (AUC) exposures were equivalent to or below those achieved in patients at the 40 mg twice daily or 80 mg once daily doses, respectively. At the dose of 25 mg/kg/day, the AUC exposures were below those achieved in patients at the 200 mg twice daily dose. In the rabbit study, adverse embryofetal findings were observed at 50 mg/kg. Findings at the 50 mg/kg dose included increases in early resorptions and post-implantation

loss, decreases in the number of live fetuses, and cardiac and/or major vessel malformations. While ossification abnormalities were observed at dose levels ≥15 mg/kg, these findings were within the historical control range. At the dose of 50 mg/kg/day, the AUC exposures were 4-fold those achieved in patients at the 40 mg twice daily or 80 mg once daily doses. At the dose of 50, the AUC exposures were below those achieved in patients at the 200 mg twice daily dose.

Asciminib was not genotoxic in an in vitro bacterial mutagenicity (Ames) assay, an in vitro micronucleus assay in human peripheral blood lymphocytes (HPBL) or an in vivo rat peripheral blood reticulocyte micronucleus assay. No carcinogenicity studies with asciminib have been submitted at this time.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of asciminib for the proposed indications.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for asciminib.

5.3. Pharmacology

Primary pharmacology

Mechanism of action

Intramolecular myristate binding plays a key role in the autoregulation of wild-type ABL1. The myristoyl group at the ABL1 N-terminus binds within the pocket to induce and stabilize a conformational change, which in turn holds the pocket in an assembled inactive state. This regulatory mechanism is lost in BCR-ABL1 since the N-terminal cap of ABL1 is replaced in the fusion protein with a fragment of the BCR protein, thus rendering the ABL1 kinase constitutively active. The binding of ligands such as asciminib in this pocket mimics that of myristate, thus stabilizing the assembled inactive state of the kinase.[5] By binding to ABL1 in the myristate pocket, the mechanism of action of asciminib differs from other BCR-ABL inhibitors, such as nilotinib, that bind to the ATP pocket.[4]

[4] Manley et al., Leukemia Research 98: 106458, 2020.

In vitro studies

Binding affinity assay

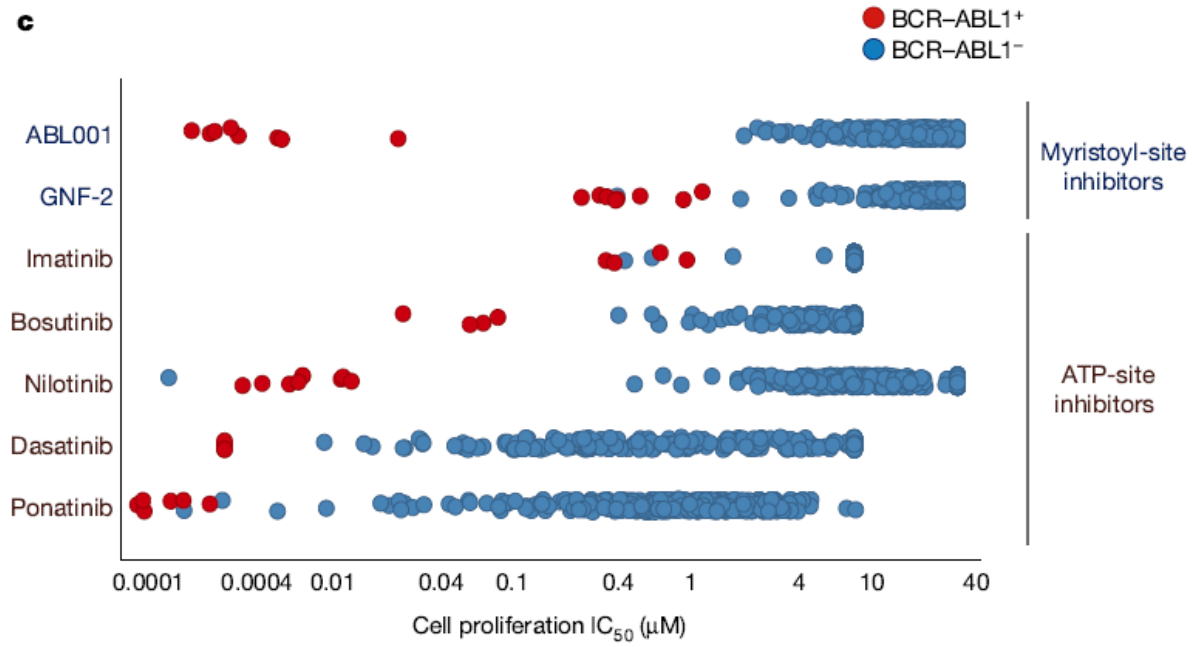
An isothermal titration calorimetry (ITC) study (RD-2020-00196) characterizing the thermodynamics of the binding of asciminib to ABL1 indicated a high binding affinity of asciminib to ABL1 with a dissociation constant (K_D) of 0.5 nM (0.32-0.9 nM). The data is consistent with nuclear magnetic resonance (NMR) and biophysical studies confirming that asciminib binds to the myristoyl pocket of ABL1 (K_D=0.5-0.8 nM).[5] A comparable K_D value (KD 0.5-0.8nM)[4]was obtained in the binding assay for the T315I mutant form of $ABL1^{46-514}$. Schoepfer and colleagues employed various techniques to elucidate the pharmacodynamic effect of asciminib via the interaction between asciminib and the myristoyl binding pocket.[6] Asciminib induced inhibition of ABL1 catalyzed transphosphorylation of substrate tyrosine residues with IC_{50} values of 2.6 ± 0.8 nM (via radiometric filter binding assay) and 0.5 ± 0.1 nM (via fluorescence resonance energy transfer assay).[6] The major metabolites M44 and M29.5 inhibited the enzymatic activity of ABL1 kinase (via a Caliper electrophoresis mobility-shift assay) with IC_{50} values of 5 and 6.6 nM, respectively, indicating less pharmacodynamic activity of the metabolites than asciminib.

Inhibition of cell proliferation

A screening of asciminib across a panel of 536 cancer cell lines demonstrated the effect of asciminib at inhibiting the proliferation of BCR-ABL expressing cancer cell lines with an IC_{50} range of 1-24 nM. The proliferation of cell lines that do not express BCR-ABL was inhibited with IC_{50} values ranging from 2000-30000 nM (RD-2019-00440).

[5] Wylie et al., Nature 543: 733-737, 2017.
[6] Schoepfer et al., J Med Chem 61: 8120-8135, 2018.

Figure 1: Anti-Proliferative Activity of Asciminib and Several TKIs in Cancer Cell Lines Containing BCR-ABL1 Oncogenic Fusion Gene



Anti-proliferative activity of asciminib, GNF-2 (a myristoyl binder), and TKIs (imatinib, nilotinib, dasatinib, bosutinib and ponatinib) across a large cancer cell line panel. (Figure adapted from Wylie et al)[5]

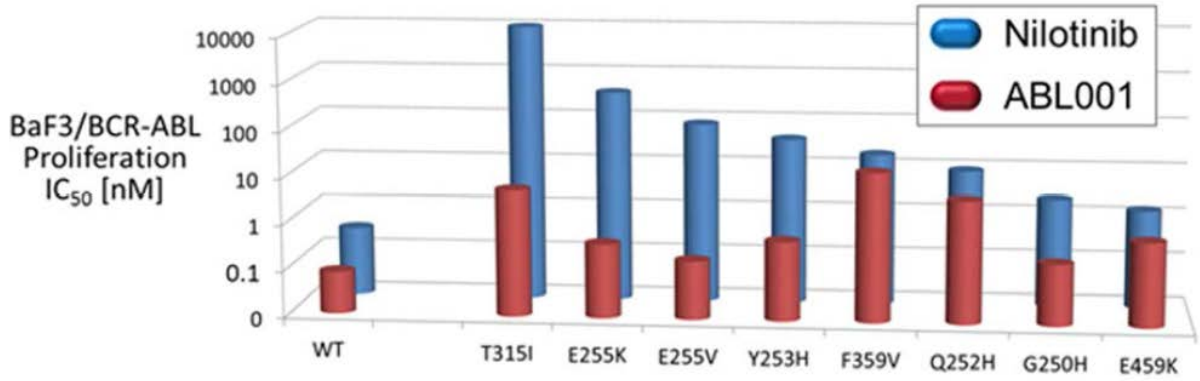
As shown in the figure above, the anti-proliferative effect of asciminib and ATP-competitive BCR-ABL tyrosine kinase inhibitors occurred at lower concentrations in BCR-ABL-driven cells (highlighted in red); therefore, the anti-proliferative activity of asciminib was dependent on the expression of BCR-ABL in the cells (RD-2013-50447; Wylie et al., 2017)[5]. The proliferation in parental BaF3 cells is IL-3 dependent. Over-expression of BCR-ABL in BaF3 cells allows the cells to grow in the absence of IL-3 and relies on signaling from the BCR-ABL oncogenic fusion for proliferation instead. In cells expressing BCR-ABL, asciminib inhibited BaF3 cell proliferation with IC_{50} values in the 0.4-1.2 nM range. In contrast, in the presence of IL-3, the inhibitory effect of asciminib was attenuated (IC_{50} > 2 μM). The ATP-competitive TKI nilotinib demonstrated similar results in this study.

ABL1 and ABL1 mutants

The anti-tumor activity of asciminib was assessed in BaF3 cells harboring wild type BCR-ABL or BaF3 cells bearing a BCR-ABL construct engineered to contain clinically observed point mutations. These mutations, including T315I, E255K, E255V, Y253H, F359V, Q252H, G250H and E459K, are described to affect the binding of currently approved TKI therapies for CML.

The anti-proliferation effects of asciminib and nilotinib were compared. The IC_{50} values for asciminib-induced inhibition of cell proliferation remained in the low nM range (0.7-10.9 nM) in cells expressing the mutant forms of BCR-ABL, with a relatively higher IC_{50} value against T315I (7.64 ± 3.22 nM). The IC_{50} against wild-type BCR-ABL was 0.61 nM. Cells bearing mutations in the SH1 ATP binding domain of the ABL1 tyrosine kinase exhibited resistance to nilotinib treatment. Similar data were reported by Manley (2020)[4] and Schoepfer et al. (2018).[6]

Figure 2: Anti-Proliferation Effects of Asciminib and Nilotinib in BaF3 Cells Harboring BCR-ABL Mutants



(Excerpted from #RD-2013-50447)

In vitro anti-cellular proliferation studies conducted by Manley and coworkers have identified BCR-ABL1 mutations that reduced the anti-proliferative activity of asciminib. Some of these mutants are associated with clinical resistance towards the drug in patients. Furthermore, mutants such as V468F, P465S, and A337V, demonstrated more sensitivity to nilotinib-associated inhibition than to asciminib.[6] Similarly, Wylie and colleagues reported two distinguished groups of BCR-ABL1 fusion oncoproteins. These two groups of mutants include: a) ABL001-resistant mutations in the myristoyl pocket and the interface between the SH3 and kinase domains, such as Ala337Val (A337V), and b) nilotinib-resistant catalytic-site mutations, such as Thr315Ile (T315I).[6] While ABL001 was inactive against Luc-BaF3 A337V cells, it retained activity against T315I cells at low nanomolar concentrations. Similarly, nilotinib showed inhibitory effects in A337V cells but not in T315I cells.[6]

In vivo studies

The KCL-22 cell line is an established CML cell line derived from a CML patient in blast crisis. Oral doses of asciminib (3-30 mg/kg) were administered once daily or twice daily to mice bearing a KCL-22 xenograft. Tumor regression and inhibition of the phosphorylation of the

down-stream signaling marker STAT-5 (signal transducer and activator of transcription protein; inhibition of pSTAT) were demonstrated. STAT-5 is activated upon expression of BCR-ABL1 and is inhibited by BCR-ABL1 inhibitors such as imatinib and nilotinib.[7] Once daily doses of asciminib at 7.5 and 30 mg/kg for 11 days resulted in 5% T/C ratio (ratio of tumor volume in drug-treated to that of control) and 33% tumor regression, respectively. All mice survived throughout the study duration (observed up to 18 days). Because the PK/PD study indicated that asciminib had a relatively short half-life in mice (< 4 hours), the asciminib-induced anti-tumor effect was improved when the mice were treated twice daily. In a 7-day course of the twice daily regimen, tumor regression was 56%, 88% and 92% at doses of 7.5, 15 and 30 mg/kg, respectively. In the same study, nilotinib at 7.5 mg/kg twice daily resulted in a tumor regression of 82% (RD-2013-50145). The same treatment of asciminib (3-30 mg/kg twice daily for 7 days) resulted in dose-dependent inhibition of tumor growth in mice with a KCL-22 xenograft harboring a T315I mutant (RD-2020-00314). At 30 mg/kg twice daily, asciminib resulted in a tumor regression of 56%, approximately one-half the anti-tumor effect of that in the wild type KCL-22 model. In contrast, the treatment of nilotinib was relatively ineffective in the T315I mutant xenograft model; oral nilotinib at 75 mg/kg twice daily resulted in an 80% T/C ratio. Wylie et al. and Manley and Stiefl (data not shown) reported similar findings.[8]

In the PK/PD study, treatment of single doses of asciminib (3-30 mg/kg) resulted in dose-dependent suppression of pSTAT (62-99%) in the tumor. Following the single dose administration of asciminib at 7.5 mg/kg, the asciminib plasma concentration at 7 hours after dosing was 0.04 μM and reached a 97% pSTAT inhibition. The AUC values at a single dose of 7.5 mg/kg and a single dose of 15 mg/kg were 2.3 μM *h and 4.66 μM *h, respectively. Assuming the exposure (AUC) would be dose-proportional, the AUC value following 7.5 mg/kg twice daily would be equivalent to 4.6 μM *h. Based on the corresponding plasma PK analysis and 56% tumor regression with twice daily dosing of 7.5 mg/kg, these results suggest that a plasma $C_{min(7h)}$ of 0.04 μM or AUC_{0-24} of 4.6 μM *h of asciminib is sufficient to achieve tumor regression (RD-2013-50145).

In the investigation of the minimally efficacious dosage of asciminib, it was found that delayed emergence of resistance in KCL-22 xenograft tumors could be achieved. In animals treated with higher dosages of asciminib at 60 or 120 mg/kg once daily to achieve more sustained target inhibition (i.e., >90% pSTAT5 inhibition over 24 hours), a more durable anti-tumor response was observed ($p < 0.05$ vs asciminib 30 mg/kg once daily group; RD-2013-50145).

[7] Ye et al., Blood 107: 4917-4925, 2006.
[8] Manly and Stiefl, Top Med Chem 28: 1-38, 2018 (published online 2017).

The enhanced anti-tumor effect of the asciminib and nilotinib combination treatment was demonstrated in the KCL-22 xenograft model (RD-2013-50274). Despite the apparent anti-tumor activity observed in this model (RD-2013-50145), the majority of the tumors developed resistance to the treatment of asciminib (30 mg/kg twice daily) or nilotinib (75 mg/kg twice daily) with a median latency of 38-52 days. However, the combination treatment resulted in a durable tumor regression, with no tumors observed 74 days after the termination of the combined treatment. A switch treatment between asciminib and nilotinib was employed to assess the ability to delay the onset of second tumors, i.e., prolongation of regression in treatment-resistant tumors. The results indicated that daily asciminib treatment was effective in regressing nilotinib-resistant tumors in relapsed mice. A reciprocated effect was observed for nilotinib treatment of asciminib-resistant tumors.

In addition, the anti-tumor effect of asciminib was evaluated in Ph^+ ALL patient-derived xenograft models (RD-2018-00292). In a representative study, oral asciminib at 7.5 mg/kg once daily or 15 mg/kg once daily administered to mice from Day 25 to Day 66 post inoculation of ALL-7015 tumor cells harboring p210 BCR-ABL1 induced inhibition of tumor growth. The growth was suppressed throughout the dosing period, but when asciminib treatment was discontinued the tumor burden increased.

Secondary Pharmacology

The Applicant's Position:

Asciminib binds to the myristoyl pocket in the ABL1 kinase domain with high affinity, K_D 0.5 nM. Consistent with this affinity, asciminib inhibits tyrosine phosphorylation catalysed by the $ABL1^{64-515}$ construct with a mean IC50 values of 2.6 ± 0.8 nM (radiometric kinase assay) and 0.5 ± 0.1 nM (fluorescence resonance energy transfer assay). The biochemical activity of asciminib translated into potent inhibition of the proliferation of Luc-Ba/F3 cells (Britelite™ luciferase reporter assay) transfected with *wild-type* BCR-ABL1 with a mean IC50 value of 0.61 ± 0.21 nM the Phase 1 metabolites (M29.5, M44) of asciminib detected in human studies show little cellular activity. Asciminib also inhibited the proliferation of BCR-ABL1 dependent cells with T315I mutation, with mean IC50 value of 7.64 ± 3.22 nM (12- 13-fold higher than *wild type*). Following oral administration to mice bearing sub-cutaneous human CML-derived KCL-22 cell (*wild type*) xenografts, asciminib dose-dependently inhibited tumor growth, with tumor regression observed at doses ≥ 7.5 mg/kg BID.

The FDA's Assessment:

The FDA notes that the Applicant's assessment above mainly describes the primary pharmacology of asciminib (ABL001). Additional secondary pharmacology studies are summarized below (Study #RD-2020-00068, RD-2020-00069).

The kinase inhibition profile of asciminib was determined by measuring residual activity values at concentrations up to 10 μM (in duplicate) in 349 kinase assays (335 protein kinase assays and 14 lipid kinase assays). The 335 wild-type protein kinases were not full-length protein but incorporated their ATP-binding sites. The negative and vehicle control was 1% DMSO. In these studies, asciminib showed no substantial effects (residual activities ≥ 66%) at concentrations up to 10 μM. These kinases included PDGFR, SRC, KIT, FGFR1, 2, 3, and 4, RET, TIE, VEGFR2, and FLT3. Asciminib also showed no effects on the 14 lipid kinases.

Affinity of asciminib to myristate recognition sites in other proteins
Asciminib did not bind to myristate recognition sites other than that of ABL/BCR-ABL1.[6] Despite the ubiquitous expression of ABL1/ABL2 kinases in human tissues, no effects of asciminib were demonstrated other than on ontogenically transformed cell lines.[9]

Off-target effects of asciminib: safety evaluation (RD-2013-50448)
Asciminib was assessed for its off-target activity on 143 G-protein-coupled receptors (GPCRs), transporters, ion channels, nuclear receptors and enzymes, a panel consisting of targets that have been linked to potential side effects. The results of an additional 85 targets assessed for the activity of asciminib and a functional rat brain vesicular monoamine transporter (VMAT2) assay were also included in the study report.

At 10 μM of asciminib, the following targets were inhibited >50%: lipoxygenase 5-lipoxygenase, VMAT2, and the serotonin 5HT2B receptor, with IC_{50} values of 3.3 μM, 3.5 μM and 5.1 μM, respectively. At 30 μM, asciminib also inhibited the type 3 adenosine (Ad3) receptor, 5HT2A receptor, and human norepinephrine transporter (NET), with IC_{50} values of 21 μM, 18 μM and 22 μM, equivalent to approximately 9450 ng/mL, 8100 ng/mL, 9900 ng/mL (based on the molecular weight 450 g/mole of free base asciminib), respectively. The relevance of the activity of asciminib at these targets for the safety of the drug in a therapeutic situation will depend on the maximum circulating or local concentrations (free Cmax or AUC) of asciminib at the therapeutic dose. The unbound concentration in human plasma at the maximum recommended dose of 200 mg BID is approximately 169.3 ng/mL (total Cmax concentration= 5642 ng/mL, unbound portion=0.03), a concentration much lower than the IC_{50} values of these targets.

Safety Pharmacology

The Applicant's Position:

[9] Khatri et al., J Cell Sci 129:9-16, 2016.

Safety pharmacology studies indicate that asciminib is not expected to cause effects on the vital functions of the CNS, and the respiratory systems. The IC50 for asciminib in the hERG patch clamp was 11.4 µM. This translates into a clinical safety margin > 200- or > 100- or 30-fold when compared to free exposure in subjects at dose of 40 mg BID or 80 mg QD or 200 mg BID, respectively. Moderate cardiovascular effects (increased heart rate, decreased systolic pressure, decreased mean arterial pressure, and decreased arterial pulse pressure) were observed in *in vivo* cardiac safety studies in dogs. QTc prolongation was not observed in dogs up to asciminib free Cmax at steady state 100- or 60- or 18-fold higher than that achieved in subjects at the dose of 40 mg BID or 80 mg QD or 200 mg BID, respectively.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment for the hERG assay and the electrocardiography assessment in the GLP single dose and 28-day studies in dogs. No adverse cardiac or respiratory effects of asciminib were observed in telemetered monkeys in the GLP 13-week and 39-week studies. No overt effects were found in the functional observational battery (FOB) and plethysmography endpoints included in the GLP 28-day repeat dose rat study.

5.4. ADME/PK

The Applicant's Position:

Asciminib was well absorbed in all species tested, with moderate to high bioavailability and high protein binding (>94%) comparable across species. Asciminib and/or its metabolites were distributed to most tissues and the overall distribution pattern was similar between male and female rats. There was no (male rats) or little distribution (female rats) to the CNS and moderate penetration to the reproductive system. All metabolites identified in humans were also detected in one or more of the animal species tested. In human plasma no major metabolite was observed, major circulating compound was asciminib with 92.7% of total drug-related exposure followed by the metabolites M30.5 (4.93% of drug-related material).

Excretion occurred almost exclusively through the fecal route (human: 78.5%) with a minor renal excretion in all species (human: 10.7%), hence alteration of the liver function and alterations of the activity of enzymes involved in the metabolism of asciminib may affect the elimination of asciminib.

The FDA's Assessment:
The FDA generally agrees with the Applicant's statement. The absorption and oral bioavailability were formulation dependent (with higher bioavailability for the (b) (4)

(b) (4) formulation than the HCl salt formulation). The quantitative whole body autoradiography (QWBA) data indicated that the elimination was rapid from most of the tissues/organs, except for the liver, skin, uveal tract and colon in rats. Based on toxicokinetics conducted in the embryo-fetal toxicity studies in the rat and rabbit, asciminib levels were detected in the fetal plasma (lower than in the maternal plasma), indicating placenta transfer. See the Reproductive and Developmental Toxicology section for the data.

Additional information obtained in the in vitro and in vivo metabolism studies indicated the main biotransformation pathways included direct glucuronidation, amide hydrolysis, oxidation at the pyrrolidine ring (ketone formation, hydroxylation, and oxidative ring opening), decarboxylation, and N-dealkylation. There were no unique human metabolites identified in the in vitro study. The prominent metabolites in vivo were the same as in vitro and involved the following major biotransformation pathway: oxidative opening of the pyrrolidine ring to form the carboxylic acid metabolites M37, M39, and M43.3.

The reviews of the toxicokinetic assessments are included in the respective toxicology studies below. The toxicokinetic parameters determined in the repeat dose toxicology studies in rats, dogs and monkeys generally retained the following characteristics: the exposures to ABL001 (C_{max} and $AUC_{0\text{-}24h}$) increased dose-proportionally (in general) as a function of increasing dose, no noticeable accumulation of ABL001 in plasma occurred following repeated administration and no effect of sex on plasma ABL001 levels was observed.

The table below is the summary of the systemic exposure margins (animal exposure/human exposure) supporting the USPI information in Sections 5.7 (Warning and Precautions), Section 8 (Use in Special Populations) and Section 13 (Nonclinical Toxicology).

Table 3: Exposure Multiples of Asciminib at Pivotal Embryo-Fetal Effect Dose Levels

	EFD rats 25 mg/kg/day	EFD rats 150 mg/kg/day	EFD rabbits 15 mg/kg/day	EFD rabbits 50 mg/kg/day	Early embryotoxicity Fertility male Rats 200 mg/kg/day*
animals	Cmax: 1890 AUC: 14500	Cmax: 13200 AUC: 161000	Cmax: 2200 AUC: 11300	Cmax: 6330 AUC: 45900	Cmax: 16500 AUC: 177000
Humans 40 mg BID	Cmax: 793.3 AUC: 10525	Cmax: 793.3 AUC: 10525	Cmax: 793.3 AUC: 10525	Cmax: 793.3 AUC: 10525	Cmax: 793.3 AUC: 10525
Margin (Cmax/AUC)	2.4/1.4	16.6/15.3	2.77/1.1	8/4.36	20.8/16.8
Human 80 mg QD	Cmax: 1781 AUC: 15112	Cmax: 1781 AUC: 15112	Cmax: 1781 AUC: 15112	Cmax: 1781 AUC: 15112	Cmax: 1781 AUC: 15112
Margin (Cmax/AUC)	1.1/0.96	7.41/10.7	1.23/0.75	3/3.55	9.3/11.7
Human 200 mg BID	Cmax: 5642	Cmax: 5642	Cmax: 5642	Cmax: 5642	Cmax: 5642

	AUC: 75094	AUC: 75094	AUC: 75094	AUC: 75094	AUC: 75094
Margin (Cmax/AUC)	0.33/0.19	2.33/2.1	0.39/0.15	1.12/0.61	2.9/2.4

*Cmax and AUC values are based on the 4-week repeat dose toxicology study in rats (Pcs-r1270619), Day 29.
Human exposures are based on Clinical Study ABL001X2101.
Exposure multiple= Exposure-animal/Exposure-human

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

The general toxicity of asciminib was assessed in rats, dogs and monkeys. Repeat dose toxicity studies identified the pancreas, liver, hematopoietic system, adrenal and gastro-intestinal tract as potential target tissues. All findings have demonstrated a partial to complete reversibility during a 4-week recovery phase.

Pancreatic effects (serum amylase and lipase increases, acinar cell lesions) occurred in dogs at AUC exposures below those achieved in patients on 40 mg BID, 80 mg QD or 200 mg BID. A trend towards recovery was observed. Additional studies were performed in order investigate the pancreas toxicity mechanism (See Section 5.5.5).

Elevations in liver enzymes and/or bilirubin were observed in rats, dogs and monkeys. Histopathological hepatic changes (centrilobular hepatocyte hypertrophy, slight bile duct hyperplasia, increased individual hepatocyte necrosis and diffuse hepatocellular hypertrophy) were seen in rats and monkeys. These changes occurred at AUC exposures either equivalent to (rats) or 8- to 18-fold (dogs and monkeys) higher than those achieved in patients on 40 mg BID or 80 mg QD, AUC exposures were below (rats), equivalent (dogs) or approximately 2-fold higher (monkeys) than the exposure in patients on 200 mg BID. These changes were fully reversible.

Effects on the hematopoietic system (reduction in red blood cells mass, increased splenic or bone marrow pigment and increased reticulocytes) were consistent with a mild and regenerative, extravascular, hemolytic anemia in all species. These changes occurred at AUC exposures either equivalent to (rats) or 10- to 14-fold (dogs and monkeys) higher than those achieved in patients on 40 mg BID or 80 mg QD, AUC exposures were below (rats), equivalent (dogs) or approximately 2-fold higher (monkeys) than the exposure in patients on 200 mg BID. These changes were fully reversible.

Minimal mucosal hypertrophy/hyperplasia (increase in thickness of the mucosa with frequent elongation of villi) was present in the duodenum of rats, at AUC exposures 30-fold or 22-fold higher than exposures achieved in patients on 40 mg BID or 80 mg QD, respectively. AUC

exposure was 4-fold higher than those achieved in patients receiving 200 mg BID. This change was fully reversible.

Minimal or slight hypertrophy of the adrenal gland and mild to moderate decreased vacuolation in the zona fasciculata occurred at AUC exposures either equivalent to (monkeys) or 13- to 19- fold (rats) higher than those achieved in patients on 40 mg BID or 80 mg QD, respectively. AUC exposures were below (monkeys) or 2-fold higher (rats) than the exposure in patients on 200 mg BID, respectively. These changes were fully reversible.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's assessment, especially the identification of the asciminib-related target organs/tissues of toxicity. See the additional information provided below for the detailed reviews of the 26-week and 13-week repeat-dose toxicity studies in Sprague Dawley rats and cynomolgus monkeys, respectively. Since the asciminib-related toxicities were more prominent in the 13-week monkey study than in the 39-week monkey study, the 13-week study was chosen for the detailed review.

Study title/Study number: 26-week oral gavage chronic toxicity and toxicokinetic study with asciminib in rats with a 13-week interim necropsy and 4-week interim recovery phase/1470225

Key findings

- Mortalities occurred in two females at 200 mg/kg/day. Based on the presence of asciminib-related microscopic findings (Harderian gland degeneration/atrophy and liver cell necrosis), these deaths appeared to be asciminib-related.
- Asciminib-related increases in liver enzymes (AST and ALT) were observed primarily in females at 200 mg/kg/day and smaller increases in ALT levels were observed at 50 mg/kg/day. These findings are consistent with histopathology findings indicating hepatocellular injury.
- The target organs for asciminib in rats included the adrenal gland (hypertrophy), bone marrow (hypercellularity), Harderian gland (degeneration/atrophy), liver (centrilobular hepatocyte hypertrophy, bile duct hyperplasia, and hepatocyte necrosis), and spleen (increased extramedullary hematopoiesis, increased pigment, and lymphocyte depletion).

GLP compliance: yes

Methods	
Drug	ABL001 (asciminib), CoA Batch no. 1010009610, 100% drug content; pure API (salt factor: (b) (4))

Dose and frequency of dosing	0 (vehicle), 15, 50 or 200 mg (base)/kg/day, once daily for 13 or 26 weeks
Route of administration	Oral gavage (10 mL/kg)
Formulation/Vehicle	Oral suspension: (b) (4), aqueous solution containing (b) (4)
Species/strain	Rat/Wistar Han
Number/Sex/Group	Main study: 20/sex/group for 0, 15, 50, and 200 mg/kg/day groups treated for 26 weeks Interim sacrifice: 10/sex/group for 200 mg/kg/day group treated for 13 weeks Interim recovery: 6/sex/group for 0 and 200 mg/kg/day groups; 4-week recovery following 13 weeks of treatment
Age	9-10 weeks; 170-354 g
Satellite groups/unique design	Toxicokinetics assessment: all animals (except for the control) in the study participated.
Deviation from study protocol affecting interpretation of result	Not remarkable
Observation and Results: changes from control	
Parameters	Major findings
Formulation	Stability and homogeneity were within the acceptable range (0.4-2.2% homogeneity); concentration verification (94.9%-99.9% of target concentrations; within the range of ± 15% of nominal concentration).
Mortality	Four asciminib-treated females were found dead: 2 at 50 mg/kg/day, 2 at 200 mg/kg/day. Cause of death: 50 mg/kg: undetermined (n=1), due to blood collection (n=1); 200 mg/kg: asciminib-related Related findings: liver cell necrosis (n=2, one each at 50 and 200 mg/kg), necrosis of thymus lymphocytes, lymphoid depletion in spleen, lesions in the GI (ulceration and inflammation) in one rat at 200 mg/kg/day.
Clinical signs	Mainly at 200 mg/kg: • 13 weeks of dosing: Clear oral discharge at 200 mg/kg/day: males (2/16), females (3/16) Audible respiration: males: (1/16), females (2/16) • 26 weeks of dosing: In females only: Hypoactivity (1/20) and lateral recumbence (1/20) Audible respiration: males (4/20), females (7/20) Irregular respiration: males (2/20), females (5/20)
Body weight	Reduction in body weight gain • 13 weeks of dosing Days 1-85: ↓up to 17% • 26 weeks of dosing Day 1-85: ↓up to 11% (males), ↓12-13% (females) Day 1-183: ↓up to 14% (males), ↓16% (females)
Food consumption	Reduction in food intake was consistent with body weight gain reduction in rats treated with 200 mg/kg/day, with the largest differences observed during the first two weeks of dosing (↓4-17%).
ECG and hemodynamics	Not conducted
Ophthalmology	Not remarkable

<table>
<tr><td>Hematology and coagulation</td><td>Hematology changes were generally similar between Days 81 and 172/173 of the dosing period. The main findings were reduced erythroid parameters and increased total and differential white blood cell counts. The findings indicated increased red blood cell turnover including decreases in red blood cell count (↓up to 14%), hemoglobin (↓up to 11%), and hematocrit (↓up to 11%) and increases in reticulocyte count (↑up to 139%). Increases in white blood cell (↑up to 69%), neutrophil (↑up to 81%), lymphocyte (↑up to 64%), and monocyte (↑up to 82%) counts at 200 mg/kg/day may be associated with inflammation.

No remarkable changes for the coagulation parameters.</td></tr>
<tr><td>Clinical chemistry</td><td>The findings were mainly asciminib-related increases in liver enzymes (AST and ALT) primarily in females at 200 mg/kg/day on Days 81 and 172/173. Based on the 200 mg/kg/day group means, AST was increased up to 2.5-fold in females and ALT was increased up to 5.1-fold in females and 1.4-fold in males compared to controls. Two individual females showed marked increases in AST (up to 14-fold) and ALT (up to 45-fold). These findings are consistent with hepatocellular injury.

While increased bilirubin levels (↑up to 200%) supported the notion of increased red blood cell turnover rate, changes such as lower triglycerides (↓25-30%) and decreases (↓4-12%) in total protein, globulin and albumin, and higher cholesterol (↑26-39%) as well as disturbed electrolytes (calcium; ↓3%) did not correlate with lesions of particular organs/tissues.</td></tr>
<tr><td>Urinalysis</td><td>Not remarkable</td></tr>
<tr><td>Gross anatomy</td><td>Not remarkable</td></tr>
<tr><td>Organ weights</td><td>The main target organs were the adrenal gland, liver, and spleen.

Interim animals: 13-weeks of dosing
<table>
<tr><td colspan="2" rowspan="2">Group and Dose</td><td colspan="4">Percentage deviation from Control</td></tr>
<tr><td colspan="4">200 mg/kg/day</td></tr>
<tr><td colspan="2">Sex</td><td colspan="2">Males</td><td colspan="2">Females</td></tr>
<tr><td colspan="2">Necropsy</td><td>Terminal</td><td>Recovery</td><td>Terminal</td><td>Recovery</td></tr>
<tr><td colspan="2">Number of animals examined</td><td>10</td><td>6</td><td>10</td><td>6</td></tr>
<tr><td rowspan="2">Adrenal gland</td><td>Absolute (g)</td><td>↑18*</td><td>↑10</td><td>↑31*</td><td>↑10</td></tr>
<tr><td>Relative (BW,%)</td><td>↑27*</td><td>↑14</td><td>↑41*</td><td>↑14</td></tr>
<tr><td rowspan="2">Liver</td><td>Absolute (g)</td><td>↑9</td><td>-</td><td>↑14*</td><td>-</td></tr>
<tr><td>Relative (BW,%)</td><td>↑15*</td><td>-</td><td>↑23*</td><td>-</td></tr>
<tr><td rowspan="2">Spleen</td><td>Absolute (g)</td><td>↑38*</td><td>-</td><td>↑50*</td><td>-</td></tr>
<tr><td>Relative (BW,%)</td><td>↑48*</td><td>-</td><td>↑62*</td><td>-</td></tr>
</table>
BW= Body weight
↑= increase ↓=decrease - = no test-article related changes
*=Significantly different from the control group

Main Study animals: 26-weeks of dosing
<table>
<tr><td rowspan="2">Group and Dose</td><td colspan="4">Percentage deviation from Control</td></tr>
<tr><td colspan="2">50 mg/kg/day</td><td colspan="2">200 mg/kg/day</td></tr>
<tr><td>Sex</td><td>Males</td><td>Females</td><td>Males</td><td>Females</td></tr>
<tr><td>Number of animals examined</td><td>20</td><td>18</td><td>20</td><td>18</td></tr>
</table></td></tr>
</table>

	Adrenal gland	Absolute (g)	-	-	↑23*	↑46*
		Relative (BW,%)	-	↑11	↑33*	↑55*
	Liver	Absolute (g)	-	-	↑9*	↑15*
		Relative (BW,%)	-	-	↑18*	↑21*
	Spleen	Absolute (g)	↑15*	-	↑56*	↑49*
		Relative (BW,%)	↑18*	↑9*	↑69*	↑57*
	BW= Body weight ↑= increase ↓=decrease - = no test-article related changes *=Significantly different from the control group					
Histopathology	The findings are summarized in the microscopic findings tables below. The target organs included the liver/bile duct, bone marrow, Harderian gland, spleen and adrenal glands. Harderian glands are pigmented lacrimal glands which are largely absent in the adult human. The glands release lipid- and porphyrin-rich material that lubricates the eyes and eyelids. The relevance of findings of degeneration and/or atrophy of these glands to humans is unknown. The finding may be rat-specific. Hyperplasia/hypertrophy and inflammation/mononuclear cell infiltrate were noted in many of the target organs. These are seen with other BCR-ABL inhibitors. Prolongation of treatment induced more findings and/or increased the severity in comparison to the interim findings.					
Toxicokinetics	See table below.					

Histopathological Findings

Table 4: 13-weeks of dosing (interim animals)

Treatment-Related Microscopic Findings			No. of animals affected			
			Males		**Females**	
Dose (mg/kg/day)			0	200	0	200
Number of animals examined			10/**6**	10/**6**	10/**6**	10/**6**
Organ	Finding					
Adrenal gland, cortex	Hypertrophy	Total	-	9/**0**	0/**1**	6/**0**
		Minimal	-	7/**0**	0/**1**	4/**0**
		Slight	-	2/**0**	-	2/**0**
Bone marrow, femur	Hypercellular	Minimal	-	7/**0**	-	9/**0**
Bone marrow, sternum	Hypercellular	Minimal	-	-	-	9/**0**
Harderian gland	Degeneration/atrophy	Total	0/**1**	10/**6**	1/**3**	10/**6**
		Minimal	0/**1**	0/**1**	1/**2**	3/**4**
		Slight	-	6/**5**	0/**1**	5/**2**
		Moderate	-	4/**0**	-	2/**0**
	Infiltrate, mononuclear cell	Total	0/**1**	10/**4**	2/**0**	8/**3**
		Minimal	0/**1**	8/**4**	1/**0**	8/**3**
		Slight	-	2/**0**	-	-
		Moderate	-	-	1/**0**	-
Liver	Infiltrate, mixed cell	Moderate	-	-	-	1/**0**
	Infiltrate, mononuclear cell	Total	5/**2**	3/**0**	4/**1**	8/**0**
		Minimal	5/**2**	3/**0**	4/**1**	4/**0**
		Slight	-	-	-	4/**0**
		Total	-	10/**0**	-	8/**0**

Treatment-Related Microscopic Findings			No. of animals affected			
			Males		**Females**	
Dose (mg/kg/day)			0	200	0	200
Number of animals examined			10/**6**	10/**6**	10/**6**	10/**6**
Organ	Finding					
	Hypertrophy, hepatocyte, centrilobular	Minimal	-	9/**0**	-	7/**0**
		Slight	-	1/**0**	-	1/**0**
	Hyperplasia, bile duct	Total	-	-	-	2/**0**
		Minimal	-	-	-	1/**0**
		Slight	-	-	-	1/**0**
Spleen	Increased extramedullary hematopoiesis	Total	2/**4**	10/**4**	2/**0**	8/**0**
		Minimal	1/**4**	6/**4**	1/**0**	4/**0**
		Slight	-	4/**0**	1/**0**	4/**0**
		Moderate	1/**0**	-	-	-
	Increased pigment	Total	-	5/**6**	2/**0**	4/**6**
		Minimal	-	1/**5**	-	3/**1**
		Slight	-	4/**1**	2/**0**	1/**2**
		Moderate	-	-	-	0/**3**

Number of animals examined and affected: Interim Sacrifice necropsy/ **Interim Recovery necropsy**
- = no test-article related changes

Table 5: 26-weeks of dosing (main Study animals)

Treatment-Related Microscopic Findings			No. of animals affected							
			Males				**Females**			
Dose (mg/kg/day)			0	15	50	200	0	15	50	200
Number of animals examined			0/20	0/20	0/20	0/20	1*/19	0/20	2*/18	2*/18
Organ	Finding									
Adrenal gland, cortex	Hypertrophy (diffuse)	Total	-	-	-	0/10	-	-	-	0/13
		Minimal	-	-	-	0/10	-	-	-	0/8
		Slight	-	-	-	-	-	-	-	0/5
Adrenal gland, medulla	Malformation	Severe	-	-	-	-	-	-	-	1*/0
Bone marrow, femur	Hypercellular	Total	-	-	-	0/18	-	-	-	0/14
		Minimal	-	-	-	0/4	-	-	-	0/9
		Slight	-	-	-	0/14	-	-	-	0/5
Bone marrow, sternum	Hypercellular	Total	-	-	-	0/19	-	-	-	0/13
		Minimal	-	-	-	0/11	-	-	-	0/8
		Slight	-	-	-	0/8	-	-	-	0/5
Eye	Malformation	Severe	-	NE	NE	0/1	-	NE	NE	-
Harderian gland	Degeneration/atrophy	Total	0/4	0/1	0/10	0/20	0/1	0/3	1*/2	2*/17
		Minimal	0/3	0/1	0/7	0/2	0/1	0/2	1*/1	0/8
		Slight	0/1	-	0/2	0/15	-	-	0/1	0/9
		Moderate	-	-	0/1	0/3	-	0/1	-	2*/0
	Atrophy (entire gland)	Total	-	-	-	0/12	-	-	-	1*/9
		Minimal	-	-	-	0/1	-	-	-	0/6
		Slight	-	-	-	0/9	-	-	-	1*/2
		Moderate	-	-	-	0/2	-	-	-	0/1

	Infiltrate, mononuclear cell	Total	0/9	0/6	0/8	0/16	0/3	0/7	0/6	1*/16
		Minimal	0/8	0/6	0/5	0/11	0/3	0/5	0/3	0/13
		Slight	0/1	-	0/3	0/5	-	0/2	0/3	1*/3
Liver	Hypertrophy, hepatocyte, centrilobular	Total	-	0/1	0/20	0/20	-	0/1	0/1	1*/18
		Minimal	-	0/1	0/16	0/7	-	0/1	0/1	1*/10
		Slight	-	-	0/4	0/12	-	-	-	0/8
		Moderate	-	-	-	0/1	-	-	-	-
	Hyperplasia, bile duct	Total	-	-	-	0/1	0/2	-	0/5	0/14
		Minimal	-	-	-	0/1	0/2	-	0/4	0/14
		Slight	-	-	-	-	-	-	0/1	-
	Infiltrate, mixed cells	Total	-	0/5	0/5	-	-	0/4	0/10	1*/13
		Minimal	-	0/5	0/4	-	-	0/4	0/10	0/2
		Slight	-	-	0/1	-	-	-	-	1*/11
	Infiltrate, mononuclear cell	Total	0/14	0/18	0/16	0/13	0/9	0/12	1*/11	0/13
		Minimal	0/14	0/13	0/12	0/13	0/8	0/12	1*/10	0/9
		Slight	-	0/5	0/4	-	0/1	-	0/1	0/3
		Moderate	-	-	-	-	-	-	-	0/1
	Necrosis, individual hepatocyte	Total	-	0/16	0/18	0/6	-	-	-	2*/6
		Minimal	-	0/16	0/15	0/5	-	-	-	1*/5
		Slight	-	-	0/3	0/1	-	-	-	1*/0
		Moderate	-	-	-	-	-	-	-	0/1
	Focus, cellular alteration, basophilic	Total	-	0/1	0/2	0/2	0/7	0/8	0/7	1*/17
		Minimal	-	0/1	0/2	0/2	0/7	0/8	0/6	1*/10
		Slight	-	-	-	-	-	-	0/1	0/7
	Pigment	Total	-	-	-	-	1*/0	-	0/2	0/1
		Minimal	-	-	-	-	-	-	-	0/1
		Slight	-	-	-	-	1*/0	-	-	-
		Moderate	-	-	-	-	-	-	0/1	-
		Marked	-	-	-	-	-	-	0/1	-
Rectum	Acute inflammation	Slight	-	NE	NE	-	-	NE	NE	1*/0
Spleen	Increased extramedullary hematopoiesis	Total	0/1	0/4	0/9	0/20	-	0/1	0/4	0/7
		Minimal	0/1	0/3	0/7	0/7	-	0/1	0/2	0/2
		Slight	-	0/1	0/2	0/12	-	-	0/2	0/4
		Moderate	-	-	-	0/1	-	-	-	0/1
	Increased pigment	Total	-	0/3	0/2	0/10	1*/8	0/8	1*/11	2*/18
		Minimal	-	0/1	0/1	0/5	0/4	0/4	0/5	0/13
		Slight	-	0/2	0/1	0/5	0/4	0/4	1*/6	0/5
		Moderate	-	-	-	-	1*/0	-	-	1*/0
		Marked	-	-	-	-	-	-	-	1*/0
	Lymphocyte depletion	Total	-	-	-	-	-	-	1*/0	2*/0
		Minimal	-	-	-	-	-	-	1*/0	-
		Moderate	-	-	-	-	-	-	-	2*/0
Stomach, non-glandular	Inflammation	Slight	-	NE	NE	-	-	NE	-	1*/0
	Ulcer	Slight	-	NE	NE	0/1	-	NE	-	1*/0
Thymus	Lymphocyte necrosis	Marked	-	NE	NE	-	-	NE	-	1*/0

Number of animals examined and affected: Early deaths*/ Main Study necropsy
- = no test-article related changes
NE= Tissue not examined in this group

Table 6: Mean Plasma Asciminib Toxicokinetic Parameters (26-Week Study in Rats)

Dose (mg/kg/day)	Study Day	Gender	AUC_{0-24h} (ng*h/mL)	±SE	AUC_{0-24h}/Dose (ng*h/mL)/ (mg/kg/day)	±SE	C_{max} (ng/mL)	C_{max}/Dose (ng/mL)/ (mg/kg/day)	T_{max} (h)
15	1	Male	9800	914	653	60.9	1120	74.7	3
		Female	8940	1950	596	130	999	66.6	3
	88	Male	13200	398	883	26.5	1880	125	3
		Female	10400	2930	697	195	1330	88.7	3
	180	Male	15600	724	1040	48.3	2140	143	1
		Female	14500	5720	966	381	1490	99.3	1
50	1	Male	45200	4130	905	82.6	4450	89.0	3
		Female	88500	3420	1770	68.4	7130	143	3
	88	Male	57300	3140	1150	62.8	7050	141	3
		Female	54600	NC	1090	NC	6620	132	3
	180	Male	65600	9740	1310	195	7210	144	3
		Female	71500	18200	1430	364	7210	144	1
200	1	Male	263000	33600	1320	168	17200	86.0	5
		Female	272000	21300	1360	107	16800	84.0	7
	88	Male	255000	22400	1270	112	17400	87.0	7
		Female	339000	30700	1700	154	21100	106	3
	180	Male	230000	24900	1150	125	15200	76.0	7
		Female	459000	25800	2290	129	26500	133	7
200 (Interim)	1	Male	236000	19400	1180	97.0	16700	83.5	5
		Female	216000	30900	1080	155	18400	92.0	3
	88	Male	203000	42700	1010	214	15900	79.5	1
		Female	293000	27100	1460	136	21500	108	5

NC = Not calculable

(Table excerpted from Applicant's submission)

Study title/Study number: 13-week oral (gavage) toxicity study with non-invasive telemetry in monkeys with a 4-week recovery period/1470095

Key Study Findings

- Oral doses of asciminib up to 100 mg/kg/day for 13 weeks were tolerated. The treatment-related findings included GI-related clinical signs, reductions in food consumption and the associated body weight gain, hematological effects (suppression of erythroid mass, increased total and differential white blood cell counts, and a slight increase in aPTT), and clinical chemistry findings due to dehydration and electrolyte imbalances.
- The target organs of toxicity for asciminib in monkeys included the liver, adrenal gland

and kidney.

GLP compliance: yes

<table>
<tr><td colspan="2">Methods</td></tr>
<tr><td>Drug</td><td>ABL001 (asciminib), Batch no. 1010004120, purity: 99.4%; hydrochloride, (salt/base ratio = (b) (4))</td></tr>
<tr><td>Dose and frequency of dosing</td><td>0 (vehicle), 10, 30 or 100 mg (base)/kg/day, once daily for at least 13 weeks

Drug holiday/dosing suspension: Animal #4505 was given treatment/supplement to alleviate the symptoms of diarrhea, slight dehydration, and abdominal distension. The administration of asciminib (100 mg/kg/day) was stopped between Days 44-49 (6 days in total).</td></tr>
<tr><td>Route of administration</td><td>Oral gavage (5 mL/kg)</td></tr>
<tr><td>Formulation/Vehicle</td><td>Oral suspension: (b) (4) aqueous solution containing (b) (4)</td></tr>
<tr><td>Species/strain</td><td>Monkey/cynomolgus</td></tr>
<tr><td>Number/Sex/Group</td><td>Main study:
3/sex/group (Control, LD, MD and HD; Day 94, terminal necropsy)
Recovery:
2/sex/group (Control and HD; Recovery Day 29 (Day 123), recovery necropsy)</td></tr>
<tr><td>Age</td><td>2-4 years; 2-3 kg</td></tr>
<tr><td>Satellite groups/unique design</td><td>Toxicokinetics assessment: animals in the main study participated.</td></tr>
<tr><td>Deviation from study protocol affecting interpretation of result</td><td>Not remarkable</td></tr>
<tr><td colspan="2">Observation and Results: changes from control</td></tr>
<tr><td>Parameters</td><td>Major findings</td></tr>
<tr><td>Formulation</td><td>Stability and homogeneity were within the acceptable range (99%-105% of target concentrations).</td></tr>
<tr><td>Mortality</td><td>None</td></tr>
<tr><td>Clinical signs</td><td>The findings were mainly at 100 mg/kg/day, including diarrhea, emesis, and changes in skin/fur. The findings resolved during the recovery period.
Summary of clinical signs
<table>
<tr><td>Dose</td><td colspan="2">30 mg/kg</td><td colspan="2">100 mg/kg</td></tr>
<tr><td>Sex</td><td>M</td><td>F</td><td>M</td><td>F</td></tr>
<tr><td>N</td><td>5</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>Diarrhea* 25%
50%
75%
100%</td><td>

1/1</td><td>3/1

1/1</td><td>3/1
2/1

</td><td>5/2
2/7
2/4
2/4</td></tr>
<tr><td>Emesis
With apparent compound
With food</td><td>

</td><td>

1/1</td><td>2/1.5

3/2
3/1.33</td><td>

4/2.75
4/1.75</td></tr>
</table></td></tr>
</table>

	<table><tr><td>Salivation</td><td></td><td></td><td>4/6.25</td><td>2/5</td></tr><tr><td>Gingiva, pale**</td><td></td><td></td><td></td><td>1/6</td></tr></table> Numbers expressed: number of animals affected/mean number of days with findings; M: males, F: females *Soft feces were observed in all monkeys with no dose-dependency in frequency or severity. **Findings in Animal #4505 (female at 100 mg/kg/day) also included fecal changes (diarrhea and soft feces: Day 8-Week 13), slight decreased motor activity, dehydration, hunched posture, pale appearance, and distended abdomen.
Body weight	Slight changes in mean group body weight and body weight gain: Males (kg) <table><tr><td>Group</td><td>Day 8-64</td><td>Days 71-85</td><td>Day 1-92</td><td>Recovery</td></tr><tr><td>Control</td><td>NA</td><td>NA</td><td>BW gain ↑0.02-0.3 *</td><td>BW gain ↑0.35-0.4</td></tr><tr><td>100 mkd</td><td>Abs BW ↓0.02-0.2</td><td>BW gain ↓0.04-0.06</td><td>Abs BW ↓0.04</td><td>BW gain ↑0-0.15</td></tr></table> Females (kg) <table><tr><td>Group</td><td>Day 8-43</td><td>Days 50-92</td><td>Day 8-92</td><td>Recovery</td></tr><tr><td>Control</td><td>---</td><td>---</td><td>BW gain ↑0.04-0.4</td><td>BW gain ↑0.4-0.6</td></tr><tr><td>30 mkd</td><td>---</td><td>---</td><td>BW gain ↓0.16-0.2</td><td>---</td></tr><tr><td>100 mkd</td><td>BW gain ↓0.06-0.16</td><td>BW gain ↓0.04-0.22</td><td>BW gain ↓0.04-0.22</td><td>BW gain ↑0.15-0.25</td></tr></table> mkd: mg/kg/day; * Day 8-92 compared to Day 1, NA: not applicable; Abs: absolute; BW: body weight Conclusion: During the course of the study, the treatment-induced reduction in body weight appeared to recover from the early greater reductions, indicating a trend of recovery. Absolute body weights: % change from the control at necropsy (Day 92) Males: -4%, 12% and 0%; females: -6%, -10% and -16%, at 10, 30 and 100 mg/kg/day, respectively.
Food consumption	Summary of food consumption (Days 1- 94) <table><tr><td>Sex</td><td>Males</td><td></td><td></td><td>Females</td><td></td><td></td></tr><tr><td>Dose mkd</td><td>Control</td><td>30</td><td>100</td><td>Control</td><td>30</td><td>100</td></tr><tr><td>N</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td></tr><tr><td colspan="7">Food consumption</td></tr><tr><td>25% 50% 75% 100% Fasted</td><td> 3/1 5/7.6 5/82.6 5/2.6</td><td> 1/1 2/1 3/89 3/3</td><td>1/1 3/1 5/17.4 5/72.6 5/2.6</td><td> 3/13 5/83.6 5/2.6</td><td> 3/3 3/26 3/62 3/3</td><td>5/2.6 5/11.2 5/25.4 5/52.2 5/2.6</td></tr></table> mkd= mg/kg/day

<table>
<tr><td></td><td>Numbers expressed: number of animals affected/mean number of days with findings; M: males, F: females

Estimated food intake was ~25-75% of food provided in most affected animals. The finding resolved during the recovery period.
The finding was consistent with the reduction in body weight gain.</td></tr>
<tr><td>ECG and hemodynamics</td><td>Not remarkable</td></tr>
<tr><td>Ophthalmology</td><td>Not remarkable</td></tr>
<tr><td>Hematology and coagulation</td><td>The main findings were reduced erythroid parameters and increased total and differential white blood cell counts.
Day 22 (week 4):
<table>
<tr><td></td><td>Males</td><td>Females</td><td></td></tr>
<tr><td>Dose mkd</td><td>100</td><td>30</td><td>100</td></tr>
<tr><td>N</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>RBC ↓</td><td>11</td><td>4</td><td>19</td></tr>
<tr><td>HGB ↓</td><td>14</td><td>6</td><td>21</td></tr>
<tr><td>Hct ↓</td><td>12</td><td>7</td><td>23</td></tr>
<tr><td>Reticulocyte ↑</td><td>309</td><td>197</td><td>247</td></tr>
<tr><td>WBC ↑</td><td></td><td></td><td>39</td></tr>
<tr><td>Neutrophil ↑</td><td></td><td></td><td>35</td></tr>
<tr><td>Lymphocyte ↑</td><td></td><td></td><td>34</td></tr>
<tr><td>Monocyte ↑</td><td></td><td></td><td>76</td></tr>
<tr><td>Eosinophil ↑</td><td>139</td><td></td><td>140</td></tr>
<tr><td>Basophil ↑</td><td></td><td></td><td>175</td></tr>
<tr><td>LUC ↑</td><td></td><td></td><td>257</td></tr>
<tr><td>aPTT ↑</td><td>12</td><td></td><td>12</td></tr>
</table>
Number indicates % change from the pretest value (Day -8)

Day 44 (unscheduled sampling): 100 mg/kg/day group
<table>
<tr><td></td><td>Males</td><td>Females</td></tr>
<tr><td>N</td><td>5</td><td>5</td></tr>
<tr><td>RBC ↓</td><td>8</td><td>13</td></tr>
<tr><td>HGB ↓</td><td>8</td><td>13</td></tr>
<tr><td>Hct ↓</td><td>7</td><td>14</td></tr>
<tr><td>Reticulocyte ↑</td><td>191</td><td>122</td></tr>
</table>
Day 79 (week 12)
<table>
<tr><td></td><td>Males</td><td>Females</td><td></td></tr>
<tr><td>Dose mkd</td><td>100</td><td>30</td><td>100</td></tr>
<tr><td>N</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>RBC ↓</td><td>3</td><td></td><td>9</td></tr>
<tr><td>HGB ↓</td><td>8</td><td></td><td>12</td></tr>
<tr><td>Hct ↓</td><td>7</td><td>7</td><td>11</td></tr>
<tr><td>Reticulocyte ↑</td><td>117</td><td>101</td><td>80</td></tr>
<tr><td>aPTT ↑</td><td></td><td></td><td>14</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>LUC: large unstained cells

In comparison to the suppression in erythroid parameters on Day 22, there was evidence of alleviation on Day 44.

The lymphocytic effect was transient, by Day 79, the findings were no longer remarkable. The values for the parameters in the asciminib-treated groups were comparable to the pretest values at the end of the recovery period.</td></tr>
<tr><td>Clinical chemistry</td><td>The findings were mainly observed at ≥ 30 mg/kg/day. The tables below are summaries of % changes from the pretest values.
Day 22
<table>
<tr><td></td><td>Males</td><td></td><td>Females</td><td></td></tr>
<tr><td>Dose mkd</td><td>30</td><td>100</td><td>30</td><td>100</td></tr>
<tr><td>N</td><td>5</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>Total bilirubin ↑</td><td>93</td><td>346</td><td>104</td><td>168</td></tr>
<tr><td>BUN ↑</td><td>NR</td><td>42</td><td>NR</td><td>33</td></tr>
<tr><td>Creatinine ↑</td><td>NR</td><td>48</td><td>NR</td><td>16</td></tr>
<tr><td>Total protein ↑</td><td>5</td><td>7</td><td>NR</td><td>5</td></tr>
<tr><td>Globulin ↑</td><td>8</td><td>16</td><td>10</td><td>22</td></tr>
<tr><td>Cholesterol ↑</td><td>40</td><td>44</td><td>31</td><td>45</td></tr>
</table>
Day 44 (unscheduled sampling): 100 mg/kg/day
<table>
<tr><td></td><td>Males</td><td>Females</td></tr>
<tr><td>N</td><td>5</td><td>5</td></tr>
<tr><td>Glucose ↑</td><td>28</td><td>17</td></tr>
<tr><td>BUN ↑</td><td>NR</td><td>51</td></tr>
<tr><td>Creatinine ↑</td><td>NR</td><td>19</td></tr>
<tr><td>Globulin ↑</td><td>12</td><td>11</td></tr>
<tr><td>Cholesterol ↑</td><td>35</td><td>55</td></tr>
<tr><td>Phosphorus ↓</td><td>14</td><td>22</td></tr>
</table>
Day 79
<table>
<tr><td></td><td>Males</td><td></td><td>Females</td><td></td></tr>
<tr><td>Dose mkd</td><td>30</td><td>100</td><td>30</td><td>100</td></tr>
<tr><td>N</td><td>5</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>Total bilirubin ↑</td><td>153</td><td>214</td><td>137</td><td>232</td></tr>
<tr><td>BUN ↑</td><td>NR</td><td>41</td><td>NR</td><td>70</td></tr>
<tr><td>Creatinine ↑</td><td>NR</td><td>30</td><td>NR</td><td>40</td></tr>
<tr><td>Total protein ↑</td><td>5</td><td>5</td><td>NR</td><td>NR</td></tr>
<tr><td>Globulin ↑</td><td>4</td><td>7</td><td>3</td><td>6</td></tr>
<tr><td>Cholesterol ↑</td><td>40</td><td>56</td><td>28</td><td>91</td></tr>
<tr><td>Phosphorus ↑</td><td>NR</td><td>NR</td><td>NR</td><td>28</td></tr>
</table>
mkd: mg/kg/day; NR=not remarkable

The trend of changes in total bilirubin and BUN (blood urea nitrogen)</td></tr>
</table>

<table>
<tr><td></td><td>levels
• Increased total bilirubin (TB) levels, attributable to indirect bilirubin, were noted in ≥ 30 mg/kg/day groups.
• Minimal increases in BUN and creatinine values in the 100 mg/kg/day groups (when compared to the pretest and control levels) were probably related to dehydration; however, some renal injury cannot be completely excluded. Dehydration may have reduced the renal blood flow and affected glomerular filtration rate. Histopathological findings were mainly hypertrophy of tubular epithelial cells and cellular infiltration, without evidence of glomerular dysfunctions.

All of the findings resolved during the recovery period.</td></tr>
<tr><td>Clinical pathology in #4505</td><td>Special veterinarian treatment, supplements and a drug holiday were provided to Animal #4505. The clinical chemistry parameters before and after the dosing interruption were summarized as follows:
% Changes from pretest values
<table>
<tr><td></td><td>BUN</td><td>Creatinine</td><td>Phosp</td><td>TP</td><td>Glob</td><td>Chole</td></tr>
<tr><td>D42</td><td>+350</td><td>+508</td><td>+50</td><td>+7</td><td>+14</td><td>+52</td></tr>
<tr><td>D49</td><td>+35</td><td>-37</td><td>-6</td><td></td><td>0</td><td>+32</td></tr>
<tr><td></td><td>Na</td><td>Cl</td><td>K</td><td>A/G</td><td>Glucose</td><td>Creat K</td></tr>
<tr><td>D42</td><td>-14</td><td>-23</td><td>-13</td><td>-7</td><td>+268</td><td>+53</td></tr>
<tr><td>D49</td><td>-1</td><td>+1</td><td>+18</td><td></td><td>+55</td><td>+121</td></tr>
</table>
Phosp: phosphorus, TP: total protein, Creat K: creatine kinase

The clinical chemistry findings in this animal were attributable to dehydration and electrolyte imbalance. The findings resolved.</td></tr>
<tr><td>Urinalysis</td><td>Not remarkable</td></tr>
<tr><td>Gross anatomy</td><td>Adrenal gland: discolored, male (1/3) and female (1/3) at 100 mg/kg/day; correlated with microscopic change of decreased vacuolation of the zona fasciculata. The findings were not observed in the recovery animals.</td></tr>
<tr><td>Organ weights</td><td>The main target organs were the liver and kidney.
Organ weight changes (% change from the control)
<table>
<tr><td></td><td colspan="4">Males</td><td colspan="4">Females</td></tr>
<tr><td>Dose*</td><td>0</td><td>10</td><td>30</td><td>100</td><td>0</td><td>10</td><td>30</td><td>100</td></tr>
<tr><td colspan="9">Liver</td></tr>
<tr><td>Ab (g)</td><td>57.4</td><td>-1%</td><td>18%</td><td>53%</td><td>59.4</td><td>1%</td><td>3%</td><td>27%</td></tr>
<tr><td>% bw</td><td>2</td><td>0</td><td>-3%</td><td>35%</td><td>1.99</td><td>8%</td><td>15%</td><td>52%</td></tr>
<tr><td>%BrW</td><td>79.2</td><td>-8%</td><td>17%</td><td>34%</td><td>92.7</td><td>-1%</td><td>-3%</td><td>31%</td></tr>
<tr><td colspan="9">Kidney</td></tr>
<tr><td>Ab (g)</td><td>12.2</td><td>-1%</td><td>18%</td><td>53%</td><td>12.3</td><td>8%</td><td>7%</td><td>25%</td></tr>
<tr><td>% bw</td><td>0.43</td><td>4%</td><td>5%</td><td>53%</td><td>0.41</td><td>15%</td><td>18%</td><td>48%</td></tr>
<tr><td>%BrW</td><td>16.9</td><td>-5%</td><td>27%</td><td>50%</td><td>19.1</td><td>6%</td><td>0</td><td>27%</td></tr>
</table>
*Dose: mg/kg/day, 0 (control)
The findings correlated with hypertrophy found in the histopathology analysis. No remarkable findings were observed in the recovery animals.</td></tr>
<tr><td>Histopathology</td><td>The findings were mainly observed at 100 mg/kg/day.</td></tr>
</table>

<table>
<tr><td></td><td>Findings in the terminal necropsy (Day 92)
<table>
<tr><td>Sex</td><td>Males</td><td>Females</td></tr>
<tr><td>Dose (mg/kg/day)</td><td>100</td><td>100</td></tr>
<tr><td>N</td><td>3</td><td>3</td></tr>
<tr><td>Liver
Hypertrophy, hepatocellular
Mild
Moderate</td><td>

1
2</td><td>

3
</td></tr>
<tr><td>Kidney (cortex)
Hypertrophy, tubular epithelium
Minimum
Mild</td><td>

1
2</td><td>

1
2</td></tr>
<tr><td>Adrenal gland (zona fasiculata)
Decreased, vacuolation
Mild
Moderate</td><td>

2
1</td><td>

1
2</td></tr>
</table>
Additionally, an indirect asciminib effect was associated with an increased incidence of pigment deposit in the spleen and bone marrow at the end of the dosing phase in animals given 100 mg/kg/day. The finding may be correlated with asciminib-induced hematology changes, i.e., lower red blood cells and higher reticulocytes, consistent with increased red blood cell turnover. The findings were not observed in the recovery animals.</td></tr>
<tr><td>Toxicokinetics</td><td>See table below.</td></tr>
</table>

Table 7: Mean Plasma Asciminib Toxicokinetic Parameters (13-Week Study in Monkeys)

Day 1

	Males					Females				
	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax
10*	2420	242	28100	2810	4.3	3050	305	32900	3290	3
30	10500	362	142000	4720	4.3	11900	398	161000	5340	2.3
100	31700	317	564000	5640	10.4	29800	298	547000	5470	7

Day 23

	Males					Females				
	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax
10*	5010	501	42400	4240	2.3	3140	314	30200	3020	4.3
30	14600	486	203000	6750	4.3	13700	458	174000	5820	3
100	33000	330	558000	5580	5.8	34600	3460	549000	5490	6.2

Day 88

	Males					Females				
	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax	Cmax	Cmax/Dose	AUC	AUC/dose	Tmax
10*	5400	540	36700	3670	2	3670	367	34000	3400	1.67
30	12600	419	155000	5150	2.3	13300	442	181000	6030	3
100	29400	294	433000	4330	3.8	48000	480	705000	7050	5.4

*Dose: mg/kg/day; Cmax: ng/mL; $AUC_{0\text{-}24h}$: ng*h/mL; Tmax: hr

Summary
- The systemic exposures to asciminib increased with increases in dose, following a generally dose proportional pattern.
- There was no apparent accumulation with repeated administration or sex difference in exposures.

Study title/Study number: 39-week oral gavage toxicity and toxicokinetic study with ABL-001 in cynomolgus monkeys/1470799

Prolonged administration of asciminib (3, 15, and 50 mg/kg/day) for 39 weeks in cynomolgus monkeys induced comparable findings to those observed in the 13-week study including GI-related clinical signs (excessive salivation) and suppressed erythroid parameters (RBC, HGB, Hct, and MCV) with compensative increases in reticulocytes (absolute and percentage). In addition, elevated total bilirubin levels were observed. Asciminib-related increased organ weights observed for the adrenal gland at ≥3 mg/kg/day and liver at 50 mg/kg/day correlated with decreased vacuolation of the adrenal cortex at ≥15 mg/kg/day and increased hepatocellular hypertrophy at 50 mg/kg/day, respectively.

There were no remarkable changes in body weight, food consumption, ophthalmology, electrocardiography (ECG), coagulation, or urinalysis. Additionally, no adverse anatomic pathology findings were noted.

Toxicokinetic summary:
- Systemic exposures increased with increases in dose and followed a greater than dose-proportional pattern.
- The exposures were slightly greater in female monkeys, but no apparent accumulation of the drug occurred following repeated administration of asciminib.

Study title/Study number: 4-Week oral gavage toxicity and toxicokinetic study with ABL001 in dogs with a 4-week recovery phase/pcs-r-1270620

Oral doses of asciminib (3, 15, and 60 mg/kg/day) administered via gavage for 4 weeks were tolerated up to 15 mg/kg/day. Although no treatment-related mortality occurred, overt clinical signs (excessive salivation, emesis, vomitus, and fecal changes), >36-fold increases in serum lipase compared to the control, and >3-fold increases in serum ALT were observed at 60 mg/kg/day. Microscopic findings of concern were observed in the pancreas of males at ≥3 mg/kg/day and females at ≥15 mg/kg, and were only partially reversible at 60 mg/kg/day. Histopathology observations in the pancreas included dose-related degeneration and/or necrosis of acinar cells varying from minimal to marked, accompanied by fibrosis (atrophy)

with increasing dose. Other treatment-related findings such as decreases in erythroid parameters and compensatory increases in reticulocytes, increases in white blood cell counts and/or platelets, and increases in total bilirubin (indicating shortened RBC life span) were observed in other toxicology studies in rats and monkeys.

Special Toxicology Studies

Study title/Study number: 4-Week impurity qualification oral gavage toxicity and toxicokinetic study with ABL001 in rats/1870206

Key findings

To qualify impurities, rats were treated with asciminib (ABL001) or impurity-spiked ABL001 at oral doses of 50 mg/kg/day and 200 mg/kg/day for 28 days. The toxicity and toxicokinetic profiles were comparable for these two test articles. Thus, the impurities did not introduce additional toxicities, and the impurities were qualified up (b) (4)% and (b) (4)% for (b) (4) and (b) (4), respectively.

GLP compliance: yes (starting date: March 25, 2019)

Methods	
Drug	ABL001 (asciminib), CoA Batch no. 1010009610, 100% drug content; pure API (salt factor: (b) (4)) TOX1/ABL001, CoA Batch no. 18/1, 99.2% drug content, impurity-spiked batch (with drug impurity at (b) (4)%) 99.2% ABL001 HCl salt + 2 impurities ((b) (4))
Dose and frequency of dosing	0 (vehicle), 50 or 200 mg (base)/kg/day, once daily for 28 days Dose selection: based on Study #1270619, oral ABL001 up to 600 mg/kg/day was tolerated in the 4-week study.
Route of administration	Oral gavage (10 mL/kg)
Formulation/Vehicle	Oral suspension: (b) (4) aqueous solution containing (b) (4)
Species/strain	Rat/Wistar Han
Number/Sex/Group	Main study: 10/sex/group (Control, LD and HD) Group 1: control, Group 2, 4: ABL001 50 and 200 mg/kg/day; Groups 3 and 5: TOX1/ABL001 50 and 200 mg/kg/day

5.5.2. Genetic Toxicology

The Applicant's Position:

Asciminib was evaluated for mutagenic potential in two reverse mutation assays (non-GLP and GLP), and for clastogenic/aneugenic potential in two in vitro micronucleus test (non-GLP and GLP) and a rat micronucleus assay (GLP). The in vitro mutagenicity studies were clearly negative and did not reveal any evidence for a genotoxic potential of asciminib up to either clearly cytotoxic concentrations (mammalian cell tests) or the maximum recommended concentration (5000 μg/plate: AMES test). In vivo, at Week 1 and after 4 weeks of oral treatment, asciminib was not found to be clastogenic or aneugenic in the peripheral blood micronucleus test in Crl: WI (Han) rats up to 600 mg/kg/day (total daily dose). In conclusion, asciminib did not show mutagenic, clastogenic or aneugenic potential in in vitro and in vivo genotoxicity studies.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. Additional details regarding the genetic toxicology studies are provided in the review below.

In vitro Reverse Mutation Assay in Bacterial Cells (Ames)
Study title/number: Reverse mutation in five histidine-requiring strains of Salmonella typhimurium/1270618 (GLP compliant)

Key findings:

- ABL001 at concentrations up to 5000 μg/plate did not increase the number of variant colonies in any of the test strains with or without S9 activation.

To test for mutagenicity, five histidine-requiring strains (TA98, TA100, TA1535, TA97a, and TA102) were incubated with ABL001 in the presence and absence of metabolic activation (rat live S9 fraction), and the resultant number of variant colonies were determined. Appropriate conventionally used positive controls or the negative control (DMSO) were used in the study. Evidence of toxicity and precipitation was observed at ≥ 158.1 and/or 500 μg/plate and 5000 μg/plate, respectively, in all strains in the absence and presence of S9.

In vitro Assays in Mammalian Cells
In vitro micronucleus test
Study title/number: Micronucleus test in vitro using TK6 cells/1214013 (non-GLP)

Key findings:

- ABL001 (CME911) did not induce increased numbers of cells containing micronuclei after 20-hour treatment without S9 activation (-S9), or after 3-hour treatment with or without S9 activation (+/- S9).

The test was to determine the clastogenic and/or aneugenic potential in the micronucleus test *in vitro* with TK6 cells with/without S9-metabolic activation.

Treatment time	Metabolic activation	Sampling time	Positive control
3 hours	+/- S9	24 hours after treatment	Cyclophosphamide (+S9) EMS (-S9)
20 hours	-S9	48 hours after treatment	Ethyl-methane sulphonate (EMS)

Criteria for positive effects: ≥ 2.5% and showed at least a 2.5-fold increase over the control; or < 2.5% and showed at least a 4-fold over the control

Study title/study number: In vitro human lymphocyte micronucleus assay/1670377 (GLP compliance)

Key findings:

- ABL001 did not induce micronuclei in cultured human peripheral blood lymphocytes with or without S9 activation.

Human lymphocyte cells were prepared from the pooled blood of two female donors. Lymphocytes were mitogen stimulated by phytohemagglutinin (PHA), then the following treatments were employed 48 hours later.

Treatment time	Metabolic activation	ABL001 concentration (μg/mL)	Sampling time	Positive control
3+21 hours	+/- S9	10, 40, 70 (-S9) 10, 40, 75 (+S9)	24 hours after treatment	MMC (-S9) CPA (+S9)
24+24 hours	-S9	5, 30, 50	48 hours after treatment	VIN

MMC:=mitomycin C; CPA =cyclophosphamide; VIN=vinblastine; vehicle (negative) control

In vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/study number: 4-Week Oral Gavage Toxicity and Toxicokinetic Study with ABL001 in Rats with a 4-Week Recovery Phase and Micronucleus Assessment/1270619-01 (GLP compliant)
The in vivo micronucleus assay was incorporated into the 4-week toxicology study in rats.

Key findings:

- Orally administered ABL001 at ≥ 200 mg/kg/day induced increases in the mean number of micronuleated reticulocytes, with associated increased reticulocytes, in comparison to the control in Week 4. Such results may be secondary to increased bone marrow proliferation because of ABL001-induced red cell mass reduction and a compensative increase in reticulocytes.
- All individual animal and group values were within the range of the laboratory's historical control data. Thus, the in vivo micronucleus assessment for ABL001 was negative.

Test article:
ABL001: supplied as a (b) (4) composed of a target of 25% active drug, (b) (4) as a suspension in 1x phosphate buffered saline.

Methods
Rats were administered ABL001 via oral gavage at 0 (vehicle), 50, 200 or 600 mg/kg (n=10/sex/group; dosing volume 12 mL/kg) once daily for 29 days. Following the treatment, a separate group of rats of control and 600 mg/kg/day were observed continuously for a 28-day recovery period (n=6/sex/group).

Micronucleus assay
Blood for the micronucleus analysis was collected via a jugular vein on Days 4 (all animals) and 30 (animals designated for terminal sacrifice; i.e., Week 1 and Week 4). The frequency of micronucleated reticulocyte (MN-RET) formation in the peripheral blood reticulocytes, a consequence of chromosome break or adverse effects on the function of the spindle apparatus due to ABL001 treatment, was assessed via flow cytometric analysis.

Results:
Micronucleus assessment
A statistically significant dose-dependent increase in the percentages of MN-RET was observed at Week 4.

Table 8: Summary of Micronucleated Reticulocytes (In Vivo Micronucleus Formation Study)

Sex	Males				Females			
Dose*	Control	50	200	600	Control	50	200	600
N	6	6	6	6	6	6	6	6
Week 1								
MN-RET %**	0.05±0.02	0.06±0.01	0.05±0.02	0.05±0.03	0.04±0.02	0.04±0.02	0.05±0.02	0.05±0.02
RET %**	2.4±0.4	1.8±0.3	1.7±0.4	2.0±0.4	3.6±0.5	3.4±0.2	3.6±0.9	3.5±0.4
Week 4								
MN-RET %**	0.06±0.01	0.06±0.03	0.11±0.05	0.11±0.02	0.06±0.03	0.04±0.02	0.09±0.03	0.13±0.03
RET %**	2.2±0.3	3.1±0.4	5.4±0.7	7.3±1.1	2.4±0.6	3.0±0.4	5.3±1.0	10.7±3.4

Approx 20000 cells/animal were analyzed.
*Dose: mg/kg/day
**frequencies are calculated as follows:
Frequency MN-RET: number of MN-RET x 100 / number of RET
Frequency RET: number of RET x 100 / number of (RET+NCE)
RET: reticulocytes, MN-RET: micronucleated reticulocytes

Corresponding with significant reductions in red blood cell mass (RBC, HGB and Hct) at the end of the 4-week repeat dose treatment phase, a compensative increase in reticulocyte count (RET) was observed at ≥ 200 mg/kg/day, indicating a regenerative anemic effect of ABL001. Increases in the absolute number and percentage of reticulocytes, a marker of cell proliferation in bone marrow, were dose-dependent and statistically significant compared to the control. Increased bone marrow proliferation is associated with increased frequencies of micronucleated reticulocytes (MN-RET).[10] According to the Applicant, all individual animal and group values were within the range of the laboratory's historical control data. The table below is the summary of the historical control data for the test facility.

Table 9: Historical micronucleus assessment control data (peripheral blood)

	Micronucleated reticulocytes % (MN-RET %)		Reticulocytes % (RET %)	
	Males	Females	Males	Females
N	54	56	54	56
Minimum	0.04	0.03	1.1	0.8
Maximum	0.28	0.38	6.4	7.5

(Facility data: 2010-2013; the Study was reported in 2013; data in the table is based on information provided by the Applicant in response to the FDA's request on August 27, 2021).

In Week 1, both MN-RET % and RET % were within in the range of historical control up to 600 mg/kg/day. Despite the values of RET % in male and female rats being above the historical control, the values of MN-RET % were within the range at 600 mg/kg/day in Week 4.

Genotoxicity Assessment for Impurities

Key finding:
No outstanding issues.

Seventeen drug substance impurities were identified with potential genotoxic risks. These impurities were assessed via the bacterial reverse mutation assay (Ames test). Among them, 11 impurities were determined negative for mutagenicity under the condition of the study (data not shown). The following is the summary of the Ames tests of the 6 impurities determined to be positive.

Ames tests:

- Study title: Bacterial reverse mutation assay (study date: January-April, 2016; #1912570: November 1, 2019)
- Compliance status: According to the study report, these studies were non-regulatory

[10] Tweats et al., Mutation Research 627: 78-91, 2007.

studies for which a claim of GLP compliance would not be made; however, the laboratory procedures were conducted in accordance with the current GLP-requirements of the UK MHRA and OECD.

Methods:
Strains of *Salmonella typhimurium* used: TA98, TA100, TA1535, TA97a and TA102
With or without S9 metabolic activation
Vehicle and negative control: DMSO
Positive control: conventionally used positive controls

Results:

Table 10: Summary of Mutagenic Impurities

Study #	Impurity	Mutagenic findings (Positive)
#1512606	(b) (4)	
#1212610		
#1512611		
#1512605		
#1612526-01 Amendment no.1		
#1512516		
#1912570		

The concentrations used in the tests: (b) (4) µg/plate
Based on the chemical structure, the last two impurities in the table are the same, (b) (4)

All the studies were valid.

The Applicant indicated that these compounds consist of reagent, synthesis intermediate and potential by-product impurities of starting materials or intermediates of the drug substance. The Applicant concluded that the overall control strategy, including limits and purge ratios, demonstrates that the impurities are completely removed to levels significantly below the threshold of toxicological concern (TTC) in the drug substance.

5.5.3. Carcinogenicity

The Applicant's Position:
Carcinogenicity studies were not conducted.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:
Fertility and early embryonic development: In the rat fertility study there was no evidence of effects on reproductive function (mean day to mating, mating and fertility indices) at any dose. There was evidence of a slight effect on male sperm motility and/or sperm count in individual animals and an embryo-lethal effect at 200 mg/kg/day. Based on these results, the no-observed-adverse-effect level (NOAEL) for paternal and maternal toxicity was considered 200 mg/kg /day and the no-observed-effect level (NOEL) for reproductive function and early embryonic development was considered to be 50 mg/kg/day. Although no toxicokinetic assessment were included in the fertility study in rats, based upon the exposure achieved in the 26-week rat toxicity study the lowest AUC exposure in males at 200 mg/kg was 203,000 ng*hr/mL. Exposures were 19-fold, 13-fold, or 2-fold higher than those achieved in patients at the dose of 40 mg BID or 80 mg QD or 200 mg BID, respectively.

Embryo-Fetal Development: In embryofetal development studies fetal malformations (cardiac malformations) and increased visceral and skeletal variants were observed in rats and increased incidence of resorptions indicative of embryo-fetal mortality and a low incidence of cardiac malformations indicative of dysmorphogenesis were observed in rabbits. No effects on reproductive function (mean day to mating, mating and fertility indices) in the rat fertility study, but a slight reduction in male sperm motility and/or sperm count in individual animals, and embryo lethality was noted at 200 mg/kg/day. Although no toxicokinetic, assessments were included in the fertility study.

Asciminib was embryotoxic, fetotoxic and teratogenic at 150 mg/kg/day and 50 mg/kg/day in rats and rabbits, respectively. The maternal systemic exposure (AUC) at these dose levels in these animal models were:

- 15- or 4-fold higher, respectively than those achieved in patients at the dose of 40 mg BID
- 10- or 3-fold higher, respectively than those achieved in patients at the dose of 80 mg QD
- 2-fold or below, respectively than those achieved in patients at the dose of 200 mg BID

Pre- and postnatal development: A pre- and postnatal development study has not been performed and is not considered necessary to support the proposed indication.

The FDA's Assessment:
Studies in this section were reviewed by Michael Manning, Ph.D.

In general, the FDA agrees with the Applicant's Position. The FDA's review of the fertility and early embryonic development (FEED) study in rats and embryo-fetal development (EFD) studies in rats and rabbits is provided below.
Decreased mean spermatozoa count and percent motility were observed in the FEED study; however, there were no correlating adverse effects on mating and fertility indices or conception rates.

In the EFD studies there were findings of embryo-fetal abnormalities and alterations to growth in rats and embryo-fetal mortality and abnormalities in rabbits at doses that did not cause maternal toxicities.

Asciminib should be considered a reproductive and developmental toxicant.

Fertility and Early Embryonic Development
An oral (gavage) fertility and early embryonic development study in the rat / study number 1570166

Key study findings

- No toxicologically significant maternal or paternal effects were observed.
- Decreased mean spermatozoa count and percent motility were observed at 200 mg/kg/day, but there were no correlating effects on mating and fertility indices or conception rates.
- A decreased mean number of live embryos was observed at 200 mg/kg/day and was attributed to a lower number of implantations and an increased number of early resorptions.

GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 10, 50, or 200 mg/kg/day Males: dosed once daily for at least 28 days prior to mating, during the 2-week mating period, and until terminal necropsy (Days 63-67) Females: dosed once daily for the 2-week premating period, during the 2-week mating

	period, and through presumed gestation day (GD) 6
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) aqueous solution
Species/Strain:	Rat/Crl:WI (Han)
Number/Sex/Group:	24/sex/group
Satellite groups:	None (TK was not assessed)
Study design:	Males were treated with vehicle or test article once daily for 28 days prior to mating, during the mating period, and continuing through the day prior to sacrifice. Dosing started on Day 1 and ended on Days 62-66. Females were treated with vehicle or test article once daily for 14 days prior to mating, during the mating period (maximum duration of 14 days), and through presumed GD 6. Cesarean section was performed on GD 13. Unmated females were sacrificed at least 8 days after completion of the mating period.
Parameters and endpoints evaluated:	Males and females: clinical signs (cageside and detailed), body weights, food consumption, mating index, copulatory interval, fertility index, and necropsy Males: sperm analysis Females: estrous cycle determination, corpora lutea, viable embryos, resorptions, implantations, and % pre- and % post-implantation loss
Deviation from study protocol affecting interpretation of results:	No

Observations and results

Parameters	Major findings
Mortality	Males and females: there were no test article-related mortalities

<table>
<tr><td></td><td>One female (200 mg/kg/day) was sacrificed in poor and deteriorating condition after the fourth dose; this premature sacrifice was attributed to gavage error.</td></tr>
<tr><td>Clinical signs</td><td>Non-adverse salivation (wet fur on lower jaw) in males (≥ 50 mg/kg/day) and females (200 mg/kg/day)</td></tr>
<tr><td>Body weights</td><td>Males: decreased mean percent body weight gains (study Days 1-25) at 200 mg/kg/day (↓4%)

Females: unremarkable</td></tr>
<tr><td>Food consumption</td><td>Males: decreased mean food consumption (premating Days 1-28) at 50 mg/kg/day (↓3%) and 200 mg/kg/day (↓7%); decreased food consumption correlated with decreased percent body weight gains at 200 mg/kg/day.

Females: decreased mean food consumption (premating Days 1-14) at 200 mg/kg/day (↓9%); there were no correlating effects on body weight.</td></tr>
<tr><td>Estrous cycle, mating, and fertility indices</td><td>Males and females: unremarkable

Estrous cycle data from rats<table><tr><th rowspan="2">Endpoint</th><th colspan="4">Dose level (mg/kg/day)</th></tr><tr><th>0</th><th>10</th><th>50</th><th>200</th></tr><tr><td>Number of animals examined</td><td>24</td><td>24</td><td>24</td><td>23</td></tr><tr><td>Number of days in estrus</td><td>4.3</td><td>3.9</td><td>4.3</td><td>4.0</td></tr><tr><td>Number of cycles seen*</td><td>3.3</td><td>3.3</td><td>3.4</td><td>3.3</td></tr><tr><td>Average cycle length of observed cycles (days)</td><td>3.85</td><td>3.90</td><td>3.88</td><td>3.91</td></tr></table>* Includes actual cycles seen in estrous and the unseen cycles determined

Mating and fertility indices in rats<table><tr><th rowspan="2">Endpoint</th><th colspan="4">Dose level (mg/kg/day)</th></tr><tr><th>0</th><th>10</th><th>50</th><th>200</th></tr><tr><td>Females paired with males</td><td>24</td><td>24</td><td>24</td><td>23</td></tr><tr><td>Total number mated</td><td>24</td><td>23</td><td>24</td><td>22</td></tr><tr><td>Mean days to mating</td><td>2.0</td><td>2.3</td><td>2.0</td><td>2.3</td></tr><tr><td>Male mating index (%)</td><td>100.0</td><td>95.8</td><td>100.0</td><td>95.7</td></tr><tr><td>Female fertility index (%)</td><td>100.0</td><td>95.8</td><td>100.0</td><td>95.7</td></tr><tr><td>Conception rate (%)</td><td>100.0</td><td>100.0</td><td>100.0</td><td>100.0</td></tr></table></td></tr>
<tr><td>Spermatozoa evaluations</td><td>Decreased mean spermatozoa count (↓10%) and percent motility (↓10%) were observed at 200 mg/kg/day; low percent spermatozoa motility correlated with low spermatozoa count in some animals.

Male reproductive assessments in rats<table><tr><th rowspan="2">Endpoint</th><th colspan="4">Dose level (mg/kg/day)</th></tr><tr><th>0</th><th>10</th><th>50</th><th>200</th></tr><tr><td>Number of animals examined</td><td>24</td><td>24</td><td>24</td><td>24</td></tr><tr><td>Cauda epididymis weight (g)</td><td>0.22800</td><td>0.23068</td><td>0.23329</td><td>0.22110</td></tr><tr><td>Spermatozoa count per gram (millions)</td><td>644.6</td><td>681.5</td><td>638.4</td><td>579.7 (-10%)</td></tr><tr><td>Percent motility</td><td>90.3</td><td>87.1</td><td>88.9</td><td>81.4 (-10%)</td></tr></table></td></tr>
</table>

<table>
<tr><td>Caesarean section</td><td>A decreased mean number of live embryos was statistically significant at 200 mg/kg/day and was attributed to a lower number of implantations and an increased number of early resorptions.

Cesarean section data (means) from rats
<table><tr><th rowspan="2">Endpoint</th><th colspan="4">Dose level (mg/kg/day)</th></tr><tr><th>0</th><th>10</th><th>50</th><th>200</th></tr><tr><td>Number of animals examined</td><td>23</td><td>23</td><td>22</td><td>19</td></tr><tr><td>Corpora lutea</td><td>13.2</td><td>13.3</td><td>12.9</td><td>12.9</td></tr><tr><td>Implantations</td><td>12.1</td><td>12.5</td><td>12.0</td><td>11.1</td></tr><tr><td>Live embryos</td><td>11.4</td><td>11.9</td><td>11.4</td><td>9.4* (-17.5%)</td></tr><tr><td>Dead embryos</td><td>0.0</td><td>0.0</td><td>0.0</td><td>0.0</td></tr><tr><td>Early resorptions</td><td>0.7</td><td>0.6</td><td>0.6</td><td>1.7</td></tr><tr><td>Total resorptions</td><td>0.7</td><td>0.6</td><td>0.6</td><td>1.7</td></tr><tr><td>Pre-implantation loss (%)</td><td>8.50</td><td>5.93</td><td>7.31</td><td>13.58 (+60%)</td></tr><tr><td>Post-implantation loss (%)</td><td>5.61</td><td>4.90</td><td>5.22</td><td>15.37 (+174%)</td></tr></table>*P≤ 0.05</td></tr>
<tr><td>Necropsy findings</td><td>Males and females: unremarkable</td></tr>
</table>

Embryo-Fetal Development

An oral gavage study of embryo-fetal development in the rat / study number 1470272

Key study findings

- Maternal mortality/moribundity was observed at 600 mg/kg/day, resulting in the premature sacrifice of this group; mortality/moribundity was attributed to findings in the GI tract.
- There were no test article-related ovarian or uterine findings at ≤ 150 mg/kg/day; uterine examinations were not conducted at 600 mg/kg/day.
- Increases in fetal weights were observed at 25 and 150 mg/kg/day, which may be related to increased ossification (i.e., increased rate of development).
- External and visceral fetal malformations (cleft palate, anasarca, and cardiac abnormalities) and variations (in the heart, kidney, and ureter) were observed at 150 mg/kg/day and were considered test article-related. Test article-related skeletal variations were observed primarily at 150 mg/kg/day. Fetal examinations were not conducted at 600 mg/kg/day.
- Embryo-fetal toxicities were observed at doses ≤ 150 mg/kg/day that did not cause maternal toxicities.

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 25, 150, or 600 mg/kg/day

	Once daily from presumed GD 6 to 17
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) aqueous solution
Species/Strain:	Rat/Crl:WI (Han)
Number/Sex/Group:	24/females/group
Satellite groups:	TK: 3 control females and 5 females/treatment group
Study design:	24 females/group were dosed once daily from presumed GD 6 to 17 and euthanized on GD 21
Parameters and endpoints evaluated:	Females: clinical signs (cageside and detailed), body weight, food consumption, necropsy, gravid uterine and placental weights, and TK Fetuses: fetal weights, external, visceral, and skeletal examinations, and TK
Deviation from study protocol affecting interpretation of results:	No

Observations and results

Parameters	Major findings
Mortality	Five main study rats and three TK rats (600 mg/kg/day) were found dead or sacrificed in poor and deteriorating condition between GD 9-12. Clinical signs included decreased activity, uncoordinated, decreased muscle tone, hunched posture, yellow/brown fur staining, soft/liquid feces, abnormal respiratory sounds, dehydration, piloerection, ptosis, weakness, and/or cold to touch. Body weight losses and reduced food intake were noted. Moribundity in select animals was attributed to digestive tract findings (watery or gelatinous content in one or more segments); test article-related macroscopic findings in the stomach included depressed or raised foci, thickening, firm content, and/or dilatation). Dosing at 600 mg/kg/day (main study and TK animals) was terminated on GD 7 and all remaining animals were sacrificed by GD 12.
Clinical signs	Clinical signs observed at 600 mg/kg/day are described above. There were no test article-related clinical signs at ≤ 150 mg/kg/day.
Body weights	A statistically significant decrease in mean body weight gain (gravid) was observed at 600 mg/kg/day compared to controls. Increased mean body weight gain (gravid) was observed between GD 15-18 at 150 mg/kg/day, and may be related to the higher mean fetal weights. The corrected body weight gains were comparable to the control group. **Mean maternal body weight gain; gravid (g)**

Study interval (GD)	Dose level (mg/kg/day)			
	0	25	150	600
0-3	15.5	14.9	13.9	15.2
3-6	13.8	12.5	14.3	11.7
6-9	8.7	12.2	9.5	-9.1***
9-12	15.3	12.8	14.6	-10.0**
12-15	12.3	14.3	12.6	N/A
15-18	29.4	29.3	33.9*	N/A
18-21	31.4	29.4	33.6	N/A

*P≤ 0.05; *P≤ 0.01; ***P≤ 0.001
N/A: not available due to unscheduled sacrifices

Food consumption

A marked reduction in mean food consumption (↓57-↓82%) was observed between GD 6-12 at 600 mg/kg/day compared to controls. Decreases in food consumption correlated with decreases in body weight gain.

Necropsy findings

Unremarkable

Cesarean section uterine data

Uterine examination data

Endpoints		Dose level (mg/kg/day)			
		0	25	150	600^
# of females mated		24	24	24	24
# of pregnant females		23	23	21	22
Pregnancy rate (%)		95.8	95.8	87.5	91.7
Gravid uterine weight (g)		78.0	79.0	86.3	N/A
Corpora lutea		12.0	12.2	12.7	N/A
Implantations		11.5	11.3	11.9	N/A
Pre-implantation loss (%)		4.73	7.33	6.29	N/A
Post-implantation loss (%)		4.48	7.78	7.08	N/A
Sex ratio (% males)		50.00	50.75	43.33	N/A
Fetuses	Live	11.0	10.4	11.0	N/A
	Dead	0.0	0.0	0.0	N/A
Resorptions	Early	0.5	0.9	0.8	N/A
	Late	0.0	0.0	0.0	N/A
	Total	0.5	0.9	0.8	N/A

^ Complete uterine examinations were not conducted due to the early termination of the group

Necropsy findings

Offspring

Increased mean fetal weights were observed at ≥ 25 mg/kg/day and correlated with increased maternal body weight gain.

External observations, including malformations (cleft palate), were observed at 150 mg/kg/day.

Test article-related visceral variations and malformations were observed in the heart and kidney (urinary tract) at 150 mg/kg/day.

Significant reductions in the incidence of incomplete ossification of several bones were observed, primarily at 150 mg/kg/day. These findings were considered test article-related and could have been associated with an increased rate of ossification (related to the increased fetal weights).

Mean fetal weights (g)

	Dose level (mg/kg/day)		
	0	25	150
Males	5.392	5.733** (+6 3%)	5.814*** (+7.8%)

Females	5.148	5.460** (+6.0%)	5.536*** (+7.5%)
Total	5.275	5.598** (+6.1%)	5.663*** (+7.4%)

**P≤ 0.01; ***P≤ 0.001; fetal examinations were not conducted at 600 mg/kg/day due to the early termination of the group

Select fetal external observations

Observations	Dose level (mg/kg/day)		
	0	25	150
Number of litters examined	23	23	21
Number of external examinations	252	240	232
Gross exam			
Subcutaneous edema over entire body (anasarca)	0/0	0/0	1/1
Face			
Cleft palate	0/0	0/0	2/2

Litter incidence/fetal incidence; fetal examinations were not conducted at 600 mg/kg/day due to the early termination of the group

Select fetal visceral observations

Observations	Dose level (mg/kg/day)		
	0	25	150
Number of litters examined	23	23	21
Number of visceral examinations	125	120	117
Heart			
Aortic arch narrowed (stenosis)	0/0	0/0	1/1
Pericardium fluid filled	0/0	0/0	1/1
Heart misshapened (cardiomegaly)	0/0	0/0	1/1
Innominate artery absent	0/0	0/0	4*/4
Kidney			
Renal papilla(e) small	0/0	0/0	5*/5*
Ureter			
Ureter(s) dilated (megaureter)	0/0	0/0	8**/16***

Litter incidence/fetal incidence; *P≤ 0.05; **P≤ 0.01; ***P≤ 0.001; fetal examinations were not conducted at 600 mg/kg/day due to the early termination of the group

Select fetal skeletal observations

Observations	Dose level (mg/kg/day)		
	0	25	150
Number of litters examined	23	23	21
Number of skeletal examinations	127	120	116
Skull			
Parietal bone(s) incomplete ossification	11/20	9/14	3*/4**
Interparietal bone incomplete ossification	16/44	13/27*	4**/5***
Hyoid bone incomplete ossification	8/13	1*/1**	1*/1**
Vertebral column			
Extra presacral vertebrae	0/0	0/0	2/2
Ossification center(s) on 1st lumbar or 14th thoracic vertebra	16/37	19/52*	19/59***
Sternebrae			
Sternebrae fused	0/0	0/0	16***/48***
Sternebrae 5 & 6 (unossified/incomplete/semibipartite/ Bipartite)	2/2	6/7	15***/21***
Ribs			
Rudimentary 14th rib with contralateral ossification center	3/3	4/4	2/2

	Rudimentary 14th rib(s)	13/25	13/23	6/9**
	Extra 14th rib with contralateral rudimentary rib	3/3	1/1	0/0
	Ossification center(s) on 7th cervical vertebra	3/3	2/2	1/1
	Wavy rib(s)	3/4	1/1	0/0

Litter incidence/fetal incidence; *P≤ 0.05; **P≤ 0.01; ***P≤ 0.001; fetal examinations were not conducted at 600 mg/kg/day due to the early termination of the group

TK

Mean TK parameters on GD 6/16^

Dose level (mg/kg/day)	$AUC_{0\text{-}24hr}$ (ng*hr/mL)	C_{max} (ng/mL)	Fetal exposure (ng/mL)
25	14500	1890	194
150	161000	13200	944
600	593000	32100	N/A

^ TK for 600 mg/kg/day on GD 6 , TK for ≤ 150 mg/kg/day on GD 16

An oral gavage study of embryo-fetal development / study number 1470271 (Rabbit study)

Key study findings

- Maternal moribundity was observed at 300 mg/kg/day, resulting in the premature sacrifice of this group. There were test-article related findings in the GI tract, but the relationship of these findings to the moribundity is uncertain.
- At 50 mg/kg/day, there were test article-related ovarian and uterine findings including increases in early resorptions and post-implantation loss and decreases in the number of live fetuses. At 300 mg/kg/day, an increased number of complete resorptions was observed, but complete uterine examinations were not performed. There were no drug-related ovarian or uterine findings at 15 mg/kg/day.
- There were visceral fetal variations and malformations (cardiac abnormalities) at 50 mg/kg/day that were test article-related. There were no fetal findings at 15 mg/kg/day. Fetal examinations were not performed at 300 mg/kg/day.
- Embryo-fetal toxicities were observed at doses that did not cause maternal toxicities.

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 15, 50, or 300 mg/kg/day
Once daily from presumed GD 7 to 20

Route of administration: Oral gavage

Formulation/Vehicle: (b) (4) aqueous solution

Species/Strain: Rabbit/Hra[NZW]SPF

Number/Sex/Group: 20/females/group

Satellite groups:	TK: 3 control females and 5 females/treatment group
Study design:	20 females/group were dosed once daily from presumed GD 7 to 20 and euthanized on GD 29
Parameters and endpoints evaluated:	Females: clinical signs (cageside and detailed), body weight, food consumption, necropsy, gravid uterine and placental weights, and TK Fetuses: fetal weights, external, visceral, and skeletal examinations, and TK
Deviation from study protocol affecting interpretation of results:	No

Observations and results

Parameters	Major findings
Mortality	Six main study rabbits (300 mg/kg/day) were sacrificed in poor and deteriorating condition between GD 13-14. Clinical signs in the early decedents included marked reduction in food intake, body weight loss, dehydration, prominent backbone/thinness, decreased/absent feces, vomitus, decreased activity, and/or cold to touch. Dosing at 300 mg/kg/day was terminated on GD 15 and all remaining animals were sacrificed by GD 18 (main study animals only). At necropsy, test article-related macroscopic findings included dark or depressed foci, dilatation and/or thickness of the stomach, watery/mucoid contents in the cecum and colon, thickness of the colon, and enlargement of the spleen.
Clinical signs	Clinical signs observed at 300 mg/kg/day are described above. A higher incidence of decreased fecal output was observed at 50 mg/kg/day, which may have been test article-related.
Body weights	A statistically significant decrease in mean body weight gain was observed at 300 mg/kg/day compared to controls. **Mean maternal body weight gain (kg)** Study interval (GD) / Dose level (mg/kg/day): 0 / 15 / 50 / 300 5-7: 0.04 / 0.07 / 0.02 / 0.05 7-10: 0.06 / 0.04 / 0.04 / -0.11*** 10-14: 0.08 / 0.11 / 0.09 / 0.04 14-17: 0.05 / 0.06 / 0.07 / 0.00 17-21: 0.09 / 0.10 / 0.05 / N/A ***P≤ 0.001 N/A: not available due to unscheduled sacrifices
Food consumption	A marked reduction in food consumption (↓19-↓42%) was observed between GD 7-17 at 300 mg/kg/day compared to controls. Decreases in food consumption correlated with decreases in body weight gain.
Necropsy findings	Ovarian/uterine examinations at 300 mg/kg/day were performed on GD 13-18 due to the early termination of this group. All but one female was pregnant at 300 mg/kg/day; however, four pregnant females had total resorptions.

Cesarean section uterine data

One female at 50 mg/kg/day had total resorptions. While not statistically significant, at 50 mg/kg/day there were increases in the mean number of early resorptions and post-implantation loss and decreases in the mean number of live fetuses. Lower gravid uterine weight at 50 mg/kg/day was attributed to the lower number of live fetuses. An increase in the sex ratio (% males) at 50 mg/kg/day was observed; the significance of this finding is unknown.

There were no findings at 15 mg/kg/day.

Uterine examination data[&]

Endpoints		Dose level (mg/kg/day)			
		0	15	50	300^
# of females mated		20	20	20	20
# of pregnant females		19	20	20	19
Pregnancy rate (%)		95.0	100.0	100.0	95.0
# with all dead or resorbed fetuses		0	0	1	4
Gravid uterine weight (g)		500.32	532.07	434.65	N/A
Corpora lutea		10.6	10.1	9.8	N/A
Implantations		9.4	9.7	9.0	N/A
Pre-implantation loss (%)		11.54	3.92	6.94	N/A
Post-implantation loss (%)		4.39	3.42	22.61	N/A
Sex ratio (% males)		44.01	48.34	59.41*	N/A
Fetuses	Live	9.0	9.4	7.2	N/A
	Dead	0.1	0.0	0.0	N/A
Resorptions	Early	0.3	0.3	1.8	N/A
	Late	0.1	0.1	0.1	N/A
	Total	0.4	0.4	1.9	N/A

[&] Data includes one female at 50 mg/kg/day that had total resorption; ^ complete uterine examinations were not conducted due to the early termination of the group; *P≤ 0.05

Necropsy findings

Fetal weights: unremarkable

Offspring

External observations, including malformations (eye bulge, depressed/small) were observed at 50 mg/kg/day.

At 50 mg/kg/day visceral variations and malformations were observed in the aorta, aortic arch, great vessels, and heart.

There were no test article-related skeletal variations or malformations.

Mean fetal weights (g)

	Dose level (mg/kg/day)		
	0	15	50
Males	41.058	41.427	41.185
Females	39.932	40.774	40.286
Total	40.484	41.136	41.262

Fetal examinations were not conducted at 300 mg/kg/day due to the early termination of the group

Select fetal external observations

Observations	Dose level (mg/kg/day)		
	0	15	50
Number of litters examined	19	20	19

Number of external examinations	172	187	143
Eye			
Eye bulge, depressed	0/0	0/0	1/1
Eye bulge, small	0/0	0/0	1/1
Limb			
Forelimb, malrotated	1/1	0/0	0/0

Litter incidence/fetal incidence; fetal examinations were not conducted at 300 mg/kg/day due to the early termination of the group

Select fetal visceral observations

Observations	Dose level (mg/kg/day)		
	0	15	50
Number of litters examined	19	20	19
Number of visceral examinations	171	187	143
Aorta			
Aorta, dilated	0/0	0/0	1/1
Aortic arch			
Aortic arch, dilated	0/0	0/0	1/2
Artery			
Artery, supernumerary branch	2/3	4/4	3/4
Great vessels			
Truncus arteriosus, persistent	0/0	0/0	1/1
Heart			
Left A-V valve, absent	0/0	0/0	1/1
Ventricle, small	0/0	0/0	1/1
Ventricular septum, defect	0/0	0/0	1/1
Lung			
Lobe, absent	4/5	6/10	6/12
Pulmonary artery			
Pulmonary artery, atretic	0/0	0/0	1/1
Gallbladder/bile duct			
Gallbladder, absent	0/0	1/1	2/2
Gallbladder, malpositioned	0/0	1/1	0/0
Gallbladder, small	1/1	4/4	2/4
Gonad			
Ovary, cyst	0/0	2/2	0/0
Kidney			
Kidney, malpositioned	1/1	1/1	0/0
Kidney, misshapen	1/1	0/0	0/0
Liver			
Lobe, additional fissure	0/0	0/0	1/1
Lobe, cyst	0/0	0/0	1/1
Lobe, supernumerary (vestigial)	1/1	1/1	5/9
Spleen			
Spleen, small	1/1	0/0	0/0
Spleen, supernumerary	0/0	0/0	1/1
Ureter			
Ureter, retrocaval	6/6	5/9	7/9

Litter incidence/fetal incidence; fetal examinations were not conducted at 300 mg/kg/day due to the early termination of the group

Select fetal skeletal observations

Observations	Dose level (mg/kg/day)		
	0	15	50
Number of litters examined	19	20	19
Number of visceral examinations	171	187	143

		Forelimb				
		Forepaw phalanges, less than expected numb ossified	0/0	0/0	1/1	
		Hindlimb				
		Tarsal bone, incomplete ossification	0/0	0/0	1/1	
		Pelvic girdle				
		Pubis, incomplete ossification	1/1	0/0	0/0	
		Rib				
		Rib, fused	1/1	0/0	0/0	
		Rib, absent	1/1	0/0	0/0	
		Rib, branched	0/0	1/1	0/0	
		Rib, supernumerary articulated	0/0	1/1	0/0	
		Skull				
		Frontal, unossified line	7/10	7/9	10/15	
		Hyoid ala, bent	3/3	5/6	3/3	
		Hyoid ala, misshapen	3/3	2/4	5/11	
		Hyoid body, incomplete ossification	8/16	6/11	10/21	
		Hyoid body, isolated ossification site	0/0	0/0	1/1	
		Hyoid body, unossified	0/0	0/0	1/1	
		Nasal, unossified line	1/1	0/0	0/0	
		Sternebra				
		Sternebra, incomplete ossification	18/50	13/32	15/37	
		Sternebra, misshapen	0/0	1/1	4/4*	
		Sternebra, bipartite ossification	6/7	4/4	5/8	
		Sternebra, fused	0/0	2/3	3/6	
		Sternebra, dumbbell ossification	4/5	1/1	3/4	
		Sternebra, unossified	16/45	7/17*	14/32	
		Sternebra, supernumerary site	5/6	9/11	9/15	
		Supernumerary rib				
		Cervical, full	1/1	1/1	1/1	
		Thoracolumbar, full	15/70	18/86	17/49	
		Thoracolumbar, short	13/19	15/32	11/17	
		Vertebra				
		Caudal vertebra, incomplete ossification	0/0	0/0	2/2	
		Caudal vertebra, misaligned	1/1	0/0	2/2	
		Caudal vertebra, misshapen	0/0	0/0	1/1	
		Cervical centrum, dumbbell ossification	0/0	0/0	1/1	
		Cervical centrum, incomplete ossification	0/0	0/0	1/1	
		Cervical centrum, misaligned	0/0	0/0	1/1	
		Lumbar arch, isolated ossification site	1/1	0/0	1/1	
		Thoracic arch, fused	0/0	1/1	0/0	
		Thoracic centrum, dumbbell ossification	12/15	2/5**	6/8	
		Thoracic centrum, bipartite ossification	1/1	0/0	0/0	
		Thoracic centrum, unossified	1/1	0/0	0/0	
		Thoracic centrum, incomplete ossification	0/0	2/2	0/0	
		Thoracic centrum, misaligned	0/0	1/1	0/0	
		Thoracic centrum, misshapen	0/0	1/1	0/0	

<table>
<tr><td></td><td>Litter incidence/fetal incidence; *P≤ 0.05; **P≤ 0.01; fetal examinations were not conducted at 300 mg/kg/day due to the early termination of the group</td></tr>
<tr><td>TK</td><td>Mean TK parameters on GD 19/20^
<table>
<tr><th>Dose level (mg/kg/day)</th><th>$AUC_{0\text{-}24hr}$ (ng*hr/mL)</th><th>C_{max} (ng/mL)</th><th>Fetal exposure (ng/mL)</th></tr>
<tr><td>15</td><td>11300</td><td>2200</td><td>5.30</td></tr>
<tr><td>50</td><td>45900</td><td>6330</td><td>30.6</td></tr>
<tr><td>300</td><td>388000</td><td>28300</td><td>181</td></tr>
</table>
^ Maternal TK on GD 19, fetal TK on GD 20</td></tr>
</table>

5.5.5. Other Toxicology Studies

The Applicant's Position:

Phototoxicity: A phototoxic potential of asciminib was identified in vitro. The in vivo mouse ultra violet-local lymph node assay demonstrated a phototoxic potential at dose ≥ 200 mg/kg/day. At the no-observed-adverse-effect level (NOAEL) of 60 mg/kg/day, the Cmax was 12000 ng/mL, exposure 15- or 6- or 2-fold higher than the Cmax exposure in patients at the dose of 40 mg BID or 80 mg QD or 200 mg BID, respectively.

Pancreatic toxicity: Overall, across all investigative studies that have been performed, the mechanism of pancreas toxicity in dogs has not been elucidated. Although systemic asciminib exposure in rats and monkeys were higher than those achieved in dogs, no effects on the pancreas were observed. There seems to be no obvious difference between rats and dogs when looking at the Cmax pancreas/blood ratio (ratio of 5.3 on day 1 in males treated with asciminib at 30 mg/kg in study and ratio of 5.2 on Day 3 in males treated with asciminib at 60 mg/kg). The metabolism and plasma protein binding in rats, dogs and monkeys is rather similar. Based on protein sequence homology and structural modelling, asciminib is likely to bind similarly to rat, dog, cynomolgus monkey and human ABL1/ABL2.

In conclusion, although the mechanism of pancreas toxicity in dogs has not been elucidated, serum amylase and lipase activities showed to be increased in close association with early histopathological changes.

The FDA's Assessment:

The FDA concurs with the Applicant's assessment that asciminib was potentially phototoxic, based on the in vitro and in vivo phototoxicity studies, and we note that no clear clinical findings of phototoxicity have been reported. The FDA also concurs with the Applicant's summary and discussion regarding pancreatic toxicity. Pancreatic findings described in 4-week toxicology study in dogs are summarized in "General Toxicology".

X	X
Primary Reviewer	Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

Asciminib is an oral inhibitor of ABL/BCR-ABL1 tyrosine kinase. The applicant is seeking indications for the treatment of patients with:

- Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs).
- Ph+ CML in CP harboring the T315I mutation.

The recommended dosage in patients with Ph+ CML in CP previously treated with 2 or more TKIs is 80 mg total daily dose [either 80 mg once daily (QD) or 40 mg twice daily (BID)]. The recommended dosage in Ph+ CML in CP harboring the T315I mutation is 200 mg BID. Asciminib should be taken orally and avoid food for at least 2 hours before and 1 hour after taking asciminib.

For patients with Ph+ CML in CP previously treated with 2 or more TKIs, the evidence of safety and efficacy was supported by a Phase 3, multi-center, active-controlled, open-label randomized study CABL001A2301, demonstrating statistically significant and clinically meaningful improvements in Major Molecule Response (MMR) rate at Week 24 (primary endpoint) of asciminib against bosutinib.

The second indication of treatment of patients with Ph+ CML in CP harboring the T315I mutation was supported by the efficacy and safety data from an expansion cohort of the first-in-human Study CABL001X2101 in patients with Ph+ CML in CP harboring the T315I mutation.

The clinical pharmacology section of the NDA is supported by single and multiple doses pharmacokinetics (PK) characterization, human mass balance study, relative bioavailability studies, food effect study, intrinsic factors/special populations (hepatic and renal impairment, UGT2B7 and UGT2B17 genotype), drug interaction studies (asciminib as victim and as perpetrator), PBPK simulation, QT/QTc assessment, population PK (PopPK) and exposure-response (efficacy and safety) analyses.

The clinical pharmacology review focused on assessments of the dose selection, dose recommendations in patients with organ dysfunctions, and drug-drug interaction (DDI) potential of asciminib as a victim and as a perpetrator, and on exploratory analysis of BCR-ABL1 mutations other than T315I and response to asciminib.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 215358 and recommends approval from a clinical pharmacology perspective. The key review issues with the specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness come from: • A phase 3 Study CABL001A2301, which demonstrated statistically significant and clinically meaningful improvements in MMR rate at week 24 for the asciminib arm at the recommended dosage regimen of 40 mg BID over the bosutinib arm in patients with Ph+ CML in CP previously treated with 2 or more TKIs. • The efficacy and safety data from an expansion cohort of the first-in-human (FIH) Phase 1/2 Study CABL001X2101 in patients with Ph+ CML in CP harboring the T315I mutation. Refer to the FDA's assessment in Section 8.1.2. Study Results for details on the statistical analyses for efficacy.
General dosing instructions	For patients with Ph+ CML-CP previously treated with 2 or more TKIs, the proposed dosage regimens of 40 mg BID or 80 mg QD are acceptable per the following rationales: • MTD was not reached for doses up to 280 mg BID in the FIH trial CABL001X2101. • At the 40 mg BID dosage, PopPK predictions indicated that approximately 90% of the patients maintained $C_{min,ss}$ (302 ng/mL) above the efficacy threshold (121 ng/mL) established in the preclinical studies. • Results of the Phase III Study CABL001A2301 demonstrated statistically significant and clinically meaningful improvements in MMR rate at week 24 of asciminib 40 mg BID as compared to bosutinib 500 mg QD. • The predicted MMR rate at Week 24 is comparable between 40 mg BID (Median: 26.3%, 95% CI [20.8%, 31.4%]) and 80 mg QD (Median: 25.8%, 95% CI [20.3%, 31.8%]). • A positive exposure-efficacy relationship was observed over the asciminib dosages of 10 mg to 200 mg BID. • Over the asciminib dosages of 10 mg to 280 mg BID, a higher exposure was associated with slightly higher incidence of certain adverse reactions.

	• The positive E-R for efficacy and relatively flat E-R for safety indicate that a higher dose compared to the proposed dosage regimens might achieve higher MMR rate without increasing toxicity in the target patient population. However, there is limited data currently at higher doses to support a robust benefit/risk assessment. For patients with Ph+ CML-CP harboring the T315I mutation, the proposed dosage regimen of 200 mg BID is acceptable: • Based on preclinical in vivo and in vitro models of CML, higher exposures (4- to 13-fold) are required to drive BCR-ABL1 IS >1% response in patients with CML-CP harboring T315I mutation. • At the dose of 200 mg BID, $C_{min,ss}$ was approximately 2-fold above the IC_{50} value of the T315I mutant cells (murine hematopoietic Ba/F3 cells expressing the BCR-ABL1 T315I mutant). • The efficacy and safety data from Study CABL001X2101 demonstrated an MMR rate at week 24 of 42% (95% CI: 28% to 58%) and an acceptable safety profiles at asciminib 200 mg BID in patients with CML-CP harboring the T315I mutation.
Dosing in patient with organ impairment	• No dose adjustment of asciminib is required for patients with mild, moderate, or severe hepatic impairment (HI) based on the NCI criteria. The asciminib exposure changes in patients with mild ($AUC_{0\text{-}inf}$ ↑10%, C_{max} ↑24%), moderate, or severe HI ($AUC_{0\text{-}inf}$ ↑33%, C_{max} ↑4%) are not considered clinically meaningful. • No dose adjustment of asciminib is required for patients with mild, moderate, or severe renal impairment (RI). Asciminib $AUC_{0\text{-}inf}$ and C_{max} increased by 57% and 6%, respectively, in subjects with eGFR between 13 to < 30 mL/min/1.73 $m^2$and not requiring dialysis compared to subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2). The exposure changes in patients with severe RI are not considered clinically meaningful.
Drug-drug interactions	• Concomitant use with a strong CYP3A inhibitor increases asciminib C_{max} and AUC which may increase the risk of adverse reactions at the higher dose. Closely monitor for adverse reactions in patients during concomitant administration of asciminib at 200 mg BID with strong CYP3A4 inhibitors. • Concomitant use with itraconazole oral solution containing hydroxypropyl-β-cyclodextrin decreased asciminib C_{max} and AUC which may reduce asciminib efficacy. Avoid coadministration of asciminib at

	all recommended doses with itraconazole oral solution containing hydroxypropyl-β-cyclodextrin. • No clinically significant differences in the PK of asciminib following a single-dose of 40 mg were observed when co-administered with rabeprazole (acid-reducing agent). The ADAM-PBPK model simulations suggested that changes on gastric pH do not significantly affect asciminib exposure due to its high solubility in bile salts attributed to supersaturation, which override the pH effect. The predicted effect of elevated gastric pH on asciminib PK following a single dose of 200 mg is unlikely to be clinically meaningful. • Concomitant use of asciminib increases the C_{max} and AUC of CYP3A4 substrates, which may increase the risk of adverse reactions of these substrates. Closely monitor for adverse reactions in patients treated with asciminib at 80 mg total daily dose with concomitant use of certain CYP3A4 substrates, where minimal concentration changes may lead to serious adverse reactions. Avoid coadministration of asciminib at 200 mg BID with certain CYP3A4 substrates where minimal concentration changes may lead to serious toxicities. If coadministration is unavoidable, reduce the CYP3A4 substrate dosage as recommended in its prescribing information. • Concomitant use of asciminib increases the C_{max} and AUC of CYP2C9 substrates, which may increase the risk of adverse reactions of these substrates. Avoid coadministration of asciminib at 80 mg total daily dose with certain CYP2C9 substrate where minimal concentration changes may lead to serious toxicities. If concomitant use is unavoidable, reduce the CYP2C9 substrate dosage as recommended in its prescribing information. Avoid coadministration of asciminib at 200 mg twice daily dose with sensitive CYP2C9 substrates and certain CYP2C9 substrate where minimal concentration changes may lead to serious toxicities. If coadministration is unavoidable, consider alternative therapy with non-CYP2C9 substrate. • Concomitant use of asciminib may increases the C_{max} and AUC of P-gp substrates, which may increase the risk of adverse reactions of these substrates. Closely monitor for adverse reactions in patients treated with asciminib at all recommended doses with concomitant use of certain P-gp substrates where minimal concentration changes may lead to serious toxicities.
Labeling	Generally acceptable. The review team has specific content and format change recommendations.

Post-Marketing Requirements and Commitments

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMR	Dosage recommendations when asciminib is co-administered with BCRP substrates	Based on the in vitro study, asciminib is a potential inhibitor of the breast cancer resistance protein (BCRP) (R values ≈16-74) in vivo. The DDI simulations intended to evaluate the effect of asciminib on the PK of a BCRP and OATP1B1/3 substrate (rosuvastatin) are inadequate because the substrate (rosuvastatin) model is inadequate. The validation of this model was considered insufficient because it was conducted with limited clinical DDI datasets with regard to the BCRP/OATP1B1/3 pathways and phenotype studies with regard to the BCRP or OATP1B1 pathway. In addition, the in vitro in vivo extrapolation (IVIVE) for these transporter-mediated pathways has not be established in the model validation. As such, it is not known if asciminib may increase systemic exposure of a BCRP substrate in vivo, which may increase the incidence and severity of adverse reactions. This PMR will assess the effect of asciminib on the PK of a BCRP substrate.	Conduct additional physiologically based pharmacokinetic analyses to assess the effect of asciminib on the pharmacokinetics of a substrate of the transporters breast cancer resistance protein (BCRP) to determine appropriate dosage recommendations when asciminib is administered concomitantly with BCRP substrates. Design and conduct the assessment in accordance with the FDA Guidances for Industry titled “Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions” and/or “Physiologically Based Pharmacokinetic Analyses — Format and Content”.
PMR	Dosage recommendations when asciminib is co-administered with OATP1B1/3 substrates	Based on the in vitro study, asciminib is a potential inhibitor of the organic anion transporting polypeptide (OATP) transporters (R values ≈1.3-1.4 for 200 mg dose) in vivo. The DDI simulations intended to evaluate the effect of	Conduct additional physiologically based pharmacokinetic analyses to assess the effect of asciminib on the pharmacokinetics of a substrate of the organic anion

		asciminib on the PK of a BCRP and OATP1B1/3 substrate (rosuvastatin) are inadequate because the substrate (rosuvastatin) model is inadequate. The validation of this model was considered insufficient because it was conducted with limited clinical DDI datasets with regard to the BCRP/OATP1B1/3 pathways and phenotype studies with regard to the BCRP or OATP1B1 pathway. In addition, the in vitro in vivo extrapolation (IVIVE) for these transporter-mediated pathways has not be established in the model validation. As such, it is not known if asciminib may increase systemic exposure of a OATP1B1/3 substrate in vivo, which may increase the incidence and severity of adverse reactions. This PMR will assess the effect of asciminib on the PK of a OATP1B1/3 substrate.	transporting polypeptide (OATP1B) to determine appropriate dosage recommendations when asciminib is administered concomitantly with OATP1B1/3 substrates. Design and conduct the assessment in accordance with the FDA Guidances for Industry titled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions" and/or "Physiologically Based Pharmacokinetic Analyses — Format and Content".
PMC	Dose recommendation when co-administration of asciminib with strong CYP3A and UGT inducer	Based on in vitro metabolism and mass balance studies, there are multiple elimination pathways of asciminib with potential for saturation. The contribution of each pathways at different asciminib doses has not been well characterized. As a result, there is currently limited data to establish a dose recommendation for patients who concomitantly use a strong CYP3A and UGT inducer at a higher dose (80 or 200 mg) of asciminib since the PK results of clinical drug-drug interaction (DDI) study CABL001A2107 cannot be used for extrapolation. In addition, a lower exposure was associated with a smaller decrease in the time course of BCR-ABL1 and a lower MMR rate at	Conduct a clinical pharmacokinetic study to evaluate the effect of repeat doses of a strong CYP3A and UGT inducer on the single dose (200 mg) pharmacokinetics of asciminib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the study in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-

		Week 24. Thus, a PMC study is needed to determine whether dose adjustment is needed in patients who require concomitant use of strong CYP3A and UGT inducers with asciminib.	Mediated Drug Interactions Guidance for Industry"
PMC	Dosing strategies with concomitant use of asciminib with oral drug products containing hydroxypropyl-β-cyclodextrin.	The PK results from the clinical DDI study CABL001A2107 and in vitro flux assays suggested that there is a potential excipient-drug interaction of oral itraconazole solution containing hydroxypropyl-β-cyclodextrin on the bioavailability of asciminib. This study led to a 40% decrease in asciminib AUC. Other oral medicinal products containing hydroxypropyl-β-cyclodextrin may cause decrease in asciminib AUC to certain extent. Thus, a PMC study is needed to evaluate the effect of different amounts of hydroxypropyl-β-cyclodextrin on the absorption of asciminib and to determine the appropriate dose recommendations for concomitant oral products that contain hydroxypropyl-β-cyclodextrin.	Conduct in vitro studies to evaluate and characterize the effect of different amounts of hydroxypropyl-β-cyclodextrin on the absorption of asciminib. Identify a threshold amount of hydroxypropyl-β-cyclodextrin that may have a clinically meaningful impact on asciminib bioavailability, which may result in a loss of efficacy. Provide appropriate dosing strategies with concomitant use of these oral drug products with asciminib.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The clinical pharmacology of asciminib has been well characterized. The data included in the application consists of basic PK properties of asciminib, physiologically based pharmacokinetic (PBPK) modeling, population PK (PopPK) analyses, and results from clinical pharmacology studies. The results from both in vitro human biomaterial studies and in vivo clinical pharmacology studies (mass balance, drug-drug interaction (DDI), food effect, relative bioavailability) conducted in healthy subjects and patients with CML were integrated to describe the ADME properties of asciminib in humans and assess intrinsic and extrinsic factors which may affect the PK of asciminib. In addition, the outcomes of the exposure-efficacy and

exposure-safety analyses for asciminib support the use of the recommended dose in the target indications.

The FDA's Assessment:

In general, FDA agrees with the Applicant's PopPK and exposure-response analyses for safety and efficacy to support the proposed dosage for the target indications.

However, FDA does not agree that the overall clinical pharmacology of asciminib has been well characterized. Based on available data, there are multiple elimination pathways of asciminib with potential for saturation. The contribution of each elimination pathways at different asciminib doses has not been well characterized. The submitted PBPK model was not adequate to assess the DDI effect of strong CYP3A and UGT inducers on the PK of asciminib. The available data on hydroxypropyl-β-cyclodextrin-asciminib interaction was not sufficient to provide appropriate dosing strategies with concomitant use of all oral drug products containing hydroxypropyl-β-cyclodextrin with asciminib. FDA does not agree with the Applicant's PBPK model to assess the DDI effect of asciminib on the PK of BCRP substrates or OATP1B1/3 substrates because the BCRP/OATP1B1/3 substrate (rosuvastatin) model is inadequate. Refer to Section 19.4.4. Physiologically based Pharmacokinetic Modeling Review for details.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

The recommended total daily dose of asciminib is 80 mg for adult patients with Ph+ CML-CP previously treated with 2 or more TKIs, to be taken orally either as 80 mg QD or 40 mg BID.

The asciminib dose of 40 mg BID in the Study CABL001A2301 was selected based on PK, efficacy, and safety data from the first-in-human Study CABL001X2101. Based on preclinical findings, asciminib 40 mg BID was predicted to achieve efficacious asciminib concentrations over the complete dosing interval and support the targeted exposure.

In human-derived leukemic cells expressing wild-type BCR-ABL1, asciminib inhibited BCR-ABL1-dependent proliferation with an IC50 values in the range of 1-30 nM. In a mouse xenograft model with wild-type BCR-ABL1 KCL-22 cells, an oral dose of asciminib at 7.5 mg/kg BID for 7 days gave 56% tumor regression. This target concentration from the xenograft model is consistent with in vitro efficacy observed in the wild-type KCL-22 cells (growth IC50 of

~3 nM). Based on PopPK predictions, a dose of 40 mg BID would allow to maintain almost all patients (89.8%) above this target at any time (PopPK Cmin estimate at steady state: 302 ng/mL (CV%: 60%) (i.e. 18.3 nM [unbound concentration]).

Based on the Cmin values being above the target concentration of 121 ng/mL (i.e. 7.3 nM [unbound concentration])) a dose of asciminib 80 mg QD (PopPK mean Cmin estimate at steady state: 255 ng/mL (CV%: 73%) (i.e., 15.3 nM [unbound concentration]) is predicted to achieve efficacious asciminib concentrations as observed for asciminib 40 mg BID.

In the first-in-human Study CABL001X2101, patients with CML-CP who had prior treatment with at least 2 prior TKIs, received treatment with increasing doses of oral asciminib monotherapy (10 mg to 200 mg BID and 80 mg to 200 mg QD schedule). The maximum tolerated dose (MTD) for asciminib monotherapy in patients with CML-CP was not achieved in Study CABL001X2101, suggesting a large therapeutic window of asciminib. Based on the available safety, efficacy and PK data at time point of decision an asciminib dose of 40 mg BID was the recommended Phase II dose (RP2D).

Results of the Phase III Study CABL001A2301 established the superior benefit/risk profile of asciminib 40 mg BID as compared to bosutinib 500 mg QD in patients with CML-CP who had prior treatment with at least 2 prior TKIs. Treatment with asciminib 40 mg BID led to almost 2-fold improvement in MMR rate at Week 24 compared to bosutinib (25.5% vs 13.2%; 95% CI: 2.19, 22.30, two-sided p-value: 0.029) in this heavily pre-treated patient population. The CCyR rates at Week 24 and by Week 24 (based on patients who were not in CCyR at baseline) were both 40.8% in the asciminib arm compared to 24.2% in the bosutinib arm.

The exposure-response models in efficacy highlights the existence of a slightly positive exposure-efficacy relationship (over a wide dose range from 20 mg to 400 mg daily). For the same daily dose, comparable efficacy is expected. The predicted MMR rate at Week 24 for asciminib 40 mg BID was 27.6 ± 4.5% and the predicted MMR rate at the same timepoint for 80 mg QD was 24.8 ± 4.2%. The predicted MMR rate at Week 48 for 40 mg BID and 80 mg QD were 32.3% (±4.8) and 30.6% (±4.7), respectively. An exposure-safety relationship analysis indicated a lack of clinically relevant association between all types of safety events tested (i.e., laboratory abnormalities, vital sign abnormalities, fatigue/asthenia (based on AEs), AEs of Grade 3 or higher, AEs leading to dose reductions) and increase in PK metrics.

The clinical results from Study CABL001A2301 and Study CABL001X2101 as well as the extensive exposure-efficacy and exposure-safety analyses, demonstrated comparable benefit-risk ratio of asciminib administered at 80 mg QD and 40 mg BID in patients with CML not harboring the T315I mutation. Overall, the dose of asciminib 80 mg QD is considered favorable and can be used as an alternative, more convenient, patient-centric dose regimen for this patient population (See Section 6.3.2).

The recommended dose 80 mg total daily can be taken either as 80 mg QD or as 40 mg BID. Asciminib administered at 80 mg daily total dose (taken as a QD or BID dose) demonstrated favorable safety profile in the treatment of patients with Ph+ CML-CP previously treated with ≥ 2 TKIs.

Patients with Ph+ CML-CP harboring the T315I mutation

The asciminib dose of 200 mg BID for patients with CML-CP harboring the T315I mutation was selected based upon preclinical findings together with the safety, efficacy, and PK data from Study CABL001X2101.

Based on preclinical in vivo and in vitro models of CML, 4- to 13-fold higher exposures would be required for patients with CML-CP harboring T315I mutation, hence higher doses of asciminib (≥ 160 mg BID) are required to drive BCR-ABL1 IS >1% response in patients with CML-CP harboring the T315I mutation.

In the KCL-22 BCR-ABL1 T315I mutation xenograft model, a 4-fold higher dose (30 mg/kg BID vs. 7.5 mg/kg) was required to achieve a regression of >50% in tumor volume compared to the wild-type KCL-22 xenograft model

In murine hematopoietic Ba/F3 cells expressing the BCR-ABL1 T315I mutant, ~13-fold higher asciminib concentrations were required to obtain the same growth inhibition than in BCR-ABL1 wild-type cells (IC50 value of 7.64 nM for T315I mutant vs 0.61 nM for wild-type).

At 200 mg BID, a geometric mean Cmin at steady state of 2747 ng/mL (16.5 nM unbound concentration) on Cycle 2 Day 1 was achieved, which is ~2-fold above the IC50 of the T315I mutant cells.

Based on preclinical findings, at least 4-times higher doses of asciminib (≥ 160 mg BID) are required to drive BCR-ABL response in patients with CML-CP harboring the T315I mutation compared to subjects not harboring the T315I mutation.

Following the analysis of asciminib single agent dose escalation data from Study CABL001X2101, a dose of 200 mg BID satisfied the adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle. This was selected as recommended dose for CML-CP/-AP patients with T315I mutation expansion cohort.

In Ph+ CML-CP patients harboring the T315I mutation, the recommended dose of asciminib is 200 mg BID. The efficacy data from Study CABL001X2101 showed that asciminib 200 mg BID was efficacious in the patients with CML harboring the T315I mutation, both in patients previously treated with ponatinib and in ponatinib-naive patients, as compared to patients treated with lower dose levels. MMR was achieved by 22/45 (48.9%) patients at any time point. The cumulative MMR rate by Week 24 was 42.2% (95% CI: 27.7, 57.8), and the MMR

rate at Week 24 was 37.8% (95% CI: 23.8, 53.5). At doses <200 mg BID, most patients harboring the T315I mutation did not experience a decrease in %BCR-ABL below -1 log10 value (0.1%), except those who had one prior TKI treatment. Further supported by exposure-response analysis, the benefit of asciminib administered at 200 mg BID in patients with CML-CP harboring the T315I mutation is considered favorable, supporting 200 mg BID as the recommended dose for this patient population.
In addition, asciminib administered at 200 mg BID in Study CABL001X2101 demonstrated favorable safety profile in the treatment of patients with CML-CP harboring the T315I mutation.

The FDA's Assessment:

For patients with Ph+ CML-CP previously treated with 2 or more TKIs, the FDA agrees with the Applicant that the recommended dosages of 40 mg BID or 80 mg QD are acceptable based on the totality of evidence below:

- MTD was not reached for doses up to 280 mg BID in the FIH trial CABL001X2101.
- PopPK predictions indicated that approximately 90% of the patients maintained $C_{min,ss}$ (302 ng/mL) above the efficacy threshold (121 ng/mL) established in the preclinical studies (IC_{90} of pSTAT5 inhibition in KCL-22 mouse xenograft model).
- Results of the Phase III Study CABL001A2301 demonstrated favorable benefit/risk profile of asciminib 40 mg BID as compared to bosutinib 500 mg QD.
- The predicted MMR rate at Week 24 is comparable between 40 mg BID (Median: 26.3%, 95% CI [20.8%, 31.4%]) and 80 mg QD (Median: 25.8, 95% CI [20.3%, 31.8%]).
- A positive exposure-efficacy relationship was observed over the asciminib dosages of 10 mg to 200 mg BID.
- Over the asciminib dosages of 10 mg to 280 mg BID, a higher exposure was associated with slightly higher incidence of some adverse reactions (e.g., Grade ≥3 lipase increase, Grade ≥3 hemoglobin decrease, Grade ≥2 ALT increase, Grade ≥2 AST increase, Grade ≥2 bilirubin increase, and any grade lipase increase).
- The positive E-R for efficacy and relatively flat E-R for safety indicate that a higher dose compared to the proposed dosage regimens might achieve higher MMR rate without increasing toxicity in the target patient population. However, there is limited data currently at higher doses to support a robust benefit/risk assessment.

For patients with Ph+ CML-CP harboring the T315I mutation, the FDA agrees with the Applicant that the recommended dosage of 200 mg BID is acceptable per the following rationales:

- Based on preclinical in vivo and in vitro models of CML, higher exposures (13-fold from the in vitro cell assay and 4-fold in the KCL-22 mouse xenograft model) are required to drive BCR-ABL1 IS >1% response in patients with CML-CP harboring T315I

mutation.
- At 200 mg BID, $C_{min,ss}$ was approximately 2-fold above the IC_{50} value of the T315I mutant cells.
- The efficacy and safety data from Study CABL001X2101 demonstrated an MMR rate at week 24 of 42% (95% CI: 28% to 58%) for asciminib 200 mg BID in patients with CML-CP harboring the T315I mutation.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No therapeutic individualization is needed in the proposed indication based on demographic factors (body weight, age, gender, race), drug-drug interactions with asciminib as a victim or as a perpetrator, or in special populations (hepatic or renal impairment). More information is in Section 6.3.2.

The FDA's Assessment:

The FDA generally agrees with the Applicant that:

- No dose adjustment is required based on sex, age (20 to 88 years), race (Asian [20%], White [70%], Black/African American [4%]), or body weight (42 to 184 kg), since no clinically significant differences in the PK of asciminib were observed based on sex, age, race/ethnicity, or body weight.
- In hepatic impairment (HI) study CABL001A2103, subjects were enrolled with varying degree of hepatic function using the Child-Pugh classification. The results (Table 11) showed that the asciminib AUCinf and C_{max} increased by 22% and 26% in subjects with mild HI and increased by 3% and decreased by 1.7% in subjects with moderate HI. The asciminib $AUC_{0\text{-}inf}$ and C_{max} increased by 66% and 29% in subjects with severe HI. However, these subjects were re-classified using the NCI classification to match the hepatic classification system used in cancer patients. The results (Table 12) showed that the asciminib $AUC_{0\text{-}inf}$ and C_{max} increased by 10% and 24% in subjects with mild HI and increased by 3% and decreased by 1.7% in subjects with moderate HI. The exposure changes in subjects with mild and moderate HI (based on both the Child-Pugh and NCI classifications) are not considered clinically meaningful. The asciminib $AUC_{0\text{-}inf}$ and C_{max} increased by 33% and 4% in subjects with severe HI, which were not considered clinically meaningful based on exposure-response analyses for safety (refer to Section 19.4.3. Exposure-Response Analysis). Thus, FDA agrees that no dose adjustment of asciminib is required for patients with mild, moderate, or severe hepatic impairment based on the NCI criteria.

Table 11: PK parameters in subjects with varying degree of hepatic impairment based on the Child-Pugh classification

PK parameter (unit)	Treatment	Number of subjects	Geo-mean ratio*	90% CI	
				Lower	Upper
AUCinf (ng*hr/mL)	Mild	8	1.22	0.964	1.54
	Moderate	8	1.03	0.813	1.30
	Severe	7	1.66	1.30	2.12
AUClast (ng*hr/mL)	Mild	8	1.21	0.960	1.53
	Moderate	8	1.03	0.812	1.30
	Severe	8	1.55	1.22	1.95
Cmax (ng/mL)	Mild	8	1.26	1.05	1.52
	Moderate	8	0.983	0.819	1.18
	Severe	8	1.29	1.08	1.55

* Compared to subjects with normal hepatic function (n=8)

Table 12: PK parameters in subjects with varying degree of hepatic impairment based on the NCI classification

PK parameter (unit)	Treatment	Number of subjects	Geo-mean Ratio*	90% CI	
				Lower	Upper
AUCinf (ng*hr/mL)	Mild	6	1.1	0.863	1.4
	Moderate	1	1.44[#]	NA	NA
	Severe	6	1.33	1.05	1.7
AUClast (ng*hr/mL)	Mild	6	1.1	0.861	1.4
	Moderate	2	1.12, 1.44[#]	NA	NA
	Severe	6	1.31	1.03	1.67
Cmax (ng/mL)	Mild	6	1.24	1.03	1.49
	Moderate	2	0.85, 1.40[#]	NA	NA
	Severe	6	1.04	0.862	1.25

* Compared to subjects with normal hepatic function (n=18)

[#] Reported as individual values divided by geomean of normal hepatic function group (n=18) for the 2 subjects in the moderate HI group.

- In renal impairment study CABL001A2105, the PK of a single oral dose of asciminib in subjects with severe renal impairment compared to control subjects with normal renal function. Degrees of renal function were determined according to the aGFR, which was derived from the estimated glomerular filtration rate (eGFR) through the conversion [aGFR = eGFR × Body Surface Area (BSA)/1.73]. Reanalysis of PK was conducted using eGFR. The results (Table 13) showed that the asciminib AUC_{inf} and Cmax increased by 57% and 6%, respectively, in subjects with eGFR between 13 to < 30 mL/min/1.73 m^2 and not requiring dialysis compared to subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2). Furthermore, FDA's independent PopPK analysis showed that aGFR

(35 - 232 mL/min) was not a significant covariate on asciminib PK parameters, demonstrating that no significant impact of mild to moderate renal impairment on asciminib PK. The exposure changes in patients with severe RI are not considered clinically meaningful based on exposure-response analyses (refer to Section 19.4.3. Exposure- Response Analysis). Thus, FDA agrees that no dose adjustment of asciminib is required for patients with mild, moderate, or severe renal impairment (RI).

Table 13: PK parameters in subjects with severe renal impairment compared to subjects with normal renal function

PK parameter (unit)	Treatment	Number of subjects	Geo-mean ratio*	90% CI	
				Lower	Upper
AUCinf (ng*hr/mL)	Severe/Normal	7/5	1.57	1.02	2.42
AUClast (ng*hr/mL)	Severe/Normal	7/5	1.50	0.985	2.29
Cmax (ng/mL)	Severe/Normal	7/5	1.06	0.680	1.66

Refer to FDA's assessment in Section 6.3.2.4 regarding drug-drug interactions with asciminib as a victim or as a perpetrator.

6.2.2.3. Outstanding Issues

The Applicant's Position:
None

The FDA's Assessment:
FDA disagrees with Applicant's position that there are no outstanding issues. There are several DDI issues that remain unresolved. Refer to the PMRs/PMCs Table in Section 6.1 Executive Summary for details.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

An overview of the ADME properties, clinical pharmacokinetics, and DDI potential of asciminib is provided below.

Absorption: Asciminib is classified as a BCS Class II compound (low aqueous solubility and high permeability). Food decreases the bioavailability of asciminib. Following low-fat and high-fat meal, AUCinf was decreased by 30% and 62.3%, respectively.

Distribution: Asciminib apparent volume of distribution at steady state was geo-mean (CV%) 89.0 L (6.1%) based on the human ADME study and a combined volume of 111 L (V1 + V2) based on population pharmacokinetic analysis, suggesting distribution into tissues. Asciminib is highly bound to human plasma proteins (97.3%) independent of concentration across a range from 20-50000 ng/mL. In blood, asciminib was mainly distributed to plasma with a low fraction in red blood cells (0.58).

Metabolism: In vivo asciminib is predominantly metabolized by oxidation at the pyrrolidinol ring and direct glucuronidation. No major plasma metabolite was observed (<10% of total drug related AUC). Enzyme phenotyping of asciminib conducted using human liver microsomes and recombinant CYP and UGT enzymes revealed oxidation to be the major pathway of asciminib hepatic metabolic clearance, followed by glucuronidation. The major metabolizing enzymes of asciminib were CYP3A4 (36%), UGT2B7 (13.3%) and UGT2B17 (7.8%). Based on PBPK simulations biliary secretion via BCRP was estimated to contribute to total systemic clearance with about 31.1%.

Excretion: Asciminib is mainly cleared through hepatic metabolism and biliary secretion via BCRP through the fecal pathway with renal excretion playing a minor role. Excretion via the urine is minor (11%), with only a small fraction of the dose being excreted as unchanged asciminib (2.5%).

Clinical pharmacokinetics: Asciminib, administered as BID and QD dosing regimen, was rapidly absorbed with a median time to reach maximum plasma concentration (Tmax) of 2 to 3 hr, independent of dose. Systemic exposure of asciminib, after oral administration of a single dose or multiple doses, as measured by Cmax and AUC, increases in a slightly more than dose proportional manner. Steady state was reached by Day 3. The apparent terminal elimination half-life was estimated to be between 7 and 15 hr, the apparent clearance of asciminib was 4.34 L/h (following a single dose of 80 mg in the human ADME study). Based on PopPK (n= 353 patients), the asciminib clearance for a typical individual (i.e. 70 kg male, with normal renal function) was 6.31 L/h for a total daily dose of 80 mg. In Study CABL001X2101, the geometric mean average accumulation ratio ranged from 1.65 to 2.29 for the BID dosing (1.65 at 40 mg BID and 1.92 at 200 mg BID) and from 1.12 to 1.30 for the QD dosing (1.30 at 80 mg QD). The variability of exposure was low to moderate with inter-patient variability (CV%) ranging from approximately 17% to 69% for AUClast and from 14% to 74% for Cmax. The inter-subject geoCV% in Study CABL001X2101 at 40 mg BID was 49.6% and 48.9% for AUClast and Cmax. In line with that, the inter-subject geoCV% in Study CABL001A2301 at 40 mg BID was 47.8% and 46.7% for AUClast and Cmax.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of the general pharmacology and

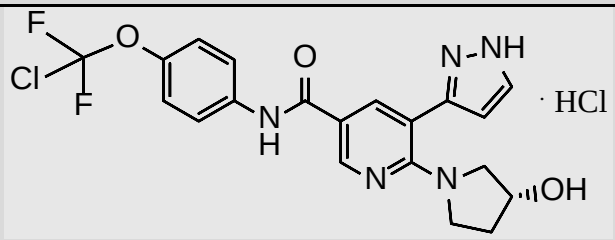
pharmacokinetic characteristics of asciminib. FDA does not agree with the percentage contribution for each metabolizing enzyme of asciminib, including CYP3A4, UGT2B7 and UGT2B17 as they cannot be verified from the human mass balance study. Furthermore, the contribution from biliary secretion via BCRP cannot be reliably estimated based on the current data.

The general overview of asciminib ADME and clinical PK information assessed by FDA are presented in Table 14:

Table 14: Highlights of Clinical Pharmacology for Asciminib

Physiochemical properties

Chemical structure and molecular weight



Chemical Structure of asciminib

Molecular weight of asciminib: 449.84 g/mol (486.30 g/mol hydrochloride salt)
The distribution coefficient (log D) of asciminib hydrochloride at 37°C for n-octanol/0.1 N HCl is 1.26.
The pKa value of the free base component of asciminib is 3.93 ± 0.02.
Asciminib exhibits pH dependent solubility characteristics (see Table below).

Solubility of asciminib hydrochloride at 25 ± 0.2°C.

Solvent	Solubility (g/100 mL)	Description [a)]
Water	0.124	Slightly soluble
pH 1.0 (HCl 0.1 N)	0.112	Slightly soluble
pH 2.0 (HCl 0.01 N)	0.437	Slightly soluble
pH 3.0 citrate buffer	0.047	Very slightly soluble
pH 4.0 acetate buffer	0.012	Very slightly soluble
pH 5.0 acetate buffer	< 0.001	Practically insoluble
pH 6.8 phosphate buffer	< 0.001	Practically insoluble
pH 8.0 borate buffer	< 0.001	Practically insoluble
pH 9.0 borate buffer	< 0.001	Practically insoluble
pH 10.0 borate buffer	< 0.001	Practically insoluble

(Source: NDA 215358, Module 3.2.S.1.3. General Properties, Table 1-1)

Pharmacology

<table>
<tr><td>Mechanism of Action</td><td>Asciminib is an inhibitor of ABL/BCR-ABL1 tyrosine kinases. Asciminib inhibits the ABL1 kinase activity of the BCR-ABL1 fusion protein, by specifically targeting the ABL myristoyl pocket. In studies conducted in vitro or in animal models of CML, asciminib showed activity against wild-type BCR-ABL1 and several mutant forms of the kinase, including the T315I mutation.</td></tr>
<tr><td>Active Moieties</td><td>Asciminib is the main circulating component in plasma (93% of the administered dose).</td></tr>
<tr><td>QT/QTc Prolongation</td><td>Asciminib does not cause a large mean increase in QTc interval (i.e., >20 msec) at the maximum recommended clinical dosage (200 mg twice daily). Based on the available clinical data, a small mean QTc increase (<10 msec) cannot be excluded.</td></tr>
<tr><td colspan="2">General Information</td></tr>
<tr><td>Bioanalysis</td><td>The bioanalytical assays were validated for the measurement of asciminib. A summary of the method validation reports and method performances is included in Section 19.4. OCP Appendices.</td></tr>
<tr><td>Healthy Volunteers vs. Patients</td><td>There was no apparent difference in the PK [C_{max}: 537 (74%) vs. 601 (42.5%) ng/mL and AUC: 5262 (39%) vs. 6100 (39%) ng*h/mL)] of asciminib in cancer patients (n=32) as compared to healthy subjects (n=227) for a single 40 mg dose.</td></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen</td><td>The steady state C_{max} and AUC_{tau} of asciminib at recommended dosages are listed in the table below.
Table 15: Steady State[a] Asciminib Exposure at Recommended Dosages
<table>
<tr><th>Asciminib Dosage</th><th>C_{max} (ng/mL)</th><th>AUC_{tau}[b] (ng*h/mL)</th><th>Accumulation Ratio</th></tr>
<tr><td>80 mg once daily</td><td>1781 (23%)</td><td>15112 (28%)</td><td>1.30</td></tr>
<tr><td>40 mg twice daily</td><td>793 (49%)</td><td>5262 (48%)</td><td>1.65</td></tr>
<tr><td>200 mg twice daily</td><td>5642 (40%)</td><td>37547 (41%)</td><td>1.92</td></tr>
</table>
a= Steady state is achieved within 3 days.
b= AUC_{tau} represents $AUC_{0\text{-}12h}$ for twice daily dosing and $AUC_{0\text{-}24h}$ for once daily dosing.</td></tr>
<tr><td>Minimal effective dose or exposure</td><td>Not determined.</td></tr>
</table>

Maximal tolerated dose or exposure	The MTD was not reached for doses up to 280 mg BID in the FIH trial CABL001X2101.
Dose Proportionality	The asciminib AUC and C_{max} after a single dose (Cycle 1 Day 1) and repeat doses (Cycle 2 Day 1) increased in a slightly more than dose proportional manner for BID dosing regimens, the asciminib exposure increased in a dose proportional manner for the QD dosing regimens (see Tablet below).
Accumulation	Refer to **Table 13** above.
Variability	The inter-subject variability (CV %) ranged from 17% to 69% for AUC_{last} and from 14% to 74% for C_{max}. The intra-subject variability ranged from 13.3% to 28.9% for Cmax and 5.6 to 22.7% for AUC_{last}.
Absorption	
Bioavailability	No absolute bioavailability study was conducted.
T_{max}	The median (range) T_{max} of asciminib is 2.5 hours (2 to 3 hours).

Dose proportionality analysis for asciminib

Parameter (unit)	Dose range (mg)	Target boundaries	Estimate of beta	90% CI Lower	90% CI Upper
b.i.d. regimen					
Cycle 1 Day 1					
AUC0-last (ng*hr/mL)	10 - 200	(0.93, 1.07)	1.16	1.08	1.23
Cmax (ng/mL)	10 - 200	(0.93, 1.07)	1.15	1.07	1.22
Cycle 2 Day 1					
AUC0-last (ng*hr/mL)	10 - 200	(0.93, 1.07)	1.22	1.14	1.29
AUCtau (hr*ng/mL)	10 - 200	(0.93, 1.07)	1.19	1.10	1.28
Cmax (ng/mL)	10 - 200	(0.93, 1.07)	1.18	1.10	1.26
q.d. regimen					
Cycle 1 Day 1					
AUC0-last (ng*hr/mL)	80 - 200	(0.76, 1.24)	1.11	0.87	1.36
Cmax (ng/mL)	80 - 200	(0.76, 1.24)	1.29	1.05	1.54
Cycle 2 Day 1					
AUC0-last (ng*hr/mL)	80 - 200	(0.76, 1.24)	0.95	0.72	1.18
AUCtau (ng*hr/mL)	80 - 200	(0.76, 1.24)	0.95	0.71	1.18
Cmax (ng/mL)	80 - 200	(0.76, 1.24)	0.92	0.70	1.14

Relative Bioavailability	Study ABL001A2101 evaluated the relative bioavailability of two-asciminib film-coated tablet (FCT) formulations (asciminib-HCl salt form FCT, (b) (4) in comparison to the clinical supply formulation (CSF) capsule formulation (used in the first-in-human study X2101) in healthy subjects after a single asciminib dose of 40 mg (2 x 20 mg tablet or capsule). Median Tmax was around 2 hours and was similar among the three formulations under fasted condition. Asciminib-HCl salt form FCT versus CSF capsule under fasted condition indicated similar exposures: The exposure was 11%-12% higher for the tablet variant as compared to the CSF capsule. The geometric mean ratios (GMRs) for AUCinf, AUClast, and Cmax were 1.12 (90% CI: 0.998, 1.25) and 1.12 (90% CI: 1.00, 1.26), and 1.11 (90% CI: 0.949, 1.29), respectively (n=19). (b) (4) The relative bioavailability of orally administered asciminib CSF capsule was evaluated in Study CABL001A2104. The CSF capsule was compared to the final market image (FMI) tablet formulation (asciminib-HCl salt form FCT) in fasted healthy subjects after a single asciminib dose of 40 mg (40 mg FMI tablet or 2 x 20 mg CSF capsule). The median T_{max} was 2.98 hours (range: 2.00-5.00) for the capsule and 2.04 hours (range: 1.01-4.99) for the tablet formulations. The GMRs and 90% CIs of asciminib PK parameters were within the reference range of 0.80 to 1.25. The GMR (tablet vs capsule) and 90% CIs for AUC_{inf}, AUC_{last} and C_{max} were 1.00 (90% CI: 0.909, 1.10), 1.01 (90% CI: 0.911, 1.11), and 0.909 (90% CI: 0.805, 1.03), respectively (n=20). In conclusion, there was no difference in the systemic exposure (C_{max} and AUC) between the FMI tablet and the capsule formulation.

Food effect (Fed/fasted)	In the food effect study CABL001E2101 with the final market image (FMI) tablet, the effect of a low-fat (less than 20% fat and not more than 400 calories) and high-fat meal (approximately 800 to 1000 calories with ~50% calories from fat, ~35% calories from carbohydrates, and ~15% calories from protein) in healthy subjects (n=24) after a single asciminib dose of 40 mg following an overnight fast was evaluated. The GMRs (low-fat meal vs. fasted) and 90% CIs for AUC_{inf}, AUC_{last}, and C_{max} were 0.700 (90% CI: 0.631, 0.776), 0.700 (90% CI: 0.630, 0.777), and 0.652 (90% CI: 0.576, 0.739). The GMRs (high-fat meal vs. fasted) and 90% CIs for AUC_{inf}, AUC_{last}, and C_{max} were 0.377 (90% CI: 0.341, 0.417), 0.372 (90% CI: 0.336, 0.413), 0.318 (90% CI: 0.282, 0.360) respectively. Hence, asciminib should be taken on an empty stomach.
Proton Pump Inhibitor (PPI) effect	In Study CABL001A1101, co-administration of the proton pump inhibitor rabeprazole (20 mg QD) in combination with a single 40 mg oral dose of asciminib has been evaluated. Administration of asciminib with rabeprazole reduced Cmax of asciminib by 9% approximately but did not change AUCinf and AUC_{last}. The estimated GMRs and 90% CIs for AUC_{inf}, AUC_{last}, and C_{max} of ABL001 when co-administered with rabeprazole were 0.986 (90% CI: 0.959 to 1.01), 0.985 (90% CI: 0.957 to 1.01), and 0.908 (90% CI: 0.849 to 0.972), respectively (n=23). The observed median difference in T_{max} was 1 h (range: −1.00 to 3.00 h) when ABL001 was co-administered with rabeprazole, as compared to ABL001 alone.
Distribution	
Volume of distribution	The apparent volume of distribution of asciminib at steady state is 151 L (135%).
Plasma protein binding	Asciminib is 97% bound to human plasma proteins *in vitro*.
Blood to plasma ratio	The mean blood-to-plasma ratio was 0.80 for asciminib.
Elimination	
Half-life	The elimination half-life of asciminib is 5.5 hours (38%) at 40 mg twice daily and 80 mg once daily, and 9.0 hours (33%) at 200 mg twice daily.
Clearance	The total apparent clearance of asciminib is 6.7 L/hour (48%) at 40 mg twice daily and 80 mg once daily, and 4.1 L/hour (38%) at 200 mg twice daily.

Metabolism	
Primary metabolic pathway(s)	In vitro, asciminib is metabolized by CYP3A4-mediated oxidation, UGT2B7- and UGT2B17-mediated glucuronidation.
Inhibitor/Inducer	In vitro, • Asciminib inhibits CYP3A4 (K_I value of 0.348 µmol/L), CYP2B6 (Ki value of 2.62 µmol/L), CYP2C8 (K_I value of 0.466 µmol/L), and CYP2C9 (Ki value of 0.407 µmol/L), but does not inhibit CYP1A2, CYP2D6, or UTG2B7. • Asciminib may reversibly inhibit UGT1A1 (K_I value of 0.35 µmol/L) at plasma concentrations reached at a total daily dose of 80 mg and 200 mg twice daily. In addition, asciminib may reversibly inhibit CYP2C19 (K_I value of 1.5 µmol/L), at concentrations reached at 200 mg twice daily dose. • Asciminib induces CYP1A2 and CYP3A4. • Asciminib is a substrate of BCRP and P-gp. • Asciminib inhibits BCRP, P-gp, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, OCT2, MATE1 and MATE2-K with K_I values of 24.3, 21.7, 2.46, 1.92, 3.41, 6.90, 1.01, 8.63, 6.22, 2.36 µmol/L, respectively. Asciminib does not inhibit BSEP.
Excretion	
Primary excretion pathways (% dose) ±SD	In the human mass balance Study CABL001A2102, 80% (57% as unchanged) and 11% (2.5% as unchanged) of the asciminib dose were recovered in the feces and in the urine of healthy subjects, respectively, following oral administration of a single 80 mg dose of [^{14}C] -labelled asciminib.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. The results from the Study CABL001A2301 and Study CABL001X2101 provide compelling evidence of positive benefit-risk supporting the efficacy claim of asciminib 80 mg total daily dose (taken either as 40 mg BID or 80 mg QD) in adult patients with Ph+ CML-CP, previously treated with two or more TKIs. While clinical pharmacology evaluation does not include a direct assessment of benefit-risk, the exposure-response models in safety and efficacy highlighted the existence of a slightly positive exposure-efficacy relationship, which did not translate into meaningful difference in median predicted MMR rates and indicated a flat exposure-safety relationship across the doses tested. Further, direct comparisons provided evidence that the safety and efficacy are similar between asciminib 80 mg QD and 40 mg BID.

Additionally, the PK-PD model for patients harboring T315I mutation supports asciminib 200 mg BID to be an appropriate dosage regimen for this patient population.

The FDA's Assessment:

FDA generally agrees with the Applicant that the clinical pharmacology program provides supportive evidence of the effectiveness of asciminib. Refer to section 6.2.2.1. General Dosing for details.

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

The Applicant's Position:

Yes. In multiple models, evidence of asciminib single agent anti-leukemic activity was demonstrated regardless of dose levels (i.e. total daily dose of 20 to 400 mg) and number of prior lines of therapy received (i.e. 1 to 5 prior lines).

The exposure-efficacy analysis of BCR-ABL transcript levels time course highlighted the existence of a slightly positive exposure-efficacy relationship with total daily dose, which did not translate into meaningful difference in median predicted MMR rates over the complete wide dose range tested. Direct comparisons provided evidence that the safety and efficacy is similar between asciminib 40 mg BID and 80 mg QD.

The exposure-safety relationship was explored using various safety endpoints such as laboratory, vital signs abnormalities, fatigue/asthenia, treatment-emergent adverse events (TEAEs) of Grade 3 or higher, TEAE leading to dose reduction or dose interruption, changes in serum creatinine and QTcF change from baseline.

For all safety endpoints analyzed, there was a lack of clinically relevant association between occurrence of safety events and increase in the asciminib PK metrics within the dose range investigated.

Concentrations-QT analyses demonstrated that at therapeutic doses, asciminib does not have a clinically relevant effect on cardiac repolarization. The estimated mean and upper bound of the 90% CIs of ΔQTcF at 40 mg BID, 80 mg QD, and 200 mg BID and at the highest clinical relevant exposure (HCRE) (which is the worst case scenario for Cmax at 200 mg BID [i.e. 1.59-fold the Cmax at 200 mg BID]) were below 10 ms, which is the threshold that is considered clinically significant according to the regulatory guidance.

In summary, the results from Study CABL001A2301 and Study CABL001X2101, supported by exposure-response analyses, provided sufficient evidence that a total daily asciminib dose of 80 mg (administered as either 40 mg BID or 80 mg QD) delivers potent anti-leukemic activity in heavily pre-treated patients with CML not harboring the T315I mutation. Based on the

available clinical data as well as the extensive exposure-efficacy and efficacy-safety analyses, the risk/benefit ratio of asciminib administered at 80 mg QD in patients with CML not harboring the T315I mutation is similar to that of asciminib 40 mg BID. Overall, the dose of asciminib 80 mg QD is considered favorable and can be used as an alternative, more convenient, patient-centric dose regimen for this patient population.

The available clinical data from Study CABL001X2101, and further supported by exposure-response analysis, the benefit of asciminib administered at 200 mg BID in patients with CML-CP harboring the T315I mutation is considered favorable, supporting 200 mg BID as the recommended dose for this patient population.

The FDA's Assessment:

FDA agrees with the Applicant that the proposed dosage regimens are appropriate for the general patient population for which the indications are being sought. Refer to section 6.2.2.1. General Dosing for details.

FDA clarifies that asciminib does not cause a large mean increase in QTc interval (i.e., >20 msec) at the maximum recommended clinical dosage (200 mg BID). Based on available clinical data, a small mean QTc increase (<10 msec) cannot be excluded.

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

The Applicant's Position:

No. Based on the assessment of intrinsic factors, no dose adjustment or change in regimen is required based on demographics or in any subpopulation.

Demographic factors
No dose adjustment of asciminib is required based on the age, gender, body weight, ethnicity or race of the patient. Based on PopPK analyses there was no clinically meaningful difference in asciminib between Asian and non-Asian as well as between Japanese and non-Japanese cancer patients.

Subpopulations

Hepatic impairment: No dose adjustment is necessary in subjects with mild, moderate, or severe hepatic impairment based on results of hepatic impairment Study CABL001A2103. Caution should be exercised in patients with severe hepatic impairment receiving asciminib 200 mg BID.

Renal impairment: No dose adjustment is necessary in subjects with mild, moderate or severe renal impairment based on results of renal impairment Study CABL001A2105. Caution should

be exercised in patients with severe renal impairment receiving asciminib 200 mg BID.

UGT2B7 and UGT2B17 genotypes
Pharmacogenomics analyses showed that UGT2B7 genotypes have no clinically relevant impact on the PK of asciminib. The data for UGT2B17 was inconclusive. However, based on the low fractional contribution of UGT2B17 to the total clearance (7.8%), a clinically relevant impact on the PK of asciminib is unlikely.

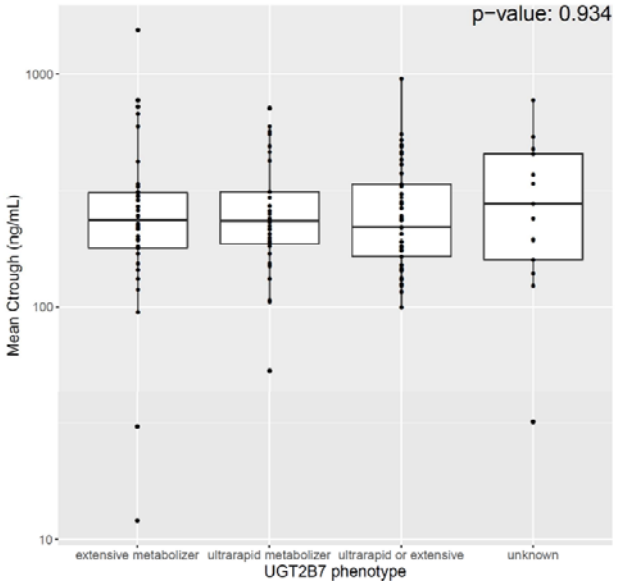
The FDA's Assessment:

FDA generally agrees with Applicant that an alternative dosage regimen or management strategy is not required for subpopulations based on intrinsic patient factors including sex, age, race/ethnicity, body weight, mild to severe hepatic or renal impairment, and UGT2B7 and UGT2B17 genotypes. Refer to the FDA's assessment below on UGT genotypes and in Section 6.2.2.2. Therapeutic Individualization for details for FDA's assessment on organ dysfunctions.

UGT2B7 and UGT2B17 germline variation and asciminib PK

UGT2B7 and UGT2B17 contribute with 13.3% and 7.8%, respectively to total systemic clearance of asciminib. The Applicant conducted pharmacogenetic analyses in study A2301 to explore the role of UGT2B7 and UGT2B17 germline variations on asciminib PK. Whole blood for UGT genotyping (Affymetrix DMET™ Plus gene chip) was collected at baseline from patients in the asciminib arm. For UGT2B7, a total of 120 out of 157 patients (76.4%) had valid UGT genotyping results and at least one C_{trough} value. Phenotypes were inferred from genotypes according to assignment rules using the genotyping assay dedicated software. No statistically significant differences in Ctrough levels were observed in patients with different UGT2B7 phenotypes (Figure 3). Of note, no poor metabolizer phenotype was assigned, and some of the observed genotypes could not be categorized into corresponding phenotypes due to lack of evidence for the mapping. UGT2B17 genotyping results were available for 29 patients (24.2%), and all were homozygous for the UGT2B17*2 (deletion variant). Although UGT2B17 and PK analyses were not conducted, UGT2B17 variation is unlikely to be clinically relevant due to the relatively minor contribution of UGT2B17 to asciminib metabolism.

Figure 3: Association between mean Ctrough levels and UGT2B7 phenotypes



Source: Applicant's Figure 3-5, Summary of Clinical Pharmacology. Extensive (normal) metabolizers: N=34, Ultrarapid metabolizers: N=32, Ultrarapid or extensive (normal) metabolizers: N=41, Unknown: N=13. Ambiguous haplotypes were categorized as unknown. UGT2B7 Alleles observed: *1A, *1G, *2A, *2C, *2E, and *3

BCR-ABL1 mutations and response to asciminib

FDA explored the association of BCR-ABL1 kinase domain mutations and treatment response (MMR at week 24) in the asciminib arm in Study A2301 (N=157). The presence of BCR-ABL1 mutations was centrally assessed by Sanger sequencing in blood samples from all patients at Week 1 Day 1 (W1D1, pre-dose) and every 12 weeks after until the end of study treatment if a mutation was detected at baseline. Of note, this approach limited the number of patients with available mutation data collected during treatment. Mutation analysis was also performed upon confirmed loss of MMR and/or at end of treatment (EOT). Patients harboring either T315I or V299L mutated BCR-ABL1 were not eligible to participate in Study A2301. A total of 17 patients (11%) had non-T315I BCR-ABL1 mutations identified at baseline, representing 11 unique mutation genotypes (Table 16). Consistent with patients having been previously treated with ATP-binding TKIs, most (N=15) mutations were in the ATP binding region (L248V, G250E, Y253H, E255K/V, F317L, F359C/V). Two additional patients had mutations in kinase C-terminal or core regions alone (F486S) or combined with an ATP binding region mutation (W478R/Y253H) and one patient had a mutation in the myristoyl pocket (E459K), which may be resistant to asciminib. Based on the 06-Jan-2021

cutoff date, 53 patients (33.8%) had discontinued treatment with asciminib and had mutation analysis performed at EOT/Discontinuation. Of these, BCR-ABL1 mutations were detected in samples of 16 patients (30%; 16/53), 5 without mutations detected at baseline. EOT mutations in these 5 patients were: T315I (=1), M244V (N=2), A337T (N=1), P485S (N=1). Also, a few patients had multiple (≥ 2) mutations detected at various timepoints (Table 16). Of six patients in MMR at Week 24, five had mutations in the ATP binding region. Although the data is limited, BCR-ABL1 mutations appear to have persisted from earlier time points to EOT in patients who discontinued treatment and did not meet MMR criteria at 24 weeks, such as observed in 4 patients with F359C/V. F359V also showed a higher mean IC50 value (11.5 ± 4.87), compared to wild-type and T315I mutated BCR-ABL1 and to mutations observed in responders, suggesting that mutations at F359 have reduced sensitivity to asciminib inhibition (Table 16). Of note, of 115 CML-CP patients without T315I mutation who received single-agent asciminib in Study X2101, approximately 18% had one or multiple (non-T315I) BCR-ABL1 kinase domain mutations detected by Sanger or NGS at screening, most occurring in one patient each, reflecting the diversity of these mutations, which was also observed in Study 2301.

Although asciminib interacts with the myristoyl pocket, these exploratory results show that in addition to T315I, other BCR-ABL1 point mutations outside of the myristoyl pocket can still confer reduced sensitivity to asciminib and thus represent a vulnerability to treatment. Ongoing asciminib studies include BCR-ABL1 mutation analyses at baseline, on treatment and at EOT and may contribute with additional data on the primary and acquired resistance profile of asciminib and help inform whether patients with mutations other than T315I may benefit from a higher asciminib dose.

Table 16: Subset of patients with BCR-ABL1 kinase domain mutations identified at baseline in Study 2301, asciminib arm [cutoff date: 06-Jan-2021]

Last Prior Therapy	Mutation at Baseline (W1D1)	Mean IC50 (nM) ± SD [&]	Mutation on Treatment	Discontinued from treatment	Mutation at EOT/Disc.	MMR at Week 24
Nilotinib	G250E	0.74 ± 0.27	G250E	No	On Treat.	No
Hydroxyurea	G250E	0.74 ± 0.27	G250E	No	On Treat.	**Yes**
Nilotinib	Y253H	1.71 ± 0.75	Y253H	Yes	Y253H	No
Nilotinib	Y253H	1.71 ± 0.75	Not done [#]	No	On Treat.	**Yes**
Dasatinib	E255K	2.35 ± 0.71	Not done[#]	No	On Treat.	**Yes**
Nilotinib	E255K	2.35 ± 0.71	Not done[#]	No	On Treat.	**Yes**
Nilotinib	E255V	1.17 ± 0.54	Not done[#]	No	On Treat.	**Yes**
Ponatinib	T315I*	7.64 ± 3.22	Not done	Yes	Not done	*
Ponatinib	T315I*	7.64 ± 3.22	Not done	Yes	T315I	*
Ponatinib	T315I/E462K*	NA	Not done	Yes	T315I/E462K	*

Dasatinib	F317L	NA	F317L	Yes	F317L	No
Ponatinib	F317L	NA	F317L or E355G◊	Yes	E355G	No
Bosutinib	L248V/F317L	NA	L248V/F317L	Yes	F317L	No
Bosutinib	Y253H/F486S	NA	M244V/Y253H/F486S	Yes	M244V	No
Ponatinib	F359V	11.5 ± 4.87	F359V	Yes	F359V	No
Nilotinib	F359V	11.5 ± 4.87	NA	Yes	F359V	No
Dasatinib	F359V	11.5 ± 4.87	F359V	Yes	F359V	No
Hydroxyurea	F359C	NA	F359C^	Yes	F359C	No
Ponatinib	E459K	3.01 ± 1.37	E459K	Yes	Not done	No
Radotinib	W478R	NA	Not done#	No	On Treat.	**Yes**

*Source: Reviewer exploratory analysis based on ADMUT, ADB1, ADSL, ADDS, ADZT datasets and Response to FDA Information Request, 9/2/2. EOT-End of treatment; W1D1-Week 1, Day 1; NA-Not available; # mutation analysis not done when BCR-ABL1 copies < 100; Disc.-Discontinuation; Treat. - treatment; MMR- Major molecular response; ^ Y253H/F359C was detected at screening; * Per protocol, patients with T315I or V299L detected at baseline were considered a protocol violation and treated as non-responders in the primary analysis;*

◊F317L was detected at week 24 and E355G was detected at week 36; & Growth inhibition of BCR-ABL1 transfected Luc-Ba/F3 cells (mean IC50 value nM± SD), Applicant's Table 2-2 - Pharmacology Written Summary.IC50 for wild type: 0.61 ± 0.21.

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

The Applicant's Position:

The clinically relevant food-drug and drug-drug interactions with concomitant medications are described in further detail below with their respective recommendation for management.

Food-drug interactions

The bioavailability of asciminib decreased when administered with food. The negative food effect was more pronounced with the high-fat meal with 62.3% decrease in AUCinf compared to 30% decrease with a low-fat meal. Asciminib due to this food effect needs to be taken in the fasted state; food consumption should be avoided for at least 2 hr prior and 1 hr after asciminib administration.

Drug-drug interactions

Co-administration of asciminib with CYP3A4 inhibitors and inducers

Based on clinical data, asciminib can be co-administered, without dose adjustment, with drugs that are inducers or inhibitors of CYP3A4, as the PK of asciminib will not be significantly altered in the presence of those agents.

To be conservative, strong CYP3A4 inducers should be used with caution at all recommended doses as they reduce the exposures of asciminib, even though by a small extent.

At asciminib 200 mg BID, strong CYP3A4 inhibitors should be used with caution.

CYP3A4 is considered to contribute to asciminib clearance by 36.0%. A clinical DDI study with clarithromycin confirmed this low fractional contribution by a small asciminib AUCinf increase of 36%. The strong CYP3A4 inducer rifampicin decreased asciminib AUCinf by 14.9%. Based on PBPK simulations, the effect of CYP3A4 inhibition or induction on asciminib PK appeared to be independent of asciminib dose.

Effect of asciminib on CYP3A4, CYP2C9 and CYP2C8 substrates

In a clinical DDI Study with the sensitive substrates midazolam (CYP3A4), warfarin (CYP2C9) and repaglinide (CYP2C8) revealed a low interaction potential of asciminib with those CYPs at a dose of 40 mg BID.

Asciminib 40 mg BID and 80 mg QD can be co-administered, without dose adjustment, with drugs that are substrates of CYP3A4, CYP2C9 and CYP2C8 as the PK of these drugs will not be significantly altered in the presence of asciminib.

However, drugs that are substrates of CYP3A4 with a narrow therapeutic index should be used with caution at all recommended doses of asciminib.

At asciminib 40 mg BID or 80 mg QD, drugs that are substrates of CYP2C9 with a narrow therapeutic index should be used with caution.

At asciminib 200 mg BID, in addition to sensitive CYP3A4 and CYP2C9 substrates known to have a narrow therapeutic window, sensitive CYP2C9 substrates should be avoided. If co-administration cannot be avoided, the CYP2C9 substrates dose should be reduced. Increase the frequency of international normalized ratio (INR) monitoring if co-administration with warfarin is unavoidable as the anti-coagulant effect of warfarin may be enhanced. No dose adjustments of asciminib are needed.

Co-administration of asciminib with P-gp inhibitors

Asciminib is a low affinity substrate of P gp. In a clinical DDI study, co-administration of asciminib with the strong P-gp inhibitor (quinidine) did not lead to any relevant change in exposure of asciminib.

Consequently, P-gp inhibitors may be co-administered at all recommended doses without restrictions.

Co-administration of asciminib with acid reducing agents

Based on clinical data, rabeprazole (regarded as the worst-case scenario with regards to pH alteration) in combination with a single 40 mg oral dose of asciminib had no effect on the

bioavailability of asciminib. Consequently, asciminib may be co administered with acid reducing agents without dose adjustment.

Co-administration of asciminib with UGT inhibitors

No clinically relevant DDI effects are expected, when inhibiting UGT2B7 and UGT2B17, based on their limited fractional contribution to the total clearance.

Co-administration of asciminib with imatinib

Higher exposures of asciminib were observed when administered in combination with imatinib compared to when asciminib was administered alone.

In a clinical DDI study, the AUC and Cmax of asciminib (40 mg single dose) when administered in combination with imatinib was approximately 2-fold and 1.59-fold higher compared to when asciminib was administered alone.

The overall increase in exposure of asciminib when co-administered with imatinib could be explained by its potential to inhibit multiple clearance pathways of asciminib (i.e., BCRP, CYP3A4, UGT2B17 and UGT1A3/4).

The FDA's Assessment:

FDA agrees with the Applicant's position that the AUC and C_{max} of a single dose of asciminib decreased by 62% and 68%, respectively, with a high-fat meal (1000 calories, 50% fat) and by 30% and 35%, respectively, with a low-fat meal (400 calories, 25% fat) compared to the fasted state. Asciminib should be taken without food. Avoid food consumption for at least 2 hours before and 1 hour after taking asciminib.

Drug-drug interactions

Table 17: Static net effect DDI risk assessment for asciminib as a perpetrator of enzymes and transporters at a dose of 200 mg b.i.d. (steady state)

	Measured inhibition / induction constant					
Protein	**Parameter [1)]**	**Total**	**Unbound**	**AUCR (only inhibition) [3)-5)]**	**AUCR (only induction) [3)-5)]**	**Net effect AUCR [3)-5)]**
Enzymes in liver and other organs including intestine for CYP3A4/5 - assessment based on [DMPK-R1300242], [DMPK-R1701235], [DMPK-R1809192] [DMPK-R2000001], [DMPK-R1600146]						
CYP1A2	IC50/2 (µM)	>50	10.4	1.05	0.40	0.42
	EC50 (µM)	0.59	0.59			
	Emax [2)]	3.50	-			
CYP2A6	IC50/2 (µM)	>50	43.6	1.02	NA	1.02
CYP2B6	Ki (µM)	3.49	2.62	1.16	NA	1.16
CYP2C8	Ki (µM)	0.54	0.466	1.75	NA	1.75
CYP2C9	Ki (µM)	0.47	0.407	2.36	NA	2.36
CYP2C19	IC50/2 (µM)	7.50	1.50	1.38	NA	1.38
CYP2D6	IC50/2 (µM)	11.5	8.50	1.07	NA	1.07
CYP2E1	IC50/2 (µM)	>50	37.5	1.02	NA	1.02
CYP3A4/5 [8]	Ki (µM)	0.400	0.348	4.90 [8]	0.182 [8]	2.85 [8]
	EC50 (µM)	2.70	2.70			
	Emax [2)]	4.40	-			
UGT1A1	Ki (µM) [7)]	1.00	0.35	3.01	NA	3.01
UGT2B7	Ki (µM) [7)]	35.0	7.28	1.10	NA	1.10
Protein	Parameter	Total	Unbound	-	-	R value [6)]
Transporters at the liver inlet (portal vein) - assessment based on [DMPK-R2000050]						
OCT1	Ki (µM) [7)]	-	3.41			1.21
OATP1B1	Ki (µM) [7)]	-	2.46			1.29
OATP1B3	Ki (µM) [7)]	-	1.92			1.37
Hepatic efflux transporters - assessment based on [DMPK-R2000050] [DMPK-R1400124]						
P-gp	Ki (µM)	-	21.7			1.02
BCRP	Ki (uM) [7)]	-	24.3			1.01
Renal transporters - assessment based on [DMPK-R2000050]						
OAT1	Ki (uM) [7)]	-	6.90			1.05
OAT3	Ki (uM) [7)]	-	1.01			1.34
OCT2	Ki (uM) [7)]	-	8.63			1.04
MATE1	Ki (uM) [7)]	-	6.22			1.05
MATE2K	Ki (uM) [7)]	-	2.36			1.14
Transporters in the intestine - assessment based on [DMPK-R2000050]						
P-gp	Ki (uM)	-	21.7			83.0
BCRP	Ki (uM) [7)]	-	24.3			74.2

Based on the R values estimated at the asciminib 200 mg BID (Table 15), FDA agrees with the Applicant that:

- Asciminib has the potential to inhibit CYP3A, CYP2C9, and CYP2C8.
- Asciminib may reversibly inhibit UGT1A1 at plasma concentrations reached at a total daily dose of 80 mg and 200 mg twice daily. In addition, asciminib may reversibly inhibit CYP2C19 at concentrations reached at 200 mg twice daily dose.
- Asciminib inhibits BCRP, P-gp, OATP1B1, OATP1B3, and OCT1.
- Based on the low R-values for OAT1, OCT2 and MATE1, no interaction potential towards these transporters is anticipated.

Table 18: DDI assessment of asciminib as a victim drug

Study #	Drug class	Concomitant drugs	Asciminib single dose	Effect on asciminib PK (GMR [90% CI])	
				Cmax	AUCinf
					(b) (4)

FDA disagrees with the Applicant's PBPK model for the prediction of DDI effect assessing asciminib as a victim drug (Refer to Section 19.4.4. Physiologically based Pharmacokinetic Modeling Review for details).

Co-administration of asciminib with CYP3A4 inhibitors and inducers

FDA agrees that coadministration of a strong CYP3A4 inhibitor with asciminib at the dosages of 40 mg and 80 mg does not affect the exposure of asciminib to a clinically relevant extent. However, concomitant use of asciminib at the dosage of 200 mg with a strong CYP3A4 inhibitor increases the asciminib C_{max} and AUC, which may increase the risk of adverse reactions. Therefore, FDA recommends closely monitor for adverse reactions in patients treated with asciminib at 200 mg twice daily with concomitant use of strong CYP3A4 inhibitors.

FDA disagrees with the Applicant that strong CYP3A4 inducers should be used with caution. Strong CYP3A inducers also induce UGT enzymes. The PBPK model and predictions have been determined to be inadequate to assess asciminib as a victim drug. Refer to Section 19.4.4. Physiologically based Pharmacokinetic Modeling Review for details. Concomitant use of strong CYP3A and UGT inducers with asciminib at 40 mg BID, 80 mg QD or 200 mg BID has not been fully characterized. FDA will issue a PMC study to evaluate the effect of repeat doses of a strong CYP3A and UGT inducer on the single dose (200 mg) pharmacokinetics of

asciminib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations.

Effect of asciminib on CYP3A4, CYP2C9, CYP2C8 and CYP2C19 substrates
The PBPK model has been determined to be adequate to assess asciminib as s perpetrator. Refer to Section 19.4.4. Physiologically based Pharmacokinetic Modeling Review for details.

Table 19: DDI assessment of asciminib as a perpetrator

Drug class	Concomitant drugs	Study #	Asciminib dose	Effect on substrate PK (GMR [90% CI])	
				Cmax	AUCinf
Sensitive CYP3A substrate	Midazolam	X2101	40 mg BID	1.19 (1.10, 1.30)	1.36 (1.27-1.46)
Sensitive CYP2C9 substrate	Warfarin (S-)	X2101	40 mg BID	1.08 (1.04, 1.13)	1.41 (1.37, 1.45)
Sensitive CYP2C8 substrate	Repaglinide (substrate of CYP3A4 OATP1B1)	X2101	40 mg BID	1.14 (1.01, 1.28)	1.08 (1.02, 1.14)

The midazolam AUC_{inf} and Cmax increased by 28% and 11%, respectively, following coadministration of a CYP3A4 substrate (midazolam) with asciminib 40 mg BID. The midazolam AUCinf and Cmax are precited to increase by 24% and 17%, respectively, following coadministration with asciminib at 80 mg QD and 88% and 58%, respectively, at 200 mg BID. Concomitant use of asciminib increases the Cmax and AUC of CYP3A4 substrates, which may increase the risk of adverse reactions of these substrates. FDA recommends Closely monitor for adverse reactions in patients treated with asciminib at 80 mg total daily dose with concomitant use of certain CYP3A4 substrates, where minimal concentration changes may lead to serious adverse reactions. Avoid coadministration of asciminib at 200 mg BID with certain CYP3A4 substrates where minimal concentration changes may lead to serious toxicities. If coadministration is unavoidable, reduce the CYP3A4 substrate dosage as recommended in its prescribing information.

The S-warfarin AUC_{inf} and C_{max} increased by 41% and 8%, respectively, following coadministration of CYP2C9 substrate (warfarin) with asciminib at 40 mg BID. The S-warfarin AUCinf and Cmax are predicted to increase by 52% and 4%, respectively, following coadministration with asciminib at 80 mg QD and 314% and 7%, respectively, at 200 mg BID.

Concomitant use of asciminib increases the C_{max} and AUC of CYP2C9 substrates, which may increase the risk of adverse reactions of these substrates. FDA recommends avoiding coadministration of asciminib at 80 mg total daily dose with certain CYP2C9 substrate where minimal concentration changes may lead to serious toxicities. If concomitant use is unavoidable, reduce the CYP2C9 substrate dosage as recommended in its prescribing information. Avoid coadministration of asciminib at 200 mg BID with sensitive CYP2C9 substrate, and certain CYP2C9 substrate where minimal concentration changes may lead to serious toxicities. If coadministration is unavoidable, consider alternative therapy with non-CYP2C9 substrate.

The repaglinide AUC_{inf} and C_{max} increased by 8% and 14%, respectively, following coadministration of a CYP2C8 substrate (repaglinide) with asciminib 40 mg BID. The repaglinide AUCinf and Cmax are predicted to increase by 12% and 8%, respectively, following coadministration with asciminib at 80 mg QD and 42% and 25%, respectively, at 200 mg BID. The exposure changes are not considered clinically meaningful. FDA agrees that no action is indicated for the concomitant use of CYP2C8 substrate with asciminib.

No clinically significant differences in the PK of omeprazole were predicted when co-administered with asciminib. FDA agrees that no action is indicated for the concomitant use of CYP2C19 substrate with asciminib.

Effect of asciminib on OATP1B, BCRP, or P-gp substrate
The PBPK analysis was inadequate to evaluate the effect of asciminib on the PK of a OATP1B/BCRP substrate because of the limited validation of the rosuvastatin model and the IVIVE has not been established for the BCRP- and OATP1B-mediated DDIs. FDA recommends PMRs of additional PBPK analysis to assess the effect of asciminib on the PK of a substrate of the BCRP and/or OATP1B to determine appropriate dosage recommendations.

The PBPK DDI-risk assessment indicated that the DDI potential of asciminib with substrates of P-gp cannot be excluded. Concomitant use of asciminib may potentially increases the plasma concentrations of P-gp substrates, which may increase the risk of adverse reactions of these substrates. FDA recommends closely monitor for adverse reactions in patients treated with asciminib at all recommended doses with concomitant use of certain P-gp substrates, where minimal concentration changes may lead to serious toxicities.

Co-administration of asciminib with P-gp inhibitors or acid reducing agents
FDA agrees with the Applicant that no clinically significant differences in the PK of asciminib were observed when co-administered with rabeprazole (acid-reducing agent), or quinidine (P-gp inhibitor). Refer to Table 16 above for details. The ADAM-PBPK model simulations

suggested that changes on gastric pH do not significantly affect asciminib exposure due to its high solubility in bile salts attributed to supersaturation, which override the pH effect. The predicted effect of elevated gastric pH on asciminib PK following a single dose of 200 mg is unlikely to be clinically meaningful.

Co-administration of asciminib with UGT inhibitors
FDA agrees with the Applicant that the potential for a clinically relevant DDI of asciminib with co-medications that inhibit a single UGT enzyme is unlikely. Refer to FDA's assessment on UGT2B7 and UGT2B17 germline variation and asciminib PK for details.

Co-administration of asciminib with imatinib
The asciminib AUC_{inf} and Cmax increase by 108% and 59% (Table 16), respectively following coadministration of a single asciminib dose of 40 mg with imatinib (an inhibitor of BCRP, CYP3A4, UGT2B17 and UGT1A3/4). The exposure changes are not considered clinically meaningful. Concomitant use of imatinib with asciminib at 200 mg BID has not been fully characterized. Patients with Ph+ CML-CP harboring the T315I mutation who will receive the 200 mg BID dose will likely be already resistant to imatinib. Imatinib is unlikely to be a concomitant medication for use with asciminib at the 200 mg BID dose. Hence, no action is indicated for concomitant use of asciminib with imatinib.

Co-administration of asciminib with hydroxypropyl-β-cyclodextrin in Itraconazole Oral Solution or other oral products
Coadministration of multiple doses at 200 mg QD of itraconazole oral solution containing hydroxypropyl-β-cyclodextrin with a single asciminib dose of 40 mg dose decreased asciminib AUC_{inf} and Cmax by 40% and 50% (Table 16), respectively, which may reduce asciminib efficacy. FDA recommends avoid coadministration of asciminib at all recommended doses with itraconazole oral solution containing hydroxypropyl-β-cyclodextrin. Concomitant use of oral products containing hydroxypropyl-β-cyclodextrin with asciminib other than itraconazole oral solution has not been fully characterized. FDA will issue a PMC to the Applicant to conduct in vitro studies to evaluate and characterize the effect of different amounts of hydroxypropyl-β-cyclodextrin on the absorption of asciminib. Identify a threshold amount of hydroxypropyl-β-cyclodextrin that may have a clinically meaningful impact on asciminib bioavailability, which may result in a loss of efficacy. Provide appropriate dosing strategies with concomitant use of these oral drug products with asciminib.

X	X

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

All studies pertinent to the evaluation of efficacy and safety are summarized in Table 3.

Table 20: Listings of Clinical Trials Relevant to this NDA

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to support efficacy and safety							
CABL001A2301	Randomized, open-label, active-controlled (bosutinib), multi-center Phase III study	Asciminib 40 mg BID Bosutinib 500 mg QD	**Primary:** MMR rate at Week 24 **Key secondary:** MMR rate at Week 96 **Other secondary:** MMR rate at and by all scheduled time-points (except 24 and 96 weeks which are already	No fixed duration. The patients are treated in the study up to end of study treatment period defined as up to 96 weeks after the last patient receives the first dose or up to 48 weeks after the	N=233 Asciminib: 157 Bosutinib arm: 76	Adult subjects with CML CP, previously treated with at least 2 prior TKIs, with resistance or	87 centers in 25 countries

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
			covered by primary and key secondary endpoints), Time to MMR, Duration of MMR, BCR-ABL1 ratio (% IS) categories at and by scheduled time points, CCyR at and by all scheduled time-points including 24, 48 and 96 weeks (the analysis of this endpoint will be performed at 96-week analysis time point), Time to CCyR, Duration of CCyR, Time to treatment failure, Progression free survival, Overall survival	last patient has switched to asciminib treatment whichever is longer unless patients have discontinued treatment earlier		intolerance to the most recent TKI	

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
CABL001X2101	Phase I, multicenter, open-label, dose escalation study	Single agent **Arm 1** (CML-CP/-AP): asciminib 10 mg BID to 200 mg BID; 80 mg to 200 mg QD **Arm 5** (CML-BP and Ph+ ALL): asciminib 40 mg BID to 280 mg BID	Primary: Incidence of dose limiting toxicities (DLTs) during the first cycle of study treatment: asciminib as single agent in patients with CML-CP/-AP, in combination with nilotinib, imatinib and dasantinib in patients with CML-CP/-AP In addition, asciminib as single agent in patients with CML-BP and Ph+ ALL. Secondary: To assess anti-CML activity t as	Until disease progression, unacceptable toxicity that precludes any further treatment, or discontinuation from the study treatment at the discretion of the Investigator or by subject decision	Overall study N = 317 (CML-CP/-AP/-BP or Ph+ ALL) Asciminib monotherapy N = 243 (Arm 1: 200; Arm 5: 43) Arm1: CML-CP patients not harboring the T315I mutation N = 115 10 mg BID (n=1), 20 mg BID (n=13), 40 mg BID (n=30), 80 mg BID (n=8), 150 mg BID (n=5), 160 mg BID (n=3), 200 mg BID (10), 80 mg QD (n=17), 120 mg	Adult subjects with CP CML, who have failed or are intolerant to at least two prior TKIs	18 centers in 10 countries

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
			measured by MMR rate by 24 weeks of treatment was the main efficacy endpoint. Secondary efficacy endpoints included hematologic, cytogenetic (MCyR, PCyR etc.), and MR (BCR-ABL transcript level), as well as time to MR and duration of MR. Frequency and severity of AEs following treatment with asciminib as single agent and in combination with either nilotinib or imatinib or dasatinib.		QD (n=17), and 200 mg QD (n=11)		
					Arm 1: CML-CP harboring the T315I mutation (N= = 70 20 mg BID (n=1), 40 mg BID (n=1), 80 mg BID (n=4), 80 mg QD (n=1), 120 mg QD (n=3), and 200 mg QD (n=1), 150 mg BID (n=5), 160 mg BID (n=6), and 200 mg BID (n=48)	Adult patients with CP CML harboring the T315I mutation, treated with asciminib single agent 200 mg BID	

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
			To characterize the safety, tolerability and efficacy of asciminib as single agent in patients with CML-CP/-AP with T315I mutation assessed similar to that of single agent arms as specified above				
Other studies (clinical pharmacological studies)							
CABL001A2101	Single-center, two-arm, four-way cross-over, randomized, open-label study in healthy subjects enrolled to evaluate relative bioavailability and food effect of asciminib following a single oral dose (40 mg) of asciminib	Single oral dose asciminib 40 mg	**Primary**: AUClast, AUCinf, Cmax, Tmax, T1/2, Lambda_z, CL/F, Vz/F **Secondary**: Frequency and severity of AEs	Subjects received a single dose of 40 mg of asciminib during each of the 4 periods	Overall study N=45 Arm1: 22 Arm 2: 23	Healthy subjects	Single center in Germany

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
CABL001A2104	Open-label, single dose, randomized cross-over study in healthy subjects to characterize relative bioavailability of asciminib FMI tablet in comparison to the capsule (fasted)	Single oral dose asciminib 40 mg	**Primary**: AUClast, AUCinf, Cmax, Tmax, Tlast, T1/2, Lambda_z, CL/F, Vz/F **Secondary**: Frequency and severity of AEs	Single oral dose of 40mg asciminib tablet on Day 1. Single oral dose of 40mg asciminib CSF capsule on Day 6	**N=20**	Healthy subjects	Single center in Germany
CABL001A1101	Single-center, open-label, adaptive, three-period, single sequence study in healthy subjects to assess the effect of acid reducing agents on the PK of a single dose (40 mg) of asciminib	Single oral dose of 40mg asciminib tablet on Day 1 of period 1 under fasting conditions and Day 4 of Period 2 Daily oral dose of 20 mg rabeprazole in Period 2, days 1-4	**Primary**: AUClast, AUCinf, Tmax, T1/2, Lambda_z, CL/F, Vz/F **Secondary**: Frequency and severity of AEs	Single oral dose of 40 mg asciminib tablet on Day 1	**N = 23**	Healthy subjects	Single center in Japan

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
CABL001A2102	Single-center, open-label study in healthy subjects to investigate the absorption, distribution, metabolism and excretion (ADME) of asciminib after a single oral dose of 80 mg [^{14}C] labelled asciminib	Single oral dose of asciminib 80 mg powder	**Primary**: [14C]ABL001 recovery, Cmax, Tmax, T1/2, AUClast, AUCinf, Vz/F, CL/F and CLr **Secondary**: Frequency and severity of AEs	Single oral dose of asciminib 80 mg powder on Day 1	**N = 4**	Healthy subjects	Single center in USA
CABL001A2103	Open-label, multi-center, single-dose, study to evaluate the pharmacokinetics of asciminib in healthy subjects with normal hepatic function and subjects with impaired hepatic function	Single oral dose of 40 mg asciminib	**Primary**: AUCinf, AUClast, and Cmax. Other PK parameters: Tmax, T1/2, CL/F, and Vz/F **Secondary**: Frequency and severity of AEs, plasma protein binding as expressed by	Single oral dose of 40 mg asciminib on Day 1	**Total N=32**	Subjects with impaired hepatic function and normal hepatic function	Three centers in USA

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
			unbound fraction in plasma, asciminib PK parameters based on unbound fraction in plasma				
CABL001A2105	Open-label and single-dose study to evaluate the pharmacokinetics and safety of a single 40 mg oral dose of asciminib in subjects with impaired renal function compared to matched control subjects with normal renal function	Single oral dose of 40 mg asciminib	**Primary**: Cmax, AUClast, AUCinf, and CL/F **Secondary**: PK parameters based on unbound fraction in plasma, frequency and severity of AEs	Single oral dose of 40 mg asciminib on Day 1	**Total N=14**	Subjects with impaired renal function and normal renal function	One center each in Bulgaria and Germany
CABL001A2106	Single-center, open-label, fixed-sequence and staged drug-drug interaction study to investigate the	Asciminib 40mg tablet Midazolam syrup for oral use 2 mg/ml Warfarin 5 mg	**Primary**: PK parameters of probe substrates (Cmax, AUClast, AUCinf, and CL/F) **Secondary**: PK	**Stage 1: asciminib in combination with midazolam + warfarin** Period 1: single oral dose of probe drug	**Total N=47**	Healthy subjects	One site in Germany

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
	effect of asciminib on the pharmacokinetics of midazolam (a sensitive CYP3A substrate), warfarin (a sensitive CYP2C9 substrate) and repaglinide (a sensitive CYP2C8 substrate)	tablet Repaglinide 0.5 mg tablet	parameters of metabolites of probe substrates (AUClast, AUCinf, Cmax, Tmax and metabolite-to parent, AUClast and AUCinf ratio) PK parameters of asciminib in healthy volunteers (Cmax, AUClast, AUCinf, CL/F, Vz/F, Tmax, Tlast, Cmin and T1/2) PD parameters of warfarin (PTmax, PTauc, INRmax and INRauc) Safety and tolerability	cocktail - 5mg Warfarin and 4mg midazolam on Day 1 Period 2: asciminib 40mg BID from Day 9, and single oral dose of probe cocktail on Day 11 **Stage 2: asciminib in combination with repaglinide** Period 1: Single oral dose of 0.5mg repaglinide on Day 1 Period 2: Asciminib 40mg BID for 3 days. Repaglinide 0.5 mg oral dose on Day 5			
CABL001A2107	Open label, two-period, single-sequence crossover	Asciminib 40 mg tablet Itraconazole 10	Primary: PK parameters of probe substrates	Total duration of the study (from baseline to end of	**Total N=79**	Healthy subjects	One site in Germany

Trial Identity NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
	DDI study to assess the effect of itraconazole, clarithromycin (strong CYP3A inhibitors), quinidine (P-gp inhibitor) and rifampicin (strong CYP3A inducer) on the PK of asciminib in healthy subjects	mg/mL solution or 100 mg capsule Quinidine 300 mg tablet Rifampicin 300 mg capsule Clarithromycin 500 mg tablet	(Cmax, AUClast, AUCinf, and CL/F)	treatment) for an individual subject in Cohort 1, Cohort 5 or Cohort 6 was approximately 14 days, and in Cohort 2 or Cohort 3 was approximately 12 days. Each cohort had an additional Screening phase of 21 days and Safety phase of 30 days after the last dosing			
CABL001E2101	Open-label, single center, two-group, to evaluate the effects of imatinib and food on the PK of asciminib (FMI formulation) in healthy subjects	Asciminib 40 mg with imatinib 400 mg tablets orally Asciminib 40 mg with food	Primary: PK parameters of probe substrates (Cmax, AUClast, AUCinf)	14 days in the DDI group 18 days in the food-effect group	DDI with imatinib n=23 **Food effect n=24**	Healthy subjects	One site in Germany

The Applicant's Position:

The efficacy claims of asciminib in patients with Ph+ CML-CP previously treated with 2 or more TKIs is primarily based on the results from the primary analysis of the registration Study CABL001A2301. Supportive evidence is provided by the data from a subset of patients with CML-CP not harboring the T315I mutation from Study CABL001X2101.

The efficacy claim of asciminib in patients with Ph+ CML-CP harboring the T315I mutation is based on data from the cohort of CML-CP patients harboring the T315I mutation from the Study CABL001X2101.

The FDA's Assessment:

FDA agrees with the summary of clinical studies presented in Table 3 above. The proposed USPI includes safety and efficacy data from Study CABL001A2301 and Study CABL001X2101. Warnings and Precautions sections of the proposed USPI is based on the Asciminib All Patients Safety Pool (N=356).

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

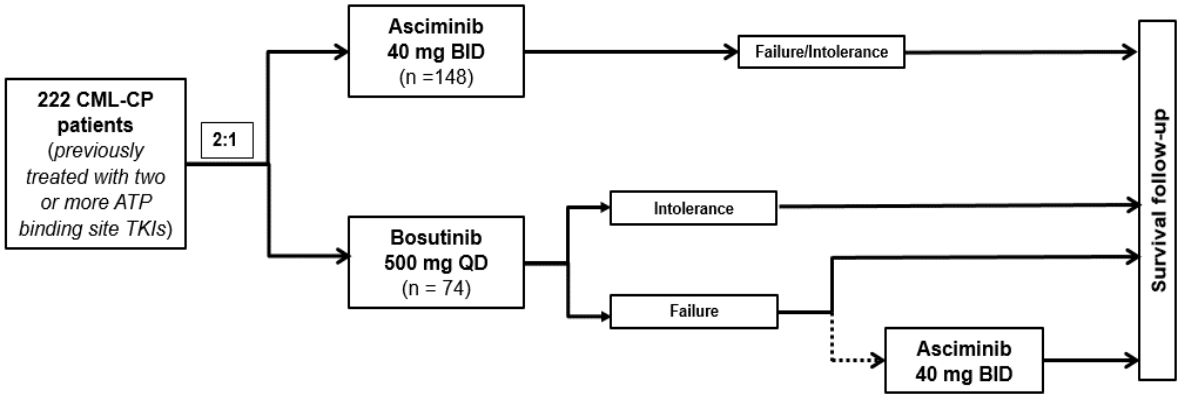
8.1.1. Trial Design – Study CABL001A2301: CML-CP ≥2 prior TKIs

The Applicant's Description:

Overview of study

Study CABL001A2301 is a randomized, open-label, active-controlled multi-center Phase III study to compare the efficacy and safety of asciminib with that of bosutinib in subjects with CML-CP, previously treated with at least 2 prior TKIs. A schematic representation of the study design is presented in Figure 4. Patients with documented treatment failure as per study protocol based on 2013 ELN recommendations (Baccarin et al 2013) were to discontinue study treatment. Patients on bosutinib meeting treatment failure criteria are offered the option to switch to asciminib treatment within 96 weeks after the last patient was randomized on the study. The switch to asciminib is possible only if the investigator considers that this treatment is in the best interest of the patient. Patients intolerant to bosutinib were not allowed to switch to asciminib.

Figure 4: Study design Study CABL001A2301



Trial locations: Overall, patients were enrolled in 87 centers from 25 countries. Those countries were: Japan and United States (10 centers each), Germany (7 centers), France, Spain, Turkey, and United Kingdom (5 centers each), Argentina, Australia, Italy, and Republic of Korea (3 centers each), Brazil and Russian Federation (4 centers each), Bulgaria, Czech Republic, Hungary, Israel, Lebanon, Netherlands, Romania, and Serbia (2 centers each), Canada, Mexico, Saudi Arabia, and Switzerland (1 center each).

Choice of control group: Bosutinib was chosen as the comparator because, in contrast to dasatinib and nilotinib, it was specifically evaluated in patients relapsed or intolerant (R/I) ≥ 2 prior TKIs, and the dose of 500 mg QD was selected as it is the approved dose for ≥ 2 lines (2L) of therapy in CML (Khoury et al 2012, Bosulif USPI).

Diagnostic criteria: The definition of CML-CP was based on European Leukemia Network (ELN) recommendations (Baccarani et al 2013).

Key inclusion/exclusion criteria: Male or female ≥ 18 years of age with a diagnosis of CML-CP, who had received prior treatment with 2 or more ATP binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib), and were treatment failure (as per guidelines adapted from the 2013 ELN recommendations) or intolerant to the most recent TKI were included in this study. Resistance to the most recent TKI was defined based on ELN 2013 recommendations (Baccarani et al 2013):

Intolerance was defined as:

- Non-hematologic intolerance: Patients with Grade 3 or 4 toxicity while on therapy, or with persistent Grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal)
- Hematologic intolerance: Patients with Grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer

As bosutinib has no activity against BCR-ABL1 T315I and V299L mutations, patients who had T315I or V299L mutations documented in their medical records were not eligible for this study. Patients were excluded if they had second chronic phase of CML after previous progression to AP/BP, previous treatment with a hematopoietic stem-cell transplantation, planned allogeneic hematopoietic stem cell transplantation, cardiac or cardiac repolarization abnormality, history of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis, acute or chronic liver disease, significant congenital or acquired bleeding disorder unrelated to cancer.

Dose selection: The asciminib dose in the registration Study CABL001A2301 was 40 mg BID, taken orally on an empty stomach, with no food to be consumed for at least 2 hour before the dose was taken, and for at least 1 hour after the dose was taken. The dose selection is detailed in Section 6.2. Bosutinib needs to be taken with food.

Study treatment and treatment assignment: Patients were assigned to one of the 2 treatment arms (asciminib 40 mg BID or bosutinib 500 mg QD) in a ratio of 2:1. Randomization was stratified by the patients' cytogenetic response status at baseline (with or without major cytogenetic response [MCyR]) to ensure this important prognostic factor for long-term outcome in CML is balanced between the treatment arms.

Considering that there are limited treatment options available for patients enrolled in the study

who met the definition of treatment failure as per the 2013 ELN guidelines (Baccarani et al 2013) on bosutinib, they were offered the option to receive asciminib (Table 21). This did not introduce any bias as patients starting on asciminib after meeting treatment lack of efficacy criteria on bosutinib were regarded as non-responders thereafter irrespective of treatment switch. Patients discontinuing bosutinib for reasons other than lack of efficacy were not allowed to switch to asciminib. The efficacy data was collected from patients who switched to asciminib following the switch due to lack of efficacy with bosutinib was analyzed separately as an exploratory endpoint. These patients were not included for primary and secondary study endpoints. In addition, safety data was collected from patients who received asciminib after lack of efficacy with bosutinib to characterize the safety profile of asciminib.

Blinding: Not applicable. An open-label study design was considered appropriate for this study, due to inherent differences in the conditions for drug administration between the two treatment arms. Randomization and use of objective efficacy endpoints, specifically, primary and key secondary endpoints assessed by central lab determined BCR-ABL1 levels, mitigate the risks of an open label study design.

Dose modification, dose discontinuation: For patients who were unable to tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated to allow the patient to continue study treatment. The criteria for dose modification were based on the dose modification guidelines for each toxicity. For asciminib, a 1-step dose reduction to a total daily dose of 40 mg was allowed, while for bosutinib 2-step sequential dose reductions to a total daily dose of 300 mg were possible.

Dose escalation beyond the standard doses of 40 mg BID for asciminib was not permitted. For bosutinib, dose escalation to 600 mg QD was permitted in patients who were taking 500 mg daily, did not had ≥ Grade 3 AEs and who: did not reach complete hematological response (CHR) by Week 8 or did not reach complete cytogenetic response (CCyR) by Week 12.

Administrative structure: Trial was managed by Novartis and supported by:

- A Steering Committee, consisting of selected investigators and Sponsor representatives, ensuring management of the study in accordance with the protocol.
- An independent data monitoring committee (DMC), comprising two physicians with appropriate disease area qualifications and one statistician. They reviewed the unblinded safety data starting approximately 6 months after the first randomized patient had started study treatment. Subsequent reviews were conducted every 6 months until the primary analysis.

Procedures and schedule:

Efficacy was assessed based on molecular response (MR) in all patients randomized to each treatment arm as well as in patients that switched from bosutinib to asciminib. Levels of BCR-

ABL1 transcripts was determined by real-time quantitative PCR (RQ-PCR) testing of peripheral blood and analyzed at a central testing laboratory. Major molecular response and related variables defined as the follows:

- Rate of Major Molecular Response (MMR) defined as a ≥ 3.0 log reduction in BCR-ABL1 transcripts compared to the standardized baseline equivalent to ≤ 0.1 % BCR-ABL1/ABL%
- Time to MMR defined as the time from the date of randomization to the date of the first documented MMR
- Duration of MMR defined as the time from the date of first documented MMR to the earliest date of loss of MMR and progression to accelerated phase .blast crises C, or CML-related death.

Loss of MMR is defined as increase of BCR-ABL1/ABL to > 0.1% by international scale (IS) in association with a ≥ 5-fold rise in BCR-ABL1 from the lowest value achieved on study treatment. This was confirmed by subsequent sample analysis within 4 to 6 weeks showing loss of MMR associated with a ≥ 5-fold rise in BCR-ABL1 from the lowest value achieved on study treatment, unless it is associated with confirmed loss of CHR or loss of CCyR or progression to AP/BC or CML-related death. Mutational analysis was performed at a Novartis designated laboratory by Sanger sequencing at Week 1 Day 1, upon confirmed loss of MMR and/or at end of treatment. If the result at Week 1 Day 1 is positive for a mutation, analysis was performed every 12 weeks.
In addition the other efficacy assessments included were as follows: cytogenetic response (assessed locally as the percentage of Ph+ metaphases in the bone marrow) and complete hematologic response (CHR). CHR as confirmed if all of these were observed for ≥4 weeks (WBC count <10 x 109/L, Platelet count <450 x 109/L, Basophils <5%, no blasts and promyelocytes in peripheral blood, Myelocytes + metamyelocytes <5% in peripheral blood and no evidence of extramedullary disease, including spleen and liver).
Safety was monitored at every visit by the assessments including physical examination, performance status, vital signs, laboratory evaluations and cardiac assessments (ECG and Echo) as well as collecting of the adverse events.

Dietary restrictions/instructions: There were no specific dietary restrictions. The patients were advised to adhere to the food restrictions during the treatment (fasting status regarding study treatment administration, avoidance of prohibited concomitant medication).

Concurrent medications: In general, the use of any concomitant medication/therapies deemed necessary for the supportive care of the patient were permitted; except as specifically prohibited (see below). Use of drugs that affect gastric pH, anti-emetics, bisphosphonates, and hormonal contraceptives was allowed for patients on asciminib, whereas CYP3A4/5, CYP2C8 and CYP2C9 substrates with narrow therapeutic index, and anticoagulants were allowed with caution. The use of other anticancer drugs, strong CYP3A4/5 inhibitors/ inducers, and strong UGT1A/2B inducers, drugs with a “Known”, “Possible” or “Conditional” risk of Torsades de Pointes , and herbal preparations/medications was prohibited with treatment with asciminib.

With bosutinib, the use of other anticancer drugs, strong or moderate CYP3A inhibitors/inducers,

and pH altering medications was prohibited.

Treatment compliance: Compliance was assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver was captured in the Drug Accountability Form. Records of study treatment administered (total daily dose with start and end date), and any Concomitant Medications and Surgical and Medical procedures were collected in the appropriate eCRF.

Rescue medication: No rescue medication was allowed.

Patient completion, discontinuation, or withdrawal: Patients receive treatment up to the end of study treatment period defined as up to 96 weeks after the last patient received the first study dose or up to 48 weeks after the last patient switches to asciminib treatment from bosutinib whichever is longer, unless subjects discontinue study treatment earlier. Patients are followed for survival, and the end of study will occur 5 years from the date the last randomized patient received his/her first dose. Patients who withdrew from the study were not replaced, regardless of reason for withdrawal.

The FDA's Assessment:
FDA agrees with the Applicant's description of the trial design of the phase 3, CABL001A2301 Study.

Study Endpoints

The Applicant's Description:

Primary and key secondary endpoints: The MMR rate at Week 24 was the primary endpoint in the study, and was agreed with the FDA. MMR (BCR-ABL1 ratio ≤0.1% on the International Scale) is indicative of successful CML treatment, being an established and clinically relevant endpoint (Chopade and Akard 2018, Hochhaus et al 2020, NCCN 2020 v2.2021). Importantly, it has been found that MMR is associated with superior long-term outcomes, including survival and progression-free survival (Hehlmann et al 2017). Therefore, MMR rate at Week 24 was selected as primary endpoint in this study, and MMR rate at Week 96 as key secondary objective to provide durability of response as well as longer follow-up.

Secondary endpoints: MMR rate at all scheduled data collection time points (except at Week 24 and Week 96 which are already covered by primary and key secondary endpoints); MMR rate by all scheduled data collection time points including 24, 48 and 96 weeks, complete cytogenetic response rate (CCyR) at and by all scheduled data collection time points including 24, 48 and 96 weeks, time to and duration of response (MMR and CCyR), time to treatment failure (TTF), progression free survival (PFS), overall survival (OS).

The FDA's Assessment:

FDA agrees with the Applicant's description of the study endpoints of the phase 3, CABL001A2301 Study.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The Statistical Analysis Plan was agreed upon and finalized prior to conduct of any analysis.

Efficacy analysis

The primary endpoint was the MMR rate at Week 24 while on study treatment without meeting any treatment failure criteria prior to 24 weeks. The primary endpoint was further clarified in the analysis plan using the estimand language. The primary clinical question of interest was "is the efficacy of asciminib (40 mg BID) superior to that of bosutinib (500 mg QD) in patients with CML-CP, previously treated with 2 or more TKIs, with regards to achieving MMR at 24 weeks while on study treatment and without meeting any treatment failure criteria prior to 24 weeks, regardless of dose modification, dose interruption, or deviation in intake of concomitant medications".

A patient was counted as having achieved MMR at Week 24 if he/she meets the MMR criterion (BCR-ABL1 ratio ≤0.1%) at Week 24 while on study treatment, unless the patient met any treatment failure criteria prior to Week 24. Patients discontinuing treatment (i.e. having performed an end of treatment visit) prior to 24 weeks due to any reason (e.g. intolerance, treatment failure, death, etc.) and patients meeting any treatment failure criteria based on the European LeukemiaNet [ELN] guidelines prior to Week 24, were considered as non responders at Week 24.

The Cochrane-Mantel-Haenszel (CMH) chi-square test, stratified by the randomization stratification factor (MCyR vs no MCyR at screening), was used to compare MMR rate between the two treatment groups, at the two-sided 5% level of significance. The MMR rate at 24 weeks was presented along with the 95% confidence interval (CI) based on the Clopper-Pearson method. The 95% CI for the difference in MMR rate between treatment groups was provided using the Wald method. The common risk difference and corresponding 95% CI were provided by using the Mantel-Haenszel method.

Various supplementary and sensitivity analyses were performed to assess the overall robustness of the primary efficacy results:

- Supplementary analyses included: primary endpoint analyses in various pre-specified subgroups of patients with important baseline and prognostic characteristics; logistic regression models adjusted for the stratification factor only, and for the stratification factor as well as for other important variables identified by the subgroup analyses were fitted to assess treatment effect; and repeating the CMH chi-square test of MMR rate at Week 24 excluding patients detected with T315I or V299L at Week 1 Day 1 visit.

- Sensitivity analyses included: repeating the CMH chi-square test of MMR rate at Week 24: by the stratum recorded in the CRF (MCyR vs no MCyR at baseline), without the imputation rule used in the main analysis in case of missing PCR evaluations at Week 24, and excluding the patients with planned Week 24 visit after the start date of COVID-19 epidemic.

Handling of missing values/censoring/discontinuations

Patients with missing PCR evaluations at Week 24 were considered as non-responders. However, if the Week 24 PCR evaluation was missing, but both a PCR evaluation at Week 16 and a PCR evaluation at Week 36 indicated MMR, the Week 24 assessment was imputed as a 'Response', assuming that MMR was maintained between 16 and 36 weeks.

Secondary endpoints: MMR and CCyR rate at and by time points: For each time point, the rate and the associated 95% CI based on the Clopper-Pearson method were presented by treatment group. The descriptive p-values obtained via CMH chi-square tests stratified by the randomization strata, were presented and 95% confidence intervals for the differences in any response rates between treatment groups were provided using the Wald method. The Mantel-Haenszel estimate of the common risk difference and the corresponding 95% CI was also provided. The same analysis of the MMR rate was performed using the number of patients with adequate follow-up as the denominator, i.e. for each time point, only patients randomized at least x weeks prior to the cut-off date were considered.

Time to response (MMR and CCyR) was summarized by descriptive statistics and by Kaplan-Meier (K-M) method. An additional analysis of time to MMR was performed, presenting the cumulative incidence of MMR, considering discontinuation from treatment due to any reason, without prior achievement of MMR, as a competing risk.

Duration of MMR/CCyR, TTF, PFS and OS were estimated using the K-M approach. The hazard ratio and 95% CIs were computed from a stratified Cox model.

Safety analysis

All safety analyses were based on the safety set, except the summaries of safety data during the switched treatment period that were based on the switch analysis set. The assessment of safety and tolerability was based mainly on the type, frequency and severity of adverse events (AEs), changes in laboratory values that fell outside the pre-determined ranges, clinically notable ECG, and other safety data. Safety summary tables included "on-treatment" events/assessments, i.e. those collected on or after the first date of study treatment and collected no later than 30 days after the date of last study treatment administration.

Changes to statistical analysis

In Study CABL001A2301, the changes compared to the protocol specified analyses were specified in the clinical study report and are outlined below:

PAS: The condition related to vomiting to consider a concentration evaluable was removed as the occurrence and time of vomiting was not collected in the CRF. Per-Protocol Set (PPS): As the estimand language was implemented for primary and key secondary endpoints analyses, the PPS and analyses based on PPS were removed.

The subgroup considering historical BCR-ABL1 mutations was removed, as it was not considered clinically relevant. Only mutations detected on Week 1 Day 1 were considered in the analyses.

The following analyses were added: ECOG status, time to event analyses for duration of MMR and CCyR, exposure adjusted AE incidence and yearly AE incidence.

Post the data base lock for the primary analysis the following analyses were added:

Analysis of time to MMR considering discontinuation from treatment due to any reason, without prior achievement of MMR as a competing risk and analysis of the MMR rate using the number of subjects with adequate follow-up as the denominator. Protocol deviations during the treatment switch period were reported separately.

Post-hoc exploration of the treatment effect in different subgroups and assessment of the possible effect of differences in distribution of baseline characteristics were conducted.

The COVID-19 pandemic led to changes in the conduct of the study, including replacement of on-site monitoring visits by remote monitoring at some sites, study visit being conducted remotely, home nursing for collection of BCR-ABL1 samples when considered necessary, adjustment of scheduled assessments and procedures, study drug supply method, and following home delivery of study treatment. The statistical analysis plan included a new protocol deviation summary table for COVID-19 related protocol deviations to address the potential impact of COVID-19 pandemic and sensitivity analyses for the primary and key secondary endpoints.

The FDA's Assessment:

In general, randomized open-label trials may be sensitive to differential missing data between the two treatment arms. FDA notes that in this case there were no patients with a missing Week 24 assessment who had both a 16-week and a 36-week assessment indicating MMR, therefore the imputation rule in case of missing PCR evaluations at Week 24 was not used in the primary analysis. Please refer to Section 8.1.2 Study Results – Study CABL001A2301: CML-CP ≥2 prior TKIs: Efficacy Results – Primary Endpoint (Including Sensitivity Analyses). FDA agrees with the Applicant's position.

Protocol Amendments

The Applicant's Description:

The study protocol was amended 3 times. The **key** features of each amendment are in Table 21.

Table 21: Protocol amendments

Version and date	Summary of key changes
Amendment 1 10-Apr-2017	The key purpose of this amendment was to identify the exclusionary mutation correctly, as "V299L" in the protocol, which was inadvertently identified as "V229L" throughout the protocol. In addition some inconsistencies were corrected
Amendment 2 13-Jul-2018	The frequency of bone marrow aspirate to perform cytogenetic analysis was decreased in accordance with treatment guidelines ELN Guidelines and NCCN guidelines. Initially BMAs were foreseen at screening, every 24 weeks thereafter and at EOT. With the protocol amendment BMA was no longer needed for patients that had achieved MMR during study, however, BMA assessment was requested at end of treatment for biomarker analysis
	Based on the identification of pancreas as potential target tissues in the toxicity studies performed in rats, dogs and cynomolgus monkeys, the screening threshold for lipase was increased from ≤ ULN to ≤ 1.5 x ULN (CTCAE v4.03 Grade 1). The requirement of amylase screening was removed, because amylase was not considered as a specific marker for pancreatitis, as up to 60% of total serum amylase originates from non-pancreatic sources.
Amendment 3 14-Dec-2018	For inclusion in the study, the threshold of ≥ 1% BCR-ABL1 was reduced to BCR-ABL1 ratio >0.1% IS for patients with intolerance to most recent TKI treatment.
	With this amendment, only patients on bosutinib meeting lack of efficacy criteria as per 2013 ELN recommendations were offered the possibility to continue in the study by receiving asciminib, if investigators considered that this treatment option was in the best interest of the patient. Patients on bosutinib discontinuing study treatment due to reasons other than lack of efficacy were not switched to asciminib.

The FDA's Assessment:

FDA agrees with the Applicant's description of the amendments of the phase 3, CABL001A2301 Study.

8.1.2. Study Results – Study CABL001A2301: CML-CP ≥2 prior TKIs

Compliance with Good Clinical Practices

The Applicant's Position:

Study CABL001A2301 has been conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) to good clinical practice (GCP). Written informed consent was obtained from each subject or legally acceptable representative of the subject, before conducting any study-specific procedures. The study protocol and all amendments were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

The FDA's Assessment:
FDA confirms the Applicant's position.

Financial Disclosure

The Applicant's Position:

Novartis has adequately disclosed any financial interests/arrangements with clinical investigators in accordance with the guidance for industry. Details of financial disclosure are presented in Appendix 19.2.

The FDA's Assessment:
A summary of the financial disclosure information is presented in Appendix 19.2. Five investigators at 5 sites had financial disclosures for research and grant support, lecture fees, review fees, manuscript fees, and guidance fees. Investigators at these sites enrolled 8 patients. With the small number of patients enrolled at any site, the enrollment of patients by these investigators is not expected to bias the outcome of the study results.

Patient Disposition

The Applicant's Position:

Overall, 233 patients with CML-CP were enrolled to Study CABL001A2301, of which, 157 patients were randomized to asciminib treatment arm and 76 patients to bosutinib treatment arm. The primary efficacy analysis was based on the FAS that included all randomized patients. Patients were analyzed according to the treatment and stratum assigned at randomization. One patient (in the asciminib arm) was excluded from the Safety set; this patient developed cytopenia after randomization and subsequently did not receive study treatment per Investigator's decision.

At the data cut-off date (25-May-2020, when all randomized patients had achieved Week 24 visit or discontinued before), twice as many patients were ongoing in the asciminib arm (61.8%) relative to the bosutinib arm (28.9%), supportive of a better efficacy and tolerability of asciminib. Overall, discontinuations in both treatment arms were predominantly due to lack of efficacy, followed by AEs and physician decision, although all were less frequent in the asciminib arm relative to the bosutinib arm (lack of efficacy: 21.0% vs. 31.6%; AE(s): 5.1% vs. 21.1%; physician decision: 6.4% vs. 7.9%). Twenty-two patients (28.9%) randomized to bosutinib switched to asciminib treatment after meeting lack of efficacy criteria as per protocol.

The FDA's Assessment:

FDA confirms the Applicant's position. The Applicant explains that one patient in the asciminib arm was not included in the safety set as the investigator excluded this patient because of development of cytopenias after randomization.

Patients with T315I and V299L were not eligible for this study; however, 5 patients (3 in the asciminib arm and 2 in the bosutinib arm) had such mutation on central mutation testing on Week 1, Day 1. These patients were discontinued from the study, but retained in the ITT population as non-responders.

Protocol Violations/Deviations

Data

Table 22: Protocol deviations during randomized treatment period (Study CABL001A2301) (FAS)

Category	Asciminib N=157 n (%)	Bosutinib N=76 n (%)	All patients N=233 n (%)
Any protocol deviation	**111 (70.7)**	**43 (56.6)**	**154 (66.1)**
Other deviation	90 (57.3)	29 (38.2)	119 (51.1)
Treatment deviation	48 (30.6)	25 (32.9)	73 (31.3)
Prohibited concomitant medication	22 (14.0)	8 (10.5)	30 (12.9)
Exclusion criteria not met	13 (8.3)	2 (2.6)	15 (6.4)
Inclusion criteria not met	12 (7.6)	2 (2.6)	14 (6.0)
Patient not withdrawn as per protocol	7 (4.5)	3 (3.9)	10 (4.3)

Source: Novartis Study CABL001A2301 - CSR Table 14.1-2.1.1

Table 23: Protocol deviations with COVID-19 relationship (Study CABL001A2301) (FAS)

Category	Asciminib N=157 n (%)	Bosutinib N=76 n (%)	All patients N=233 n (%)
Any protocol deviation	45 (28.7)	16 (21.1)	61 (26.2)
Other deviation	44 (28.0)	15 (19.7)	59 (25.3)
Treatment deviation	33 (21.0)	12 (15.8)	45 (19.3)

Start date of COVID-19 pandemic: China: 01-Jan-2020; South Korea: 20-Feb-2020; Japan: 21-Feb-2020; Italy: 23-Feb-2020; and Rest of World: 01-Mar-2020
Source: Novartis Study CABL001A2301 - CSR Table 14.1-2.1.2

The Applicant's Position

Overall, protocol deviations were reported in 66.1% of patients; the proportion of patients with protocol deviations was higher in the asciminib arm (70.7%) compared to the bosutinib arm (56.6%) (Table 20), which may be explained by a longer duration on study treatment in patients randomized to asciminib compared to bosutinib (median 43.36 weeks vs. 29.21 weeks). Protocol deviations specific to the COVID-19 pandemic were reported in 61 patients (26.2%) with no significant imbalance between the two treatment arms (Table 21).

The most frequently reported protocol deviation category corresponded to 'Other deviations' driven by those with COVID-19 relationship. Treatment deviations (related to study medication guidelines not met) and use of prohibited medications were relatively similar between treatment arms. Upon review, no safety issue was identified. Training on study medication guidelines, and prohibited medications was given to the sites.

The protocol deviation 'Patient Not Withdrawn as Per Protocol' was observed at a similar frequency in patients on asciminib and bosutinib. Patients enrolled in Study CABL001A2301 are in high medical need of treatment as more than half of them entered the study with the randomized treatment being the 4th or greater line of therapy. For some patients, limited treatment options existed outside of the study and Investigators considered they were deriving clinical benefit despite meeting treatment failure criteria as per protocol and continued them in the study. However, efficacy data collected after meeting treatment failure criteria were not used in any efficacy analyses. On the contrary, all safety data were included in the analyses of safety.

The protocol deviations observed have no impact on the reliability of the study results nor on the safety of the patients in this study.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Protocol deviations were more frequent in the asciminib arm compared to the bosutinib arm which might be explained by the longer duration on treatment in the asciminib arm. Protocol deviations due to COVID-19 were also more frequent in the asciminib arm. The protocol deviations were unlikely to bias the study in favor

of the study drug. Therefore, all patients, including those with important protocol deviations, were included in our analysis of efficacy endpoints.

Table of Demographic Characteristics

Data

Table 24: Demographic summary (Study CABL001A2301) (FAS)

Demographic variable	Asciminib N=157	Bosutinib N=76	All patients N=233
Age (years)			
n	157	76	233
Mean (SD)	51.0 (13.49)	51.0 (13.95)	51.0 (13.61)
Median	52.0	52.0	52.0
Min-Max	24-83	19-77	19-83
Age category - n (%)			
18 - < 65 years	128 (81.5)	61 (80.3)	189 (81.1)
65 - < 75 years	25 (15.9)	13 (17.1)	38 (16.3)
≥ 75 years	4 (2.5)	2 (2.6)	6 (2.6)
< 65 years	128 (81.5)	61 (80.3)	189 (81.1)
≥ 65 years	29 (18.5)	15 (19.7)	44 (18.9)
Sex - n (%)			
Female	75 (47.8)	45 (59.2)	120 (51.5)
Male	82 (52.2)	31 (40.8)	113 (48.5)
Race - n (%)			
White	118 (75.2)	56 (73.7)	174 (74.7)
Asian	22 (14.0)	11 (14.5)	33 (14.2)
Black or African American	8 (5.1)	2 (2.6)	10 (4.3)
American Indian or Alaska Native	1 (0.6)	0	1 (0.4)
Other	5 (3.2)	7 (9.2)	12 (5.2)
Unknown	3 (1.9)	0	3 (1.3)
Ethnicity - n (%)			
Hispanic or Latino	15 (9.6)	17 (22.4)	32 (13.7)
Not Hispanic or Latino	102 (65.0)	43 (56.6)	145 (62.2)
Not Reported	23 (14.6)	11 (14.5)	34 (14.6)
Unknown	17 (10.8)	5 (6.6)	22 (9.4)
Body mass index (kg/m^2)			
n	152	76	228
Mean (SD)	27.9 (6.52)	27.4 (7.16)	27.7 (6.73)
Median	26.7	25.8	26.3

Demographic variable	Asciminib N=157	Bosutinib N=76	All patients N=233
Min-Max	18-74	18-68	18-74
ECOG performance status - n (%)			
0	126 (80.3)	62 (81.6)	188 (80.7)
1	28 (17.8)	14 (18.4)	42 (18.0)
2	2 (1.3)	0	2 (0.9)
Missing	1 (0.6)	0	1 (0.4)

Source: Novartis Study CABL001A2301 - CSR Table 14.1-4.1

The Applicant's Position:

The two treatment arms in Study CABL001A2301 were well balanced for the demographic characteristics assessed, apart from differences observed in ethnicity and sex. There were fewer Hispanic/Latino patients in the asciminib arm (9.6%) compared to the bosutinib arm (22.4%). The proportion of males was higher in the asciminib arm (52.2%) compared to the bosutinib arm (40.8%) (Table 22).

Of the 233 patients randomized, the largest country enrollments were for the Russian Federation (n = 33, 14.2%), United States of America (n = 22, 9.4%), Brazil (n = 19, 8.2%), Germany (n = 18, 7.7%), France (n = 17, 7.3%), and Japan (n = 16, 6.9%).

The FDA's Assessment:

FDA agrees with the Applicant's assessment. FDA notes that Black or African American patients are significantly underrepresented compared to the population of the US. In addition, majority of study subjects are enrolled in non-US sites. These demographics are sufficient to be generalizable to the US population.

Demographics were generally well balanced between arms except sex and ethnicity. There were more males and less Hispanic or Latino patients in the asciminib arm. These differences are unlikely to influence the outcome of the study.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data

Table 25: Prior antineoplastic therapy (Study CABL001A2301) (FAS)

Characteristic	Asciminib N=157 n (%)	Bosutinib N=76 n (%)	All patients N=233 n (%)
Prior TKIs - n (%)			
Dasatinib	131 (83.4)	65 (85.5)	196 (84.1)
Imatinib	130 (82.8)	63 (82.9)	193 (82.8)
Nilotinib	104 (66.2)	56 (73.7)	160 (68.7)

Characteristic	Asciminib N=157 n (%)	Bosutinib N=76 n (%)	All patients N=233 n (%)
Ponatinib	23 (14.6)	18 (23.7)	41 (17.6)
Other	5 (3.2)	4 (5.3)	9 (3.9)
Radotinib	4 (2.5)	2 (2.6)	6 (2.6)
Number of lines of prior TKI therapy - n (%)			
2	82 (52.2)	30 (39.5)	112 (48.1)
3	44 (28.0)	29 (38.2)	73 (31.3)
4	24 (15.3)	10 (13.2)	34 (14.6)
≥ 5	7 (4.5)	7 (9.2)	14 (6.0)
Reason to discontinue last TKI - n (%)			
Lack of efficacy	95 (60.5)	54 (71.1)	149 (63.9)
Lack of tolerability	59 (37.6)	22 (28.9)	81 (34.8)
Other	3 (1.9)	0	3 (1.3)

Prior TKIs starting and completing prior to start of the study treatment are summarized.
Last TKI is based on start date of first dose.
Source: Novartis Study CABL001A2301 - CSR Table 10-9

The Applicant's Position:

Baseline disease characteristics

Overall, the heavily pre-treated patients enrolled in this study (Study CABL001A2301) reflect the broad population of patients with Ph+ CML in CP, previously treated with two or more TKIs, and are relevant to the indication sought (Table 23).

Disease histories were well balanced across treatment arms, with the exception of prior lines of TKI treatment, reasons of discontinuation of prior treatment and prior TKIs received:

The imbalances noted at baseline did not have any impact on the primary endpoint of the study as shown by the multivariate analysis performed (see below).

The FDA's Assessment:

FDA agrees with the Applicant's position. Although the percentages of patients who used dasatinib and imatinib were similar in both arms, the percentages of patients who used nilotinib and ponatinib were higher in the bosutinib arm. Patients in the asciminib arm had fewer prior lines of therapy compared to the bosutinib arm. More patients in the asciminib arm discontinued their prior TKI therapy because of lack of tolerability and less patients because of lack of efficacy. These differences in baseline disease characteristics could bias the results towards higher responses in the asciminib arm; however, these differences are relatively small and are unlikely to have a significant impact on the primary endpoint of the study. Subgroup analyses based on baseline disease characteristics were performed to evaluate the potential impact.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment compliance

Total daily dose of study treatment administered with start and end date was collected on the Dosage Administration Record CRf page.

The planned dose on asciminib was 40 mg BID and on bosutinib 500 mg QD. The median dose intensities were 79.8 mg/day (min-max: 33-80) and 478.6 mg (min-max: 181-566) for the asciminib and bosutinib treatment groups, respectively. Overall, 71.2% of patients had a relative dose intensity (RDI) of > 90 to 110% in the asciminib treatment group compared to 59.2% in the bosutinib treatment group. Dose interruptions, dose reductions, and permanent discontinuations were less frequent in the asciminib treatment group compared with the bosutinib treatment group. The dose adjustments were primarily due to AEs.

Concomitant medication

Overall, concomitant medications to treat ongoing conditions at study entry or adverse events requiring additional therapy were reported in 86.5% of patients in the asciminib arm compared to 96.1% of patients in the bosutinib arm. The concomitant medications by ATC class which were reported more frequently in the bosutinib arm relative to asciminib arm (with a ≥ 10% relative difference) included: alimentary tract and metabolism (65.4% in the asciminib arm vs. 82.9% in the bosutinib arm), systemic hormonal preparations, excl sex hormones and insulins (14.1% vs. 26.3%). In contrast, medications belonging to musculo-skeletal system (46.2% vs. 26.3%), anti-infectives for systemic use (36.5% vs. 22.4%) were reported more frequently in the asciminib arm compared to bosutinib arm.

Rescue medication

No rescue medication was allowed.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. FDA analysis revealed a median dose intensity of 417 mg (min-max: 27-566) for bosutinib which likely reflects higher dose interruptions and reductions in the bosutinib arm, and may reduce efficacy in the bosutinib arm with a planned dose of 500 mg daily. However, similar dose intensity is reported in the bosutinib prescribing information for the CML-CP population, and is reflected in the expected efficacy.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 9: MMR rate at Week 24 (Study CABL001A2301) (FAS)

	Asciminib N=157	Bosutinib N=76
Response - n (%)	40 (25.48)	10 (13.16)
95% CI for response [1]	(18.87, 33.04)	(6.49, 22.87)
Unstratified difference in response rate (vs. bosutinib) (%)	12.32	
95% CI for difference in response rate [2]	(2.11, 22.53)	
Common risk difference (%) [3]	12.24	
95% CI for difference	(2.19, 22.30)	
CMH test p-value [4]	0.029	

[1] -Clopper-Pearson 95% 2-sided CI.
[2] Wald 95% 2-sided CI.
[3] The common risk difference after adjusting for stratum: baseline major cytogenetic response status (based on randomization data) and its 95% CI were estimated using the Mantel-Haenszel method.
[4] CMH 2-sided test was stratified by baseline major cytogenetic response status (based on randomization data).
Source: Novartis Study CABL001A2301- CSR Table 14.2-1.1

The Applicant's Position:

This study met its primary objective. Superiority was demonstrated for asciminib 40 mg BID relative to bosutinib 500 mg QD for the primary endpoint of MMR at 24 weeks while on study treatment without meeting any treatment failure criteria before Week 24. The MMR rate at Week 24 was almost twice as high (25.5%) in the asciminib arm compared to the bosutinib arm (13.2%). This treatment difference in MMR rate at Week 24 is both statistically significant and clinically meaningful in this heavily pretreated population: 12.2% (95% CI: 2.19, 22.30, two-sided p-value: 0.029) (per the Cochran–Mantel–Haenszel two-sided test, stratified by the MCyR status at baseline) (Table .

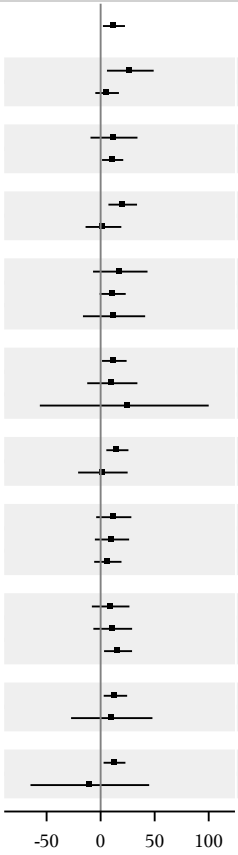
Supportive analyses: Supplementary and sensitivity analyses

Subgroup analysis

A homogeneous and consistent treatment effect in MMR at Week 24 was observed across all the subgroups assessed, supporting the benefit of asciminib over bosutinib across the variables analyzed and, most importantly, across those behaving as strong predictors of response such as baseline cytogenetic response, and number of prior lines of TKI therapy (Figure 5). The MMR rate at Week 24 was also higher in patients on asciminib regardless of the detection of BCR-ABL1 mutations at baseline. This further supports the superior clinical benefit of asciminib over bosutinib considering that mutations are a common cause of TKI resistance in patients sequentially treated with different TKIs targeting the ATP-binding site (Soverini et al 2014, Jabbour et al 2013).

Figure 5: Forest plot of risk difference with 95% confidence interval for MMR rate at 24 weeks from subgroup analysis (Study ABL011A2301) (FAS)

Subgroup	Asciminib n/N (%)	Bosutinib n/N (%)	Risk difference (95% CI)
All subjects	40/157 (25.5)	10/76 (13.2)	12.3 (2.1 to 22.5)
Strata based on randomization data			
Major cytogenetic response	21/46 (45.7)	4/22 (18.2)	27.5 (5.9 to 49.1)
No major cytogenetic response	19/111 (17.1)	6/54 (11.1)	6.0 (-4.9 to 16.9)
Strata based on CRF data			
Major cytogenetic response	23/57 (40.4)	7/25 (28.0)	12.4 (-9.4 to 34.1)
No major cytogenetic response	17/100 (17.0)	3/51 (5.9)	11.1 (1.3 to 20.9)
Sex			
Female	22/75 (29.3)	4/45 (8.9)	20.4 (7.2 to 33.7)
Male	18/82 (22.0)	6/31 (19.4)	2.6 (-13.9 to 19.1)
Race			
Asian	6/22 (27.3)	1/11 (9.1)	18.2 (-7.0 to 43.4)
White	30/118 (25.4)	8/56 (14.3)	11.1 (-0.9 to 23.2)
Others	4/17 (23.5)	1/9 (11.1)	12.4 (-16.4 to 41.2)
Age category			
18-65 years	33/128 (25.8)	8/61 (13.1)	12.7 (1.3 to 24.0)
≥ 65 years	7/29 (24.1)	2/15 (13.3)	10.8 (-12.4 to 34.0)
≥ 75 years	3/4 (75.0)	1/2 (50.0)	25.0 (-56.3 to 100.0)
Reason for disc. of the last prior TKI			
Failure	20/95 (21.1)	3/54 (5.6)	15.5 (5.3 to 25.7)
Intolerance	20/59 (33.9)	7/22 (31.8)	2.1 (-20.8 to 25.0)
Number of prior TKI therapies			
2	27/89 (30.3)	6/33 (18.2)	12.2 (-4.1 to 28.4)
3	12/53 (22.6)	4/33 (12.1)	10.5 (-5.3 to 26.4)
≥ 4	1/15 (6.7)	0/10 (0.0)	6.7 (-6.0 to 19.3)
Line of therapy of randomized treatment			
3	24/82 (29.3)	6/30 (20.0)	9.3 (-8.1 to 26.6)
4	11/44 (25.0)	4/29 (13.8)	11.2 (-6.7 to 29.1)
≥ 5	5/31 (16.1)	0/17 (0.0)	16.1 (3.2 to 29.1)
BCR-ABL1 mutation at day 1 of week 1			
Unmutated	31/125 (24.8)	7/63 (11.1)	13.7 (2.8 to 24.5)
Mutated	6/17 (35.3)	2/8 (25.0)	10.3 (-27.3 to 47.9)
BCR-ABL1 transcript level (IS) at basel.			
≥ 1%	34/142 (23.9)	8/72 (11.1)	12.8 (2.7 to 22.9)
< 1%	6/15 (40.0)	2/4 (50.0)	-10.0 (-64.9 to 44.9)



Source: Novartis Study CABL001A2301 - CSR Figure 14.2-1.3

Multivariate analysis

The treatment effect after adjusting for important demographic and prognostic factors between treatment arms was assessed by logistic regressions. The results indicate a consistent treatment effect, independent of the demographic and prognostic variables tested, including those that were imbalanced between treatment arms at baseline (less females in the asciminib arm, more patients intolerant to their prior TKI in the asciminib arm and patients in the asciminib arm were less heavily pre-treated) (Table 10).

Table 10: Odds ratio of MMR at 24 weeks adjusted for stratification factor and other important variables (Study CABL001A2301) (FAS)

	Adjusted for stratification factor (MCyR)[1]	
	Based on randomization data Odds ratio (95% CI)	**Based on CRF data Odds ratio (95% CI)**
Treatment		
Asciminib vs. bosutinib	2.35 (1.08, 5.12)	2.27 (1.04, 4.96)
Adjusted for stratification factor (MCyR) and other important variables[2]		
Treatment		
Asciminib vs. bosutinib	2.38 (1.06, 5.35)	2.37 (1.04, 5.37)
Strata		
MCyR vs. No MCyR	3.07 (1.53, 6.16)	3.81 (1.90, 7.66)
Sex		
Female vs. Male	1.54 (0.77, 3.10)	1.69 (0.83, 3.45)
Line of therapy of randomized treatment		
4 vs. 3	0.75 (0.35, 1.60)	0.69 (0.32, 1.49)
≥ 5 vs. 3	0.27 (0.09, 0.80)	0.26 (0.09, 0.78)
Reason for discontinuation of last prior TKI		
Intolerance vs. failure	2.48 (1.23, 5.01)	2.69 (1.33, 5.44)

[1]The adjusted odds ratio was obtained by a logistic regression including treatment and the stratification factor (based on randomized data and CRF data) as main effects.
[2]The odds ratio was obtained by a logistic regression including treatment, baseline major cytogenetic response status (based on randomized data and CRF data) and important variables identified for subgroup analyses (line of therapy of randomized treatment, reason for discontinuation of the last prior TKI, sex) as main effects
Source: Novartis Study CABL001A2301 - CSR Table 11-2

MMR rate at Week 24 excluding patients with T315I or V299L mutation at Week 1 Day 1
Patients with T315I or V299L BCR-ABL1 mutations were not eligible in the study. However, the mutation analysis performed at Week 1 Day 1 visit revealed five patients with these mutations. As per protocol, these patients were discontinued from the study and considered as non-responders in the primary analysis. The results from the analysis of the primary endpoint in patients without those mutations are consistent with those from the primary analysis (Table

Table 11: MMR rate at 24 weeks – excluding patients with T315I or V299L mutations at Week 1 Day 1 (Study CABL001A2301) (FAS)

		Asciminib N=157	**Bosutinib N=76**
Number of patients included in the analysis		**154**	**74**
	Response - n (%)	40 (25.97)	10 (13.51)
	95% CI for response [1]	(19.25, 33.65)	(6.68, 23.45)

		Asciminib N=157	Bosutinib N=76
	Unstratified difference in response rate (vs. bosutinib) (%)	12.46	
	95% CI for difference in response rate [2]	(2.04, 22.88)	
	Common risk difference (%) [3]	12.43	
	95% CI for difference	(2.15, 22.71)	
	CMH test p-value [4]	0.030	

[1] Clopper- Pearson 95% 2-sided CI for response rate
[2] Wald 95% 2-sided CI.
[3] The common risk difference after adjusting for stratum: baseline major cytogenetic response status (based on randomized data) and its 95% CI were estimated using the Mantel-Haenszel method.
[4] CMH 2-sided test was stratified by baseline major cytogenetic response status (based on randomization data).
Source: Novartis Study CABL001A2301 - CSR Table 11-3

Sensitivity analysis

Results of the predefined sensitivity analyses demonstrated consistency with the primary results thereby confirming their robustness (Table 26).

Table 26: Sensitivity analyses of MMR rate at 24 weeks (Study CABL001A2301) (FAS)

		Asciminib N=157	Bosutinib N=76
By stratum recorded in the CRF	**Response - n (%)**	**40 (25.48)**	**10 (13.16)**
	95% CI for response [1]	(18.87, 33.04)	(6.49, 22.87)
	Unstratified difference in response rate (vs. bosutinib) (%)	12.32	
	95% CI for difference in response rate [2]	(2.11, 22.53)	
	Common risk difference (%) [3]	11.54	
	95% CI for difference	(1.73, 21.34)	
	CMH test p-value [4]	0.037	
Missing PCR evaluations - without the imputation rule	Response - n (%)	40 (25.48)	10 (13.16)
	95% CI for response [1]	(18.87, 33.04)	(6.49, 22.87)
	Unstratified difference in response rate (vs. bosutinib) (%)	12.32	
	95% CI for difference in response rate [2]	(2.11, 22.53)	
	Common risk difference (%) [5]	12.24	
	95% CI for difference	(2.19, 22.30)	
	CMH test p-value [6]	0.029	

	Asciminib N=157	Bosutinib N=76

[1] Clopper-Pearson 95% 2-sided CI for response rate
[2] Wald 95% 2-sided CI.
[3] The common risk difference after adjusting for stratum: baseline major cytogenetic response status (based on CRF data) and its 95% CI were estimated using the Mantel-Haenszel method.
[4] CMH 2-sided test was stratified by baseline major cytogenetic response status (based on CRF data).
[5] The common risk difference after adjusting for stratum: baseline major cytogenetic response status (based on randomized data) and its 95% CI were estimated using the Mantel-Haenszel method.
[6] CMH 2-sided test was stratified by baseline major cytogenetic response status (based on randomization data).
Source: Novartis Study CABL001A2301 - CSR Table 11-4

Further, the results from the sensitivity analysis excluding patients (29 patients in the asciminib arm and 13 patients in the bosutinib arm) with a planned Week 24 visit after the start of the COVID-19 pandemic were consistent with the results from the primary analysis.

The FDA's Assessment:

Based on FDA's assessment, the results from Study CABL001A2301 showed that the MMR rate at Week 24 in the asciminib arm was 25% (95% CI: 19, 33) compared to that in the bosutinib arm 13% (95% CI: 6.5, 23). The treatment difference in MMR rate at Week 24 was 12% (95% CI: 2.2, 22; two-sided p-value: 0.029 per the Cochran–Mantel–Haenszel test, stratified by the MCyR status at baseline). These results are identical to those that the applicant presented in Section Efficacy Results below (i.e., Table 27: MMR rate at and by scheduled time points (Study CABL001A2301) (FAS)). FDA was able to replicate the Applicant's results for the sensitivity analyses and subgroup analyses. These analyses generally supported the finding that the MMR rate at Week 24 was higher in the asciminib arm than that in the bosutinib arm.

Data Quality and Integrity

The Applicant's Position:

No data integrity concerns were reported following completion of site inspections.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Efficacy Results – Secondary and other relevant endpoints

Data

Major molecular response

Table 27: MMR rate at and by scheduled time points (Study CABL001A2301) (FAS)

	At time points		By time points	
	Asciminib N=157	**Bosutinib N=76**	**Asciminib N=157**	**Bosutinib N=76**
Week 4				
Response - n (%)	3 (1.91)	0 (0.00)	3 (1.91)	0 (0.00)
95% CI for response[1]	(0.40, 5.48)	(0.00, 4.74)	(0.40, 5.48)	(0.00, 4.74)
Unstratified difference in response rate (vs. bosutinib) (%)	1.91		1.91	
95% CI for difference in response rate[2]	(-0.23, 4.05)		(-0.23, 4.05)	
Common risk difference (%)[3]	1.90		1.90	
95% CI for difference	(-0.24, 4.03)		(-0.24, 4.03)	
CMH test p-value[4]	0.224		0.224	
Week 8				
Response - n (%)	12 (7.64)	4 (5.26)	12 (7.64)	4 (5.26)
95% CI for response[1]	(4.01, 12.97)	(1.45, 12.93)	(4.01, 12.97)	(1.45, 12.93)
Unstratified difference in response rate (vs. bosutinib) (%)	2.38		2.38	
95% CI for difference in response rate[2]	(-4.14, 8.90)		(-4.14, 8.90)	
Common risk difference (%)[3]	2.34		2.34	
95% CI for difference	(-4.08, 8.77)		(-4.08, 8.77)	
CMH test p-value[4]	0.501		0.501	
Week 12				
Response - n (%)	28 (17.83)	7 (9.21)	30 (19.11)	7 (9.21)
95% CI for response[1]	(12.19, 24.73)	(3.78, 18.06)	(13.28, 26.14)	(3.78, 18.06)
Unstratified difference in response rate (vs. bosutinib) (%)	8.62		9.90	
95% CI for difference in response rate[2]	(-0.21, 17.46)		(0.95, 18.85)	
Common risk difference (%)[3]	8.58		9.85	
95% CI for difference	(-0.18, 17.34)		(1.00, 18.69)	
CMH test p-value[4]	0.083		0.051	
Week 16				
Response - n (%)	36 (22.93)	8 (10.53)	39 (24.84)	8 (10.53)
95% CI for response[1]	(16.61, 30.30)	(4.66, 19.69)	(18.30, 32.36)	(4.66, 19.69)
Unstratified difference in response rate (vs. bosutinib) (%)	12.40		14.31	
95% CI for difference in response rate[2]	(2.87, 21.93)		(4.66, 23.97)	
Common risk difference (%)[3]	12.33		14.25	
95% CI for difference	(2.90, 21.75)		(4.68, 23.81)	
CMH test p-value[4]	0.021		0.010	

	At time points		By time points	
	Asciminib N=157	**Bosutinib N=76**	**Asciminib N=157**	**Bosutinib N=76**
Week 24				
Response - n (%)	40 (25.48)	10 (13.16)	43 (27.39)	11 (14.47)
95% CI for response[1]	(18.87, 33.04)	(6.49, 22.87)	(20.58, 35.07)	(7.45, 24.42)
Unstratified difference in response rate (vs. bosutinib) (%)	12.32		12.91	
95% CI for difference in response rate[2]	(2.11, 22.53)		(2.37, 23.46)	
Common risk difference (%)[3]	12.24		12.85	
95% CI for difference	(2.19, 22.30)		(2.40, 23.29)	
CMH test p-value[4]	0.029		0.027	

[1] Clopper-Pearson 95% 2-sided CI.
[2] Wald 95% 2-sided CI.
[3] The common risk difference after adjusting for stratum: major baseline cytogenetic response status (based on randomization data) and its 95% CI were estimated using the Mantel-Haenszel method.
[4] CMH 2-sided test was stratified by baseline major cytogenetic response status based on randomization data. Nominal p-values are presented for descriptive purpose only.
Source: Novartis Study CABL001A2301 - CSR Table 11-5

The Applicant's Position:

At each scheduled time point, the MMR rate was higher for the asciminib arm compared to the bosutinib arm, with relevant differences starting to be noted from Week 12 onwards (Table 25). Data beyond Week 24 were not mature; however, trends in favor of asciminib were consistently observed. For each later time point beyond Week 24, when considering the number of patients with adequate follow-up, the MMR rate was higher for the asciminib arm at each specific time point (at Week 36: 29.13% vs. 9.68% in the bosutinib arm; at Week 48: 29.36% vs. 11.11%, at Week 60: 30.59% vs. 11.63%, and at Week 72: 34.78% vs. 11.43%). By the data cut-off, the cumulative MMR rate was 34.4% in patients on asciminib and 18.4% in patients on bosutinib.

Time to MMR and duration of MMR

Time to MMR adjusting for competing risk: The probability of achieving MMR by Week 24 was 25.0% (95% CI: 18.5, 32.0) and 12.0% (95% CI: 5.8, 20.5) in the asciminib arm and the bosutinib arm, respectively.

Time to MMR: Among patients, who achieved MMR, median time to MMR was 12.7 weeks asciminib arm and 14.3 weeks in bosutinib arm.

Duration of MMR: The majority of patients who achieved MMR continued to have MMR (51/54; 94.4%) at the time of their last molecular assessment in the asciminib arm. The KM estimated proportion of patients maintaining their MMR for at least 24 weeks was 95.4% (95% CI: 82.8, 98.8) in the asciminib arm vs 100.0% (95% CI: NE, NE) in the bosutinib arm and the KM estimated median of the duration of MMR has not been reached for both arms.

BCR-ABL ratio categories at Week 24

At Week 24, patients in the asciminib arm showed deeper responses as compared with patients on bosutinib. BCR-ABL1 IS ≤ 0.01% (MR4 or better) was observed in 10.8% of patients on asciminib and on 5.3% of patients on bosutinib with majority on asciminib achieving MR4.5 (8.9% vs 1.3%). The percentage of patients on asciminib with BCR-ABL1 IS ≤ 1% at Week 24 was higher than that observed in patients on bosutinib (49.0% vs 23.7%); regardless of the BCR-ABL1 IS baseline level (Table 28). When only patients with BCR-ABL1 IS >1% at baseline were included in the analysis (142 in the asciminib arm and 72 in the bosutinib arm), the percentage of patients with BCR-ABL1 IS ≤ 1% at Week 24 was 44.37% in the asciminib arm and 20.83% in the bosutinib arm showing a clinically relevant difference of 23.92%.

Table 28: BCR-ABL1 ratio (% IS) categories at 24 weeks (Study CABL001A2301) (FAS)

Category	Asciminib N=157 n (%)	Bosutinib N=76 n (%)
≤0.0032%	14 (8.9)	1 (1.3)
>0.0032% - ≤ 0.01%	3 (1.9)	3 (3.9)
>0.01% - ≤ 0.1%	23 (14.6)	6 (7.9)
>0.1% - ≤ 1%	37 (23.6)	8 (10.5)
>1% - ≤ 10%	21 (13.4)	12 (15.8)
>10%	23 (14.6)	17 (22.4)
Missing	36 (22.9)	29 (38.2)
Ongoing without treatment failure	4 (2.5)	4 (5.3)
Ongoing with treatment failure	9 (5.7)	3 (3.9)
Discontinued due to lack of efficacy/progressive disease/death	7 (4.5)	7 (9.2)
Discontinued due to other reasons	16 (10.2)	15 (19.7)

Source: Novartis Study CABL001A2301 - CSR Table 11-7

Cytogenetic response rate (CCyR)

CCyR rate at and by scheduled time points: The CCyR rates at Week 24 and by Week 24 (based on patients who were not in CCyR at baseline) were both 40.8% in the asciminib arm compared to 24.2% in the bosutinib arm. The treatment difference in the CCyR rate was 17.3% (95% CI: 3.62, 30.99, nominal p-value= 0.019). By the cut-off, CCyR rates were 42.7% in the asciminib arm and 30.7% in the bosutinib arm.

Time to CCyR: Time to CCyR among patients who achieved CCyR was the same between the two treatment arms, with medians of approximately 24 weeks. When interpreting time to CCyR it is important to consider that the scheduled assessments may have influenced on the results. Bone

marrow was assessed at screening and after that every 24 weeks up to Week 96. Consequently, no patient can be in CCyR before Week 24.

Duration on CCyR: The data was not mature at time of the Week 24 analysis. The majority of patients who achieved CCyR continued to have CCyR: subsequent loss of response was reported in one patient each in the asciminib and the bosutinib arm, respectively.

Time to treatment failure

The probability to experience a treatment failure was higher in the bosutinib arm compared to the asciminib arm (HR=0.5; 95% CI: 0.3, 0.7). The KM estimated proportion of patients with treatment failure by the cut-off date was higher in the bosutinib arm (73.7%) compared to the asciminib arm (45.2%). The median time to treatment failure was 5.6 months for the bosutinib arm whereas it was 16.6 months for the asciminib arm.

Progression free survival

Progression-free survival (PFS) data were immature at the time of this report with 7 patients (4.5%) and 5 patients (6.6%) with PFS events in the asciminib and bosutinib arms, respectively.

Overall survival

Overall survival data were immature at time of the Week 24 analysis. Four patients (2.5%) randomized to the asciminib arm died (two on-treatment and two during survival follow-up) and one in the bosutinib arm (1.3%, on-treatment).

The FDA's Assessment:

FDA agrees with the Applicant's assessment in general.

The applicant provided an updated data set based on a data cutoff date of 06 January 2021. These results are reported in the USPI. As of this cutoff date, the MMR rate at 48 weeks was 29% (95% CI: 22, 37) in patients receiving asciminib and 13% (95% CI: 6.5, 23) in patients receiving bosutinib. With a median duration of follow-up of 20 months (range: 1 day to 36 months), the median duration of response had not yet been reached for patients with MMR at any time.

In addition, the key secondary endpoint of MMR rate at Week 96 for Study CABL001A2301 was not analyzed due to immaturity of the data.

Dose/Dose Response

The Applicant's Position:

Exposure-response analyses are described in FDA disagrees with Applicant's position that there are no outstanding issues. There are several DDI issues that remain unresolved. Refer to the PMRs/PMCs Table in Section 6.1 Executive Summary for details.

The FDA's Assessment:

Please refer to FDA's assessment in Section 6.3.

Durability of Response

The Applicant's Position:

In Study CABL001A2301, the majority of patients who received asciminib and achieved MMR continued to have MMR (51/54; 94.4%) at the time of their last molecular assessment. The KM estimated proportion of patients maintaining their MMR for at least 24 weeks was 95.4% (95% CI: 82.8, 98.8) in the asciminib arm vs 100.0% (95% CI: NE, NE) in the bosutinib arm. For at least 48 weeks: 95.0% (95% CI: 85.4, 100.0) and for at least 96 weeks: 86.0% (95% CI: 65.9, 100.0). The median duration of MMR was not reached for either arm.

The FDA's Assessment:

We agree with the Applicant's assessment.

Persistence of Effect

The Applicant's Position:

Treatment with asciminib should continue for as long as clinical benefit is evident, or until unacceptable toxicity occur. PFS and OS were the efficacy endpoints assessed after discontinuation of treatment. These are not mature to have a conclusion.

The FDA's Assessment:

FDA agrees that MMR at 48 weeks was numerically higher on the asciminib arm, thus providing evidence to support intermediate-term benefit of asciminib. However, FDA notes that 1) all analyses at 48 weeks were post hoc analyses, and therefore, exploratory in nature; 2) the pre-specified key secondary endpoint, MMR rate at 96 weeks was not analyzed due to immaturity of the data.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

The patient-reported outcomes were ranked as exploratory endpoints. Overall, compared to bosutinib, treatment with asciminib was associated with better improvement in disease-related symptoms and health-related quality of life (as assessed by MDASI CML, PGIC along with EQ-5D-5L); and in work productivity and activity impairment (as assessed by WPAI-CML).

The FDA's Assessment:

FDA notes that these analyses are exploratory in nature.

Additional Analyses Conducted on the Individual Trial

Data:

No additional analysis other than those described in the study report were performed.

The FDA's Assessment:

FDA confirms the Applicant's assessment.

8.1.3. Trial Design – Study CABL001X2101

The Applicant's Description:

For the purpose of this application the Study CABL001X2101 provides:

- Supportive evidence for the treatment effect of asciminib as single-agent in patients with CML-CP previously treated with 2 or more TKIs is based on data from a subset of patients with CML-CP not harboring the T315I mutation.
- The efficacy of asciminib in patients with CML in CP harboring the T315I mutation is based on data from the cohort of CML-CP patients harboring the T315I mutation.

Details of this study are summarized in Table 29.

Overview of study

This is an ongoing Phase I, multi-center, open-label, dose escalation first-in-human (FIH) study to define the maximum tolerated dose and/or recommended dose for expansion (MTD/RDEs, to characterize safety and tolerability, and to assess the PK profile and preliminary evidence of efficacy of asciminib given as single agent or in combination with either nilotinib or imatinib or dasatinib in patients with CML or Ph+ ALL. Details are summarized in Table 29.

There are 5 arms in this study. Each arm began with a dose escalation part. After determination of the MTD, or the RDE(s), further safety and tolerability was evaluated in an expansion part:

- Arm 1: asciminib as single agent in CML-CP and AP patients
- Arm 2: asciminib in combination with nilotinib in CML-CP and AP patients
- Arm 3: asciminib in combination with imatinib in CML-CP and AP patients
- Arm 4: asciminib in combination with dasatinib in CML-CP and AP patients
- Arm 5: asciminib as single agent in CML blast phase (BP) and Ph+ ALL patients

The primary objective of Study CABL001X2101 was to determine the MTD and/or the RDE for expansion of asciminib as single agent or in combination with other TKIs. The assessment of antileukemic activity/efficacy and characterization of safety of asciminib were part of the secondary objectives.

Trial locations: Overall, patients were enrolled in 18 centers from 10 countries: Those countries were Australia (1 site), France (2 sites), Germany (3 sites), Italy (1 site), Japan (1 site), Singapore (1 site), South Korean (1 site), Spain (1 site), The Netherlands (1 site), United States (6 sites).

Diagnostic criteria: The definition of CML-CP/AP/BP was based on European Leukemia Network (ELN) recommendations (Baccarani et al 2013). The Philadelphia chromosome (Ph) is the most common cytogenetic abnormality in adult patients with acute lymphoblastic leukemia (ALL), occurring in about 20% to 30% of all cases. Elderly and less fit patients who are not candidates for transplantation have few, if any, curative options with presently available TKI-based therapies, and new agents are urgently needed for these patients.

Key inclusion/exclusion criteria

1) Adult patients with previously diagnosed and cytogenetically confirmed:

For Arms 1, 2, 3 and 4, either:

- Ph+ CML-CP/-AP previously treated with at least two different tyrosine kinase inhibitors (TKIs) prior to study entry and had relapsed, were refractory to or intolerant of TKIs as determined by Investigators OR
- Ph+ CML-CP/-AP exhibiting relapsed disease associated with the presence of the T315I "gatekeeper mutation" after at least one TKI were also eligible provided no other effective therapy exists (criteria introduced with protocol amendment 4).

There was no restriction on the number of prior therapies administered to patients, and patients with status of post bone marrow transplant were eligible provided they met the inclusion/exclusion criteria.

For Arm 5: Ph+ CML-BP or Ph+ ALL who had a cytopathologically confirmed diagnosis and were relapsed or refractory to at least one prior TKI or intolerant of TKIs. TKI failure in Ph+ ALL patients was defined as at least the loss of Molecular Response (MR) 4.5 (BCR-ABL1 ≤ 0.0032%).

Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.

Table 29: Summary of Study CABL001X2101

Study population	Patients with chronic myeloid leukemia in chronic phase (CML-CP) pre-treated with at least 2 prior TKIs; for patients harboring the T315I mutation prior treatment with at least one TKI and with no other effective therapy available was required;

Efficacy endpoints	Major molecular response (MMR) by and at each point time point, time to MMR and duration of MMR
No of patients enrolled*	A total of 317 patients were recruited. 115 CML-CP patients not harboring the T315I mutation were enrolled to various asciminib single agent treatment cohorts: 10 mg BID (n=1), 20 mg BID (n=13), 40 mg BID (n=30), 80 mg BID (n=8), 150 mg BID (n=5), 160 mg BID (n=3), 200 mg BID (10), 80 mg QD (n=17), 120 mg QD (n=17), and 200 mg QD (n=11). 70 patients with CML-CP harboring the T315I mutation were enrolled to various asciminib single agent treatment cohorts: 20 mg BID (n=1), 40 mg BID (n=1), 80 mg BID (n=4), 150 mg BID (n=5), 160 mg BID (n=6), 200 mg BID (48), 80 mg QD (n=1), 120 mg QD (n=3), and 200 mg QD (n=1).
Regimen pertinent to the indication	The BID regimen was explored in patients enrolled in dose escalation and expansion cohorts, with a starting dose of 10 mg asciminib BID up to 200 mg BID, orally. The QD regimen was explored in patients at the following dose levels: 80 mg QD, 120 mg QD and 200 mg QD.
Treatment duration	Until disease progression, unacceptable toxicity, new mutations causing potential resistance to asciminib, new clonal chromosome abnormalities in Ph+ cells, pregnancy, death, or discontinuation from the study treatment for any other reason.
Efficacy assessment	Molecular response was assessed based on levels of BCR-ABL1 transcripts which was determined by real-time quantitative polymerase chain reaction (RQ-PCR) testing of peripheral blood and analyzed at a Novartis designated laboratory with validated PCR technology that has a sensitivity of at least 4.5 logs. The percent ratio of BCR-ABL1 transcripts versus control gene transcripts converted to International Standards (IS) was calculated for each sample.

CML-CP: chronic myeloid leukemia in chronic phase; FAS: full analysis set; MMR: major molecular response; RQ-PCR: real-time quantitative polymerase chain reaction.

* The total number of patients treated with asciminib single agent was 200, including 115 patients with CML-CP not harboring T315I mutation, 70 patients with CML-CP harboring T315I mutation and 15 patients with CML-AP. The 15 patients with CML-AP are presented in this document as part of the 'All patient safety pool' in Section 8.2.

Study treatment and treatment assignment:

This was an open label study. Treatment assignment of patients to a particular arm was not randomized and was coordinated by Novartis. Initially the study was designed to evaluate asciminib as a single agent in CML or Ph+ ALL. Treatment with asciminib in combination with nilotinib imatinib, and dasatinib was introduced with various protocol amendments.

Asciminib was administered BID in the fasted state (food was not allowed for at least 2 hours prior and 1 hour after administration) approximately 12 hours apart or was to be taken QD at around the same time every morning, depending on the dose of the allocated cohort.

Dose modification, dose discontinuation: For patients who were unable to tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions (to either monotherapy or combination therapies) were either recommended or mandated to allow the patient to continue study treatment. The criteria for dose modification were based on the dose modification guidelines for each toxicity. If the toxicity was resolved after interruption, the study drug was resumed at the same dose and the same toxicity reoccurred with the same or worse severity, then the dose was reduced by at least 1 dose level. For patients with CML-CP and AP harboring the T315I mutation - dose modification included a dose level reduction to 160 mg BID in case of treatment related toxicity, re-escalation to 200 mg BID was considered upon resolution of toxicity to Grade 1 or baseline. It was not permitted to increase the dose above 200 mg BID.

Procedures and schedule:

The primary objective of X2101 was to determine the MTD and/or the recommended dose for expansion (RDE) for expansion of asciminib as single agent or in combination with other TKIs. The assessment of antileukemic activity/efficacy and characterization of safety of asciminib were part of the secondary objectives and the assessments were similar to the assessments described in Trial Design – Study CABL001A2301.

Dietary restrictions/instructions: There were no specific dietary restrictions. The patients were advised to adhere to the food restrictions during the treatment (fasting status regarding study treatment administration, avoidance of prohibited concomitant medication).

Concurrent medications: The use of any concomitant medication/therapy, including over-the-counter medications deemed necessary for the patient was permitted during the study except those specified as prohibited. Medications required to treat AEs, manage cancer-related symptoms, including pain medications were allowed. Investigational therapies other than the study treatment and other antineoplastic therapies were prohibited throughout the study.

Treatment compliance: Compliance was assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver was captured in the Drug Accountability Form. Records of study treatment administered (total daily dose with start and end date), and any Concomitant Medications and Surgical and Medical procedures were collected in the appropriate eCRF.

Rescue medication: No rescue medication was allowed.

Patient completion, discontinuation, or withdrawal: Patients could voluntarily discontinue from the study treatment for any reason at any time. Patients could be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other

reason. Patients will receive treatment up to the end of study treatment defined as the time when the last patient completes the study evaluation completion follow-up visit. At the end of the study, every effort has to be made to continue provision of study drug outside this study through an alternative setting to patients who in the opinion of the Investigator were still deriving clinical benefit.

The FDA's Assessment:
FDA agrees with the Applicant's description of the trial design of the phase 1, CABL001X2101 study.

Study endpoints

The Applicant's Description:

Determination of MTD/RDE

The primary endpoint was the incidence of DLTs in Cycle 1 (each cycle was defined as 28 days). Estimation of the MTD/RDE of the treatment was based upon the estimation of the probability of DLT in Cycle 1 for patients in the DDS.

The MTD was defined as the highest drug dosage that is unlikely (<25% posterior probability) to cause DLT in 33% or more of the treated patients in the first cycle of study treatment under that schedule.

An adaptive Bayesian logistic regression model guided by the escalation with overdose control principle was used during the dose escalation to make dose recommendations and estimate the MTD/RDE(S) during the dose escalation part for each Arm of the study. Separate BLRMs were used for asciminib as single agent and when given in combination with either nilotinib or imatinib or dasatinib in patients with CML, and for asciminib as a single agent in patients with CML-BP and Ph+ ALL. Separate BLRM was used for each dosing regimen tested (BID and QD).

Safety

All safety analyses were based on the safety set. In Arm 1, summary analyses were also conducted in the subset of patients with CML-CP/-AP harboring the T315I mutation at screening.

Adverse event summaries included all AEs occurring during the on treatment period. The following AE summaries were produced by study arm and treatment group: DLTs in the DDS, overview of AEs, on treatment deaths and all deaths, AEs and SAEs by SOC and PT, summarized by relationship, seriousness, leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy, and AESI. Laboratory data including hematology and biochemistry parameters, vital signs, ECGs, ECOG performance status were also summarized by study arm and treatment group.

Efficacy

Major molecular response (MMR) was defined as a value of ≤ 0.1% of BCR-ABL1 ratio on the International Scale (IS).

Duration of first MMR was defined as the period between the time-point when the first BCR-ABL1 ratio ≤0.1 % (IS) was observed until and the time-point of confirmed loss of MMR.

MR4 and MR4.5 was defined as a value of ≤ 0.01% and ≤ 0.0032% BCR-ABL1 ratio by IS, respectively.

Molecular response (MR) rate by scheduled time point was defined as the proportion of patients who achieved MR at or before the specified time point. Molecular response rate at scheduled time point was defined as the proportion of patients who achieved MR at or before the specified time point and were able to maintain this response until the specified time point.

Efficacy analyses for each arm were performed using the FAS, and presented by treatment group. The following analyses were conducted:

- Achievement of MMR by scheduled time points (including Week 24 and 48, overall and by line of therapy)
- Achievement of MMR at scheduled time points (including Week 24 and Week 48, overall and by line of therapy)
- Duration of first MMR among patients who achieved MMR
- Time to MMR among patients who achieved MMR.

For patients with CML harboring the T315I mutation from Arm 1, the following additional analyses were conducted:

- MMR rate by 24 weeks (95% CI) in overall T315I mutation analysis set
- MMR rate at 24 weeks (95% CI) in overall T315I mutation analysis set
- MMR rate by 24 weeks (90% CI) in CML-CP/-AP and CML-CP patients who previously received ponatinib and did not have an MMR at screening
- MMR rate at 24 weeks (90% CI) in CML-CP/-AP and CML-CP patients who previously received ponatinib and did not have a MMR at screening
- MMR rate by 24 weeks (90% CI) in CML-CP/-AP and CML-CP ponatinib naive patients not in MMR at screening
- MMR rate at 24 weeks (90% CI) in CML-CP/ AP and CML-CP ponatinib naive patients not in MMR at screening
- MMR rates at and by 48 weeks (90% CI) for the above populations with at least 48 weeks follow-up
- Time to MMR including ponatinib pre-treated and ponatinib naive patients
- Duration of MMR including ponatinib pre-treated and ponatinib naive patients.

Confidence intervals (CI) were calculated by the Clopper-Pearson method. Analyses for T315I mutation in patients with CML-CP/-AP are provided in the CSR.

Cytogenetic response was assessed as the percentage of Ph+ metaphases in the bone marrow. Achievement of cytogenetic response categories was summarized by time points (including Week 24 and Week 48) and treatment group using the FAS. In addition, analyses of cytogenetic

response by time point were conducted in the subset of patients harboring the T315I mutation at study entry from Arm 1.

A **complete hematologic response (CHR)** was defined when all of the following criteria were present at any assessment, and was confirmed by another assessment at least after 4 weeks:

- WBC count < 10 x 10^9 /L
- Platelet count < 450 x 10^9 /L
- No extra medullary involvement (spleen, liver, lymph nodes)
- Myelocytes + metamyelocytes < 5% in peripheral blood
- No evidence of blasts or promyelocytes in the peripheral blood

Achievement of CHR at and by time points (including Week 24 and Week 48) was summarized using the FAS by treatment group.

Pharmacokinetics

PK parameters were determined for all PK-evaluable patients using non-compartmental method(s) using Phoenix version 8.0 (Pharsight, Mountain View, CA). PK parameters were estimated and reported, when feasible.

Pharmacokinetic parameters were summarized using descriptive statistics by analyte, study arm, treatment group and study day. For Tmax only median values and ranges were provided.
Assessment of dose-proportionality and steady-state attainment for asciminib single agent and in combination with nilotinib/imatinib/dasatinib was conducted. An analysis of variance (ANOVA) was performed on log-transformed AUCs and Cmax (Cycle 1 Days 1, 15 and Cycle 2 Day 1) using linear mixed effect models to assess day effect and dose-proportionality.

The FDA's Assessment:
FDA agrees with the Applicant's description of the study endpoints of the phase 1, CABL001X2101 Study.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The Full analysis set (FAS) consisted of all patients who received at least one dose of study treatment. Patients were analyzed according to the planned treatment. The FAS was used for all listings of raw data. Unless otherwise specified, the FAS was the default analysis set used for all analyses.

T315I mutation analysis set: subset of FAS consisting of CML-CP patients with centrally confirmed T315I mutation (Sanger sequencing), treated with asciminib 200 mg BID, with evaluable RQ-PCR data (IS) who were not in MMR at baseline.

The Safety set consisted of all patients who received at least one dose of the study treatment. Patients were analyzed according to the study treatment they received.

The dose-determining analysis set (DDS) consisted of all patients from the safety set who met both the following minimum exposure criterion and had sufficient safety evaluations, during the first 28 days (Cycle 1) of dosing or discontinued earlier due to dose limiting toxicity (DLT). Minimum exposure criteria defined as a patient who had received at least 75% of the planned doses of the study treatment in the first 28 days of dosing. For BID and QD schedules, this corresponds to a minimum of 42 out of the 56, and minimum of 21 out of the 28 planned doses, respectively.

The pharmacokinetic analysis set (PAS) consisted of all patients who had at least one blood sample providing an evaluable full PK profile (Cycle 1 Day 1, Cycle 1 Day 15 or Cycle 2 Day 1).

The primary analysis was performed when all patients in the monotherapy arms were treated for at least 6 cycles and had their 24-week efficacy evaluation performed, or had discontinued treatment earlier.

The main efficacy, safety and PK endpoints analyzed are described in the previous section.

In Study CABL001X2101, the following changes were made to the protocol specified analyses:

PK parameters were updated. PAS definition was updated to clarify the criteria for a PK profile to be characterized as non-evaluable. DDS definition was updated to exclude patients enrolled in expansion cohorts.

The analysis of cytogenetic response 'at' specified time points was omitted because bone marrow aspirate was not mandatory for patients after achieving CCyR. Only the analysis of cytogenetic response 'by' specified time points was considered appropriate.

The protocol specified analysis for patients with CML-CP/-AP harboring the T315I mutation was performed as per the protocol, but further emphasis was given to patients with CML-CP. A sensitivity analysis considering all-treated patients was added for the analysis of the main efficacy endpoint in patients with CMP-CP harboring the T315I mutation.

After finalization of the analysis plan, based on the discussion at the Type C meeting with FDA in July 2020, additional outputs related to the analysis of ponatinib naive and ponatinib pre-treated patients in the cohort of patients in Arm 1 harboring the T315I mutation, outputs related to the sensitivity analyses, and one output for Arm 5 related to the analysis of MMR by time point were added. The sensitivity analysis for the main efficacy endpoint (i.e., MMR rate by Week 24) included patients who had non-measurable disease in the International Scale (IS) due to the expression of p190/atypical/unknown transcripts as non-responders (all-treated analysis).

Dose selection:

Asciminib single agent in patients with CML-CP/-AP:

The starting dose of asciminib for patients with CML-CP/-AP selected for the dose escalation part of this study was set at 10 mg orally administered BID under fasted conditions. The selection of the starting dose of asciminib was based on 4-week GLP toxicology studies conducted in rats and dogs. In addition, the PK-pharmacodynamic (PD) mouse model suggested a BID regimen was

required to maintain PD effect. The starting dose of 10 mg BID was expected to be safe and tolerated in adult patients with CML-CP/-AP. Based on further PK modeling and pre-clinical studies which suggested response in BCR-ABL1 transcripts also when a QD regimen was considered in Study CABL001X2101, decision was taken to open a cohort of patients dosed on a QD regimen at 120 mg QD as starting dose level.

The dose range covered were initially based on the projections for the human PK of asciminib and projections for the relationship between asciminib systemic exposure and toxicity. The dose levels were updated as more PK and safety data became available. Clinical experience was used to elucidate the relationships between dose, systemic exposure, and toxicity. Based on the above, actual dose levels evaluated in patients with CML-CP/-AP included 10 mg BID, 20 mg BID, 40 mg BID, 80 mg BID, 150 mg BID, 160 mg BID, 200 mg BID, 80 mg QD, 120 mg QD, 200 mg QD.

Asciminib single agent in patients Ph+ CML-CP harboring the T315I mutation (200 mg BID):
Preclinical evidence supported the use of asciminib in CML harboring the T315I mutation. Asciminib maintained activity against all BCR-ABL1 constructs, including T315I, inhibiting cell proliferation. Pre-clinical study showed that an approximate 4- to 5-fold increase in asciminib exposure was required to inhibit T315I mutation relative to other mutations. Based on such evidence, patients with CML-CP/-AP harboring the T315I mutation received asciminib 150 mg BID as the starting dose in this study. Enrichment cohorts were opened to explore dose levels of asciminib at 150, 160 and 200 mg BID in patients with CML-CP/-AP harboring the T315I mutation. Further, based on the overall single agent dose escalation data, a dose of 200 mg BID satisfied the adaptive BLRM guided by the EWOC principle for this patient population and an expansion cohort to further evaluate this dose level was opened.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Protocol Amendments

The Applicant's Description:
The study protocol was amended ten times. The **key** features of each amendment are given in the Table 30.

Table 30: Protocol amendments

Version and date	Summary of key changes
Amendment 1 (22-Jan-2014)	This amendment addressed changes requested following post health authority review and revised DLT criteria and included phototoxicity assessment and follow-up plan
Amendment 2 (07-Mar-2014)	This amendment addressed changes requested following administrative correction identified during health authority submission process:
Amendment 3 (14-Mar-2014)	This amendment addressed changes requested following health authority review:

Version and date	Summary of key changes
	• Visit evaluation schedule table footnote clarified that only Japan patients were required to be hospitalized during Cycle 1 in principle.
Amendment 4 (06-Jan-2015)	This amendment had the following changes: • Introduced the evaluation of the combination of asciminib with nilotinib, to determine the recommended combination regimen for future studies, and to describe the safety and preliminary antitumor activity. • Inclusion criteria was broadened to include those patients who exhibited relapsed disease associated with the presence of a T315I mutation after therapy with at least one TKI. • Inclusion criteria was updated regarding the eligibility of patients with CML harboring the T315I mutation. Clarified that patients with Ph+ ALL who were status post bone marrow transplant were eligible • Exclusion criteria was updated • Patients who were intolerant to the nilotinib were excluded from being enrolled in the combination arm (asciminib + nilotinib)
Amendment 5 (26-Jun-2015)	This amendment had the following changes: • Introduced a new tablet formulation of asciminib in replacement of the (b) (4) capsule • Updated to clarify women of child bearing potential • An additional ECG on Day 8 of Cycle 1 was captured only for patients who received asciminib in combination with nilotinib to align with nilotinib product safety specifications.
Amendment 6 (14-Oct-2015)	This amendment introduced the following changes: • Introduced the evaluation of additional combinations of asciminib with imatinib or dasatinib to determine the recommended combination regimens for future studies, and to describe the safety and preliminary antitumor activity in CML. • Arm 1 – Dose expansion: Sample size for this expansion was increased to approximately 60 patients in order to support the benefit-risk assessment for patients with CML. • Given the aggressive nature of CML-BP, a different dose was required to attain disease responses in this patient population. Therefore, the potential need for a different recommended dose for CML-BP patients were explored along with that for Ph+ ALL patients in the Expansion part of the study. • Study objectives and endpoints were updated • DLT criteria revised - pleural effusion added and period for DLT observation/assessment added (within the first 28 days (Cycle 1) of study treatment) • Patients enrolled in combination arm could continue asciminib in single agent in case of discontinuation of the combination drug

Version and date	Summary of key changes
Amendment 7 (10-Mar-2016)	This amendment introduced the following changes: • Modified female contraception requirements for patients enrolled to asciminib + imatinib. Female patients of childbearing potential were required to use highly effective methods of contraception during dosing and for 14 days instead of 3 days after the last dose of study treatment. • Intra-patient dose escalation was allowed after 1 cycle of treatment for Ph+ ALL patients who required increased drug exposures to achieve disease control. • The frequency of abdominal imagining modalities (CT/MRI) performed for early detection of fibrotic change in the pancreas was reduced to baseline screening, C12D1, and End of treatment or as clinically indicated. • Abdominal imagining modalities were broadened to include the use of CT in addition to MRI. • Sodium was added to the Local Lab Parameters Collection Plan as this was previously omitted in error. • PK collection schedules were clarified by replacing footnote that was inadvertently deleted in the previous amendment specifying that 12 hour post dose collections were only required for patients in Japan, as they were housed overnight on intensive PK collection days. • Added outcome required evaluation of AEs
Amendment 8 (26-Jan-2017)	This amendment introduced the following changes: • Included hepatitis B virus testing as one of the study procedures to identify study patients who could be at risk of hepatitis B reactivation. • Aligned with Tasigna (nilotinib) core data sheet and Investigators Brochure, the required period of female contraception for females of childbearing potential enrolled to Arm 2 (asciminib +nilotinib) was changed from 3 to 14 days. • Clarified fasting condition of asciminib in combination with imatinib • Optional biomarker testing to study patterns of resistance was removed due to technical infeasibility. • A statement was added to allow collection of PK samples at non-protocol defined time points if determined necessary by the treating physician for patient safety concerns. • Discontinuation from study was been revised and sections added for withdrawal of consent and lost to follow up.
Amendment 9 (03-Aug-2018)	This amendment introduced the following changes: • Expanded the cohort of CML-CP/-AP patients harboring the T315I mutation in Arm 1 to approximately 65 patients to evaluate the efficacy and safety of asciminib 200 mg BID in this population.

Version and date	Summary of key changes
	• Dose modification and safety management guidelines were provided for CML-CP/-AP patients harboring the T315I mutation treated at 200 mg BID (including but not limited to dose level reduction to 160 mg asciminib BID). • Details on efficacy analyses planned for the cohort of patients harboring the T315I mutation were added. • PFS was removed • Criteria for discontinuation of study treatment following >21 days dose delay was updated • Updated provisional dose levels for asciminib • Updated monitoring and dose modification guidelines to refer to product labels for imatinib, nilotinib and dasatinib toxicity management • Updated to clarify events considered for disease progression • Updated requirements to detect new mutations or new clonal abnormalities in Ph+ cells at any time after start of study treatment • Peripheral blood collection was removed for the cytogenetic analysis • AESI were added • Sample size calculation updated • Updated on prohibited and permitted CYP substrates when patients were on single agent asciminib • Updated on the use of substrates of CYP2C8 and CYP2C9 with caution for asciminib combination with nilotinib or imatinib or dasatinib • Withdrawal of consent section was added/updated to incorporate and reflect the European Economic Area (EEA) General Data Protection Regulation (GDPR) requirements. Following distribution issues with the protocol amendment 9 in the USA, the document was submitted, approved and implemented late in this country. This delay did not affect the conduct of the study.
Amendment 10 (24-Oct-2019)	This amendment introduced the following changes: • Defined the main endpoint for efficacy analysis (part of the secondary objectives) as the rate of MMR by 24 weeks of treatment • Clarified that the primary analysis was conducted as soon as all patients in Arm 1 and Arm 5 (asciminib as single agent) had been treated for at least 6 cycles and had their 24-week efficacy evaluation performed or have discontinued the study treatment earlier. This analysis included: o analysis of primary endpoint, PK and safety and tolerability of asciminib as single agent, driven by the fact that dose escalation for single agent asciminib had been completed and RDE identified o analysis of efficacy data for Arms 1 and 5, including the pre-planned sub-group analysis of patients with CML-CP harboring the T315I mutation

Version and date	Summary of key changes
	○ preliminary analysis of safety and tolerability of asciminib in combination with imatinib, nilotinib or dasatinib (Arms 2, 3 and 4) • Updated provisional dose levels for asciminib when given QD.

The FDA's Assessment:
FDA agrees with the Applicant's description of the protocol amendments of the phase 1, CABL001X2101 Study.

8.1.4. Study Results – Study CABL001X2101: supportive of CML-CP ≥2 prior TKIs

Compliance with Good Clinical Practices

The Applicant's Position:

The study (Study ABL00X2101) has been conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) to good clinical practice (GCP). Written informed consent was obtained from each subject or legally acceptable representative of the subject, before conducting any study-specific procedures. The study protocol and all amendments were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

The FDA's Assessment:
FDA confirms the Applicant's position.

Financial Disclosure

Novartis has adequately disclosed any financial interests/arrangements with clinical investigators in accordance with the guidance for industry. Details of financial disclosure are presented in Appendix 19.2.

The FDA's Assessment:
A summary of the financial disclosure information is presented in Appendix 19.2. Five investigators from 3 sites had financial disclosures for research funding, advisory board, study consultations, presentations and educational events honoraria, equity interest and royalties from the Applicant. Investigators at these sites enrolled 6 of patients. With the small number of patients enrolled at any site, the enrollment of patients by these investigators is not expected to bias the outcome of the study results.

Patient Disposition

The Applicant's Position:

Overall, 115 patients with CML-CP without the T315I mutation were enrolled to various asciminib single agent treatment cohorts: 10 mg BID (n=1), 20 mg BID (n=13), 40 mg BID (n=30), 80 mg BID (n=8), 150 mg BID (n=5), 160 mg BID (n=3), 200 mg BID (10), 80 mg QD (n=17), 120 mg QD (n=17), and 200 mg QD (n=11).As of the data cut-off date of 02-Apr-2020, 83 (72.2%) patients were receiving treatment with asciminib single agent and 32 (27.8%) patients had discontinued treatment; 19/30 patients and 12/17 patients were continuing to receive asciminib at 40 mg BID and 80 mg QD doses respectively.

The FDA's Assessment:
FDA confirms the Applicant's position.

Protocol Violations/Deviations

The Applicant's Position:

Overall, 45/115 (39.1%) patients had at least one protocol deviation. The most frequently reported protocol deviations were related to selection criteria (inclusion/exclusion criteria) not being met in 20 (17.4%) patients.

Among patients reporting at least one protocol deviation under the 'other deviation' category, 11 patients had deviation(s) related to at least one visit performed remotely or outside of the study site due to COVID-19, for 1 patients IMP was shipped to the patient's home due to COVID-19, and for 1 patient assessment/procedure was changed due to missed RQ-PCR assessment for the Week-24 due to COVID-19.

The FDA's Assessment:
FDA agrees with the Applicant's position. Protocol deviations were less frequent in Study CABL001X2101 compared to Study CABL001A2301.

Table of Demographic Characteristics

Data:

Table 31: Demographics by treatment – single agent asciminib in CML-CP without the T315I mutation at screening (FAS)

Demographic Variable	ABL001 40 mg BID. N=30	ABL001 80 mg QD. N=17	ABL001 200 mg BID. N=10	All patients N=115
Age (years)				
n	30	17	10	115
Mean	51.8	58.9	55.9	55.3
SD	14.29	14.02	17.18	14.07
Median	53.0	59.0	55.5	56.0
Minimum	27	30	25	25

Demographic Variable	ABL001 40 mg BID. N=30	ABL001 80 mg QD. N=17	ABL001 200 mg BID. N=10	All patients N=115
Maximum	75	86	78	88
Age category (years) -n (%)				
18 - <65 years	24 (80.0)	11 (64.7)	6 (60.0)	85 (73.9)
≥65 years	6 (20.0)	6 (35.3)	4 (40.0)	30 (26.1)
≥75 years	1 (3.3)	2 (11.8)	2 (20.0)	10 (8.7)
Sex -n (%)				
Male	17 (56.7)	7 (41.2)	6 (60.0)	60 (52.2)
Female	13 (43.3)	10 (58.8)	4 (40.0)	55 (47.8)
Race -n (%)				
Black or African American	2 (6.7)	1 (5.9)	0	4 (3.5)
White	23 (76.7)	14 (82.4)	9 (90.0)	89 (77.4)
Asian	5 (16.7)	2 (11.8)	0	18 (15.7)
Other	0	0	0	1 (0.9)
Unknown	0	0	1 (10.0)	3 (2.6)
Ethnicity -n (%)				
Hispanic or Latino	0	1 (5.9)	2 (20.0)	7 (6.1)
East Asian	4 (13.3)	1 (5.9)	0	16 (13.9)
Southeast Asian	1 (3.3)	0	0	1 (0.9)
Other	18 (60.0)	8 (47.1)	5 (50.0)	57 (49.6)
Not Reported	4 (13.3)	5 (29.4)	2 (20.0)	21 (18.3)
Unknown	3 (10.0)	2 (11.8)	1 (10.0)	13 (11.3)
ECOG performance status -n (%)				
0	20 (66.7)	13 (76.5)	9 (90.0)	87 (75.7)
1	8 (26.7)	4 (23.5)	1 (10.0)	26 (22.6)
2	2 (6.7)	0	0	2 (1.7)

T315I mutation status at screening = Negative/Missing
Source: Novartis Study CABL001X2101- CSR Table 14.1-3.1.1.2

The Applicant's Position:

The median age was 56.0 years (min-max: 25-88 years) with 73.9% of patients belonging to the '18 to < 65' years age category. The proportion of males was 52.2% and females was 47.8%. The majority of patients were White (77.4%), followed by Asians (15.7%). Except 2 patients (with ECOG of 2; both in 40 mg BID dose cohort), all other patients (98.3%) had ECOG of 0 or 1 (Table 29).

The FDA's Assessment:

FDA agrees with the Applicant's assessment of demographic features of patients using single-agent asciminib in CML-CP without the T315I mutation at screening. We again note that Black or African American patients are significantly underrepresented compared to the population of the US.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

Of the 115 CML-CP patients not harboring the T315I mutation who were enrolled across treatment cohorts, 112 (97.4%) patients received at least 2 prior TKIs including 82 (71.3%) patients who had received at least 3 prior TKIs. The most frequent prior TKIs received (≥ 50% of all patients) were dasatinib (85.2%), nilotinib (77.4%), and imatinib (73.9%).

The FDA's Assessment:
FDA agrees with the Applicant's position.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Overall, the median duration of exposure to asciminib single agent in 115 CML-CP patients not harboring the T315I mutation was 183.4 weeks (min-max: 2 to 302 weeks) with 103 (89.6%) patients being exposed to asciminib at any dose for at least 24 weeks.

Concomitant medications
Overall, most (191/200; 95.5%) patients received concomitant medications (other than study drugs) which were ongoing at the start date of study treatment and/or started during study treatment. The most frequent (≥ 10% of all patients) and relevant concomitant medications received by PT were paracetamol (36.5%), ibuprofen (19.5%), acetylsalicylic acid (19.0%), allopurinol (17.0%), furosemide (14.0%), ondansetron (12.5%), omeprazole (11.5% each), amoxicillin and lorazepam (11.0% each), amlodipine (10.5%), diclofenac, metoclopramide, oxycodone, tramadol (10.0% each).

Rescue medication

No rescue medication was allowed

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Efficacy Results – Primary Efficacy endpoint (Including Sensitivity Analyses)

The Applicant's Position:

MMR rate by scheduled time-points

As of the data cut-off date, 50/86 (58.1%) evaluable patients achieved MMR; the MMR rate by Week 24 was 23.3% (Table 32). Overall, meaningful responses were observed across all dose levels ≥ 40 mg total daily dose and regimens.

Clinically meaningful MMR rates were achieved by the patients with CML-CP not harboring the T315I mutation across all lines (3L+) of therapy.

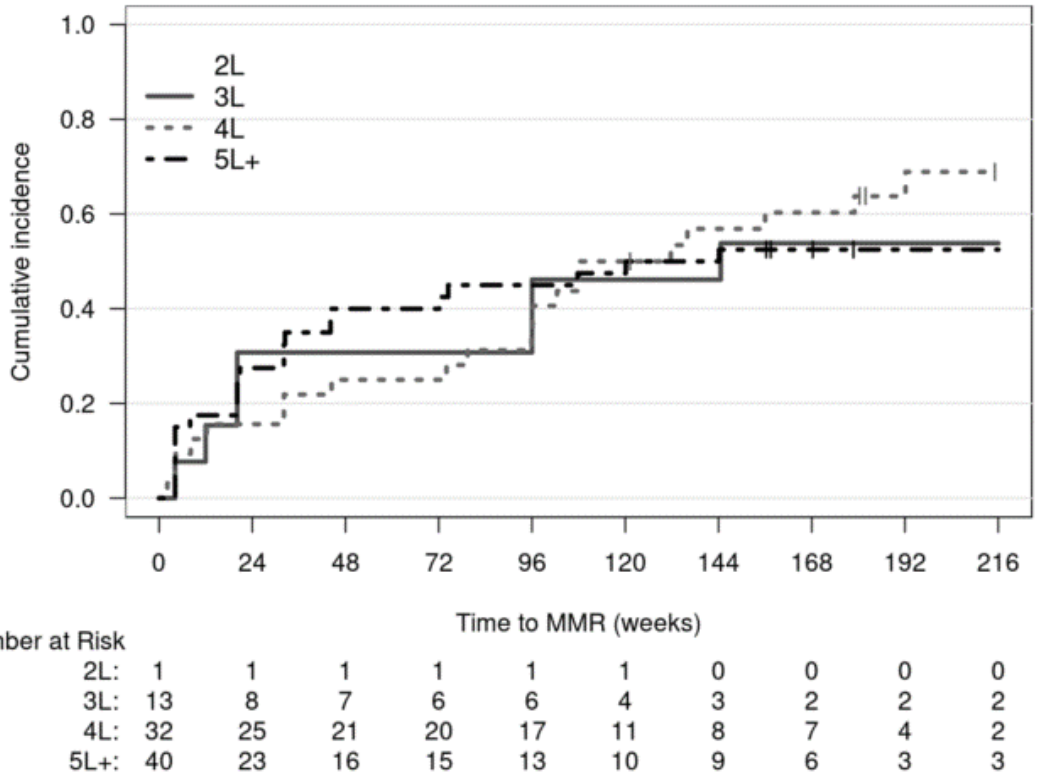
Table 32: MMR rate by each time point – single agent asciminib in CML-CP, not harboring the T315I mutation and not in MMR at screening-MMR evaluable (Study CABL001X2101) (FAS)

Response category	Asciminib 40 mg BID N=25 n (%)	Asciminib 80 mg QD N=14 n (%)	All patients [1] N=86 n (%)
Overall MMR	15 (60.0)	7 (50.0)	50 (58.1)
MMR by Week 24	4 (16.0)	4 (28.6)	20 (23.3)

[1] MMR evaluable patients at different dose levels: 10 mg BID (n=1), 20 mg BID (n=13), 40 mg BID (n=25), 80 mg BID (n=6), 150 mg BID (n=3), 160 mg BID (n=1), 200 mg BID (n=6), 80 mg QD (n=14), 120 mg QD (n=9), 200 mg QD (n=8).
BCR-ABL % measured at the International Scale.
T315I mutation status at screening = Negative/Missing
Source: Novartis Study CABL001X2101 - CSR Table 11-7

The majority of responses were observed within the first 48 weeks of treatment, but the cumulative incidence rate of MMR kept increasing steadily up to Week 144 for all lines of therapy, with new responses observed up to Week 192 (Figure 6**: Cumulative MMR by line of therapy – single agent asciminib in CML-CP patients not harboring the T315I mutation and not in MMR at screening-MMR evaluable (Study CABL011X2101) (FAS)).**

Figure 6: Cumulative MMR by line of therapy – single agent asciminib in CML-CP patients not harboring the T315I mutation and not in MMR at screening-MMR evaluable (Study CABL011X2101) (FAS)



Number at Risk

2L:	1	1	1	1	1	1	0	0	0	0
3L:	13	8	7	6	6	4	3	2	2	2
4L:	32	25	21	20	17	11	8	7	4	2
5L+:	40	23	16	15	13	10	9	6	3	3

L: Line of Asciminib treatment (e.g. 3L: patients treated with Asciminib as 3rd line treatment).
Treatment discontinuations or deaths are treated as competing events.
Curve for 2L was omitted from the graph (only 1 patient).
Source: Novartis Study CABL001X2101 - CSR Figure 11-3

Sensitivity analysis

Sensitivity analysis was not performed for primary efficacy endpoint in CML-CP patients not harboring T315I mutation.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Of note, the MMR rate by 24 weeks for the two dose cohorts in above Table 30 were 16% (95% CI: 4.5, 36) for asciminib 40 mg BID cohort and 29% (95% CI: 8.4, 58) for asciminib 80 mg QD cohort. The overall MMR rate by 24 weeks was 23% (95% CI: 15, 34).

Data Quality and Integrity

The Applicant's Position:

No data integrity concerns were reported following completion of site inspections.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Efficacy Results – Secondary and Other Relevant Endpoints

The Applicant's Position:

MMR rate at scheduled time-points

Among 86 evaluable CML-CP patients not harboring the T315I mutation, 50 (58.1%) patients achieved MMR at any time-point. An increasing MMR rate (for patients who were not in MMR at baseline) over time was observed; the MMR rates at Week 24, Week 48, and Week 96 were 23.3%, 27.9%, and 38.8% respectively (Table 33: MMR rate at each time-point – single agent asciminib in CML-CP, not harboring the T315I mutation and not in MMR at screening-MMR evaluable (Study CABL001X2101) (FAS).

A similar trend of increasing MMR rate over time was observed across all lines of therapy for all patients evaluable for MMR with CML-CP not harboring the T315I mutation. The MMR rate at 96 weeks with asciminib as 3rd-line, 4th-line and 5th-line + treatment were 38%, 38%, and 41%, respectively (Figure 7: MMR at specific time-points by line of therapy – single agent (all doses) asciminib in CML-CP patients not harboring the T315I mutation and not in MMR at screening-MMR evaluable (Study CABL001X2101) (FAS).

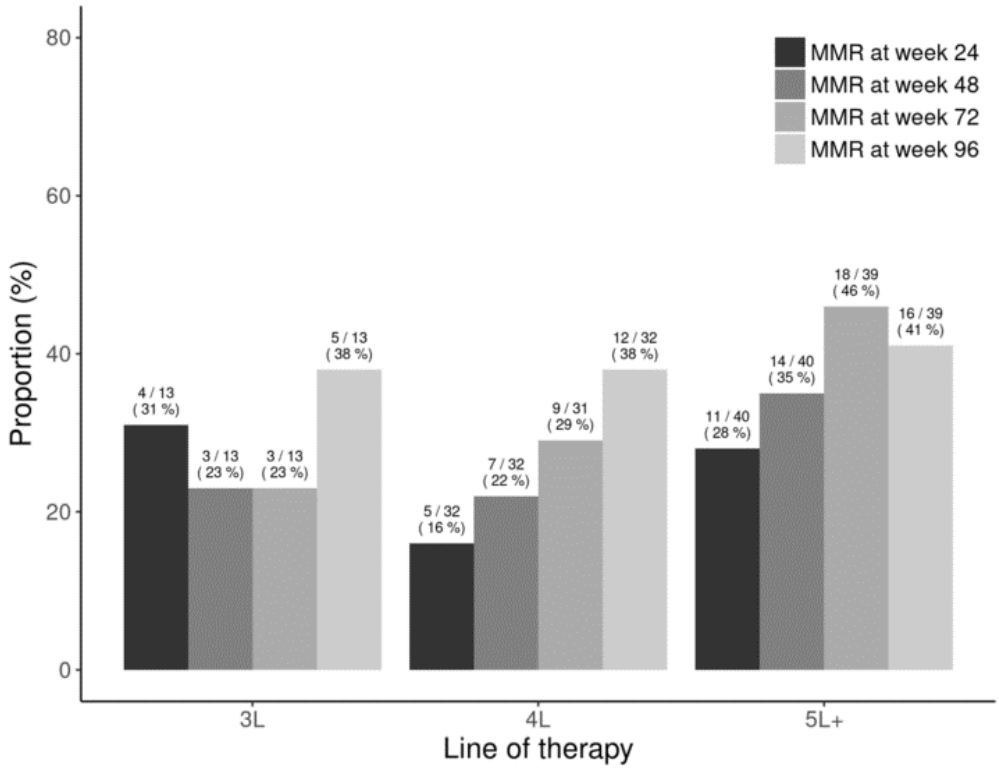
Table 33: MMR rate at each time-point – single agent asciminib in CML-CP, not harboring the T315I mutation and not in MMR at screening-MMR evaluable (Study CABL001X2101) (FAS)

Response category	Asciminib 40 mg BID N=25 n (%)	Asciminib 80 mg QD N=14 n (%)	All patients N=86 n (%)
Overall Major Molecular Response[1]			
Yes	15 (60.0)	7 (50.0)	50 (58.1)
No	10 (40.0)	7 (50.0)	36 (41.9)
Major Molecular Response at week 24, n	25	14	86
Yes	4 (16.0)	4 (28.6)	20 (23.3)
No	21 (84.0)	10 (71.4)	66 (76.7)
Major Molecular Response at week 48, n	25	14	86
Yes	4 (16.0)	5 (35.7)	24 (27.9)
No	21 (84.0)	9 (64.3)	62 (72.1)
Major Molecular Response at week 72, n	24	14	84

Response category	Asciminib 40 mg BID N=25 n (%)	Asciminib 80 mg QD N=14 n (%)	All patients N=86 n (%)
Yes	7 (29.2.0)	6 (42.9)	30 (35.7)
No	17 (70.8)	8 (57.1)	54 (64.3)
Major Molecular Response at week 96, n	25	13	85
Yes	8 (32.0)	6 (46.2)	33 (38.8)
No	17 (68.0)	7 (53.8)	52 (61.2)

T315I mutation status at screening=Negative/Missing
[1] N is used as a denominator to calculate the percentage of overall Major Molecular Response rate
n is the number of patients who had evaluation within the specific time window, or discontinued the treatment before that time window and was used as denominator to calculate the percentages for post-baseline visits. Responders with missing intermediate visits (other than Week 24 and 48) were considered as not having maintained their response for that visit (non-responders).
Source: Novartis Study CABL001X2101 - CSR Table 11-8

Figure 7: MMR at specific time-points by line of therapy – single agent (all doses) asciminib in CML-CP patients not harboring the T315I mutation and not in MMR at screening-MMR evaluable (Study CABL001X2101) (FAS)



The denominator to calculate the MMR rate for post-baseline visits includes patients who had an evaluation within the specified time window, or discontinued treatment earlier. Patients ongoing treatment who did not reach their 48/72/96 week assessment due to inadequate follow-up were not included in the calculation of MMR rate at the respective timepoints
Bars for 2L were omitted (only 1 patient)
Source: Novartis Study CABL001X2101 - CSR Figure 11-4.

Time to MMR and duration of MMR

Time of MMR: Overall, among 50/86 patients with CML-CP without the T315I mutation who achieved MMR, the median time to first MMR was 38.3 weeks, ranging from 2 to 192 weeks after starting treatment with single agent asciminib. Similarly, a wide range of time to response was observed across all dose levels with the majority of responses being observed within the first 48 weeks of treatment.

Duration of MMR: Overall, among 50/86 patients with CML-CP without the T315I mutation who achieved MMR, most (46 patients) maintained this response level or improved it to a deeper level of response up to the cut-off date. Given the median (maximum) duration of treatment exposure of 183.4 (302) weeks, this indicates that the responses achieved were highly durable. The KM estimated proportion of patients maintaining their first MMR for at least 96 weeks was 93% (95% CI: 85.7, 100.0).

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Dose/Dose Response

The Applicant's Position:

Exposure-response analyses are described in FDA disagrees with Applicant's position that there are no outstanding issues. There are several DDI issues that remain unresolved. Refer to the PMRs/PMCs Table in Section 6.1 Executive Summary for details.

Comprehensive Clinical Pharmacology Review.

The FDA's Assessment:

Please refer to FDA's assessment in Section 6.3.

Durability of Response

The Applicant's Position:

Among the 50 patients with CML-CP not harboring the T315I mutation who achieved MMR, majority (46 patients) maintained this response level or improved it to a deeper level of response

up to the cut-off date. Given the median (maximum) duration of treatment exposure of 183.4 (302) weeks, this indicates that the responses achieved were highly durable. The KM estimated proportion of patients maintaining their MMR for at least 96 weeks was 93% (95% CI: 85.7, 100.0).

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Persistence of Effect

Treatment with asciminib should continue for as long as clinical benefit is evident, or until unacceptable toxicity occurs. Following discontinuation of therapy, the natural course of the disease, i.e. progression, can be expected**.** In Study CABL001X2101 all patients discontinued from the study 30 days after discontinuation of treatment hence, persistence effect could not be assessed.

No studies have been conducted to assess withdrawal and rebound effects.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

The FDA's Assessment:

Not applicable. In addition, PRO endpoints may not be interpretable in trials without a control arm.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

No additional analysis other than those described in the study report were performed.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.1.5. Study Results – Study CABL001X2101: CML-CP harboring T315I mutation

Compliance with Good Clinical Practices

The Applicant's Position:

Details are described in Section 8.1.4

The FDA's Assessment:

FDA confirms the Applicant's position.

Financial Disclosure

The Applicant's Position:

Novartis has adequately disclosed any financial interests/arrangements with clinical investigators in accordance with the guidance for industry. Details of financial disclosure are presented in Appendix 19.2.

The FDA's Assessment:
FDA confirms the Applicant's position.

Patient Disposition

The Applicant's Position:

Efficacy claims for the patients with Ph+ CML-CP harboring the T315I mutation are based on the results from Study CABL001X2101 corresponding to a data cut-off date of 02-Apr-2020. This section describes the subset of patients from Study CABL001X2101, receiving single agent asciminib for CML-CP harboring the T315I mutation. The data for patients enrolled in the 200 mg BID treatment group (n=48) are as follows:

As of the data cut-off date, 33 patients (68.8%) continued to receive treatment with asciminib 200 mg BID and 15 (31.3%) patients discontinued treatment. The most frequent reason for discontinuation of treatment was 'physician's decision' (primarily due to lack of efficacy) in 9 (18.8%) patients. One (1.4%) patient discontinued treatment due to death (Grade 4 depression and completed suicide).

The FDA's Assessment:
FDA confirms the Applicant's position.

Protocol Violations/Deviations

The Applicant's Position:

Overall, 25/70 (35.7%) patients had at least one protocol deviation. The most frequently reported protocol deviations were related to selection criteria (inclusion/exclusion criteria) not being met in 12 (17.1%) patients.

Among patients reporting at least one protocol deviation under the 'other deviation' category, 5 patients had deviation(s) related to at least one visit performed remotely or outside of the study site due to COVID-19, for 3 patients investigational product was shipped to the patient's home due to COVID-19, and one patient had at least one missed visit due COVID-19 (Cycle 6 Day 15 and Cycle 7 Day 15 related visits).

The FDA's Assessment:
FDA agrees with the Applicant's position. FDA notes that protocol deviations were less frequent in Study CABL001X2101 compared to Study CABL001A2301.

Demographic Characteristics

Data:

Table 34 Demographics by treatment – single agent asciminib in CML-CP harboring the T315I mutation at screening (FAS)

Demographic Variable	ABL001 150 mg BID. N=5	ABL001 160 mg BID. N=6	ABL001 200 mg BID. N=48	All patients N=70
Age (years)				
n	5	6	48	70
Mean	47.8	56.0	55.3	53.5
SD	19.46	15.66	15.45	15.64
Median	48.0	58.0	56.5	53.5
Minimum	25	36	26	22
Maximum	69	72	86	86
Age category (years) -n (%)				
18 - <65 years	3 (60.0)	4 (66.7)	32 (66.7)	49 (70.0)
≥ 65 years	2 (40.0)	2 (33.3)	16 (33.3)	21 (30.0)
≥75 years	0	0	4 (8.3)	4 (5.7)
Sex -n (%)				
Male	4 (80.0)	4 (66.7)	37 (77.1)	52 (74.3)
Female	1 (20.0)	2 (33.3)	11 (22.9)	18 (25.7)
Race -n (%)				
Black or African American	0	1 (16.7)	1 (2.1)	2 (2.9)
White	0	3 (50.0)	28 (58.3)	36 (51.4)
Asian	5 (100)	2 (33.3)	12 (25.0)	25 (35.7)
Other	0	0	2 (4.2)	2 (2.9)
Unknown	0	0	5 (10.4)	5 (7.1)
Ethnicity -n (%)				
Hispanic or Latino	0	0	3 (6.3)	3 (4.3)
East Asian	4 (80.0)	2 (33.3)	10 (20.8)	21 (30.0)
Southeast Asian	1 (20.0)	0	2 (4.2)	4 (5.7)
Other	0	0	16 (33.3)	19 (27.1)
Not Reported	0	1 (16.7)	13 (27.1)	16 (22.9)

Demographic Variable	ABL001 150 mg BID. N=5	ABL001 160 mg BID. N=6	ABL001 200 mg BID. N=48	All patients N=70
Unknown	0	3 (50.0)	4 (8.3)	7 (10.0)
ECOG performance status -n (%)				
0	5 (100)	5 (83.3)	36 (75.0)	55 (78.6)
1	0	1 (16.7)	12 (25.0)	15 (21.4)

Source: Novartis Study CABL001X2101- CSR Table 14.1-3.1.1.4

The Applicant's Position:

Among CML-CP patients harboring the T315I mutation, in the asciminib 200 mg BID treatment group, the median age was 56.5 years (range: 26-86 years), with 66.7% of patients aged 18 to < 65 years. Majority of patients were males (77.1%) and were predominantly white (58.3%). Baseline ECOG performance status was 0 (75%) or 1 (25%) (Table 32).

The FDA's Assessment:
FDA agrees with the Applicant's assessment of demographic features of patients using single agent asciminib in CML-CP harboring the T315I mutation at screening. With regards to race, white and black or African American patients were underrepresented while Asian patients were overrepresented. Concerning ethnicity, Hispanic or Latino patients were underrepresented. However, this is not thought to affect the generalizability of the results to the US population.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

In the 200 mg BID cohort, among 48 CML-CP patients harboring the T315I mutation, no patient had MMR at screening, but 3 patients had atypical/unknown transcripts and therefore excluded from the efficacy analysis. Among 45 patients with CML-CP in the T315I mutation analysis set, 26 patients had received prior treatment with ponatinib and 19 patients were ponatinib-naive.

The FDA's Assessment:
FDA agrees with the Applicant's statement that 3 patients had atypical/unknown transcripts. Therefore, the efficacy population in the label will include 45 patients with T315I mutations who were treated rather than 48 patients who were evaluated for safety.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
The Applicant's Position:

As per protocol requirement, all patients harboring the T315I mutation had previously received at least one TKI. In the 200 mg BID treatment group, 40 (83.3%) patients had received at least 2 prior TKIs, including 25 (52.1%) patients who had received at least 3 prior TKIs. The most frequent

prior TKI received (≥ 50% of all patients) were dasatinib (68.8%), ponatinib (60.4%), imatinib (56.3%), and nilotinib (54.2%). In the asciminib 200 mg BID treatment group, the median duration of exposure was 69.8 weeks (range: 2-175) in 48 patients. Of these, 40 patients (83.3%) were exposed to study treatment for at least 24 weeks.

Concomitant medication was not specifically analyzed for patients with T315I mutation. Refer to Section 8.1.4

No rescue medication was allowed.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

MMR rate by/ MMR rate at scheduled time points

A clinically meaningful MMR rate was observed in CML-CP patients harboring the T315I mutation. MMR was achieved by 22/45 (48.9%) patients in the CML-CP T315I mutation analysis set, as of the data cut-off date. The cumulative MMR rate by Week 24 was 42.2% (95% CI: 27.7, 57.8), and the MMR rate at Week 24 was 37.8% (95% CI: 25.6, 56.7).

- **Ponatinib-naive:** MMR was achieved by 13 (68.4%) out of 19 ponatinib-naive patients. The cumulative MMR rate by Week 24 (including patients who achieved MMR at or before Week 24) was 57.9% (90% CI: 36.8%-77.0%), and the MMR rate at Week 24 was 52.6% (90% CI: 32.0, 72.6).
- **Ponatinib pre-treated:** A total of 9 (34.6%) out of 26 ponatinib pre-treated patients achieved MMR. The cumulative MMR rate by Week 24 (including patients who achieved MMR at or before Week 24) was 30.8% (90% CI: 16.3%-48.7%), and the MMR rate at Week 24 was 26.9% (90% CI: 13.4, 44.7).

Sensitivity analysis

A similar MMR rate was observed in the sensitivity analysis including patients with the expression of BCR-ABL atypical/unknown transcripts as non-responders. Overall, MMR was achieved by 45.8% of patients and the cumulative MMR rate by Week 24 was 39.6%.

The FDA's Assessment:

Of note, for the subgroup of Ph+ CML-CP harboring the T315I mutation, efficacy was based on 45 patients with Ph+ CML-CP harboring the T315I mutation who received asciminib at a dose of

200 mg twice daily in the Study CABL001X2101. Patients continued treatment until unacceptable toxicity or treatment failure occurred.

Of the 45 patients, 80% were male and 20% female; 31% were 65 years or older, while 9% were 75 years or older with a median age of 54 years (range, 26 to 86 years). The patients were White (47%), Asian (27%), and Black or African American (2.2%), and 24% were unreported or unknown. Seventy-three percent and 27% of patients had ECOG performance status 0 and 1, respectively. Patients who had previously received 1, 2, 3, 4, and 5 or more TKIs were 18%, 31%, 36%, 13%, and 2.2%, respectively.

MMR was achieved by 24 weeks in 42% (95% CI: 28% to 58%) of the 45 patients treated with SCEMBLIX. MMR was achieved by 96 weeks in 49% (95% CI: 34% to 64%) of the 45 patients treated with asciminib. The median duration of treatment was 108 weeks (range, 2 to 215 weeks).

Data Quality and Integrity

The Applicant's Position:

Details are provided in Section 8.1.4

The FDA's Assessment:
FDA confirms the Applicant's position.

Efficacy Results – Secondary and Other Relevant Endpoints

The Applicant's Position:

In patients with Ph+ CML-CP harboring the T315I mutation Time to and duration of MMR

Time to MMR: The median time to MMR was 12.2 weeks (range: 4-84) in 200 mg BID treatment group who achieved MMR (n = 22). The median time to MMR was 20.1 weeks (range: 4-84) in the ponatinib-naive patients (n = 13) and 12.1 weeks (range: 4-36) in the ponatinib pre-treated (n = 9).

Duration of MMR: Among 22 CML-CP patients in T315I mutation analysis set, who achieved MMR, 20 patients maintained this response or improved it to a deeper level of response, up to the cut-off date. Of the 2 patients who lost MMR, one patient had prior treatment with ponatinib and one was ponatinib-naive. The KM estimated proportion of patients maintaining their MMR for at least 96 weeks was 86.0% (95% CI: 65.9, 100.0).

- **Ponatinib-naive:** Among 13 CML-CP ponatinib-naive patients in T315I mutation analysis set, who achieved MMR, 12 patients maintained this response up to the cut-off date. The KM estimated proportion of patients maintaining their MMR for at least 96 weeks was 88.0% (95% CI: 64.6, 100.0).

- **Ponatinib pre-treated:** Among 9 CML-CP ponatinib pre-treated patients in the T315I mutation analysis set who achieved MMR, 8 patients maintained this response up to the cut-off date. The KM estimated proportion of patients maintaining their MMR for at least 96 weeks was 88.0% (95% CI: 64.6, 100.0).

BCR-ABL1 ratio ≤1% by Week 24
In the CML-CP T315I mutation analysis set, 37/45 patient had BCR-ABL% >1% at baseline, of which 17 (45.9%, 95% CI: 29.5, 63.1) patients achieved BCR-ABL% ≤1% by Week 24.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Dose/Dose Response

The Applicant's Position:

Exposure-response analyses are described in FDA disagrees with Applicant's position that there are no outstanding issues. There are several DDI issues that remain unresolved. Refer to the PMRs/PMCs Table in Section 6.1 Executive Summary for details.

Comprehensive Clinical Pharmacology Review.

The FDA's Assessment:

Please refer to FDA's assessment in Section 6.3.

Durability of Response

The Applicant's Position:

Among 22 patients in the T315I mutation analysis set who achieved MMR, 20 patients maintained this response up to the cut-off date, suggesting a sustained treatment effect of asciminib in CML-CP patients harboring the T315I mutation. The KM estimated proportion of patients maintaining their MMR for at least 96 weeks was 86.0% (95% CI: 65.9, 100.0).

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Persistence of Effect

Treatment with asciminib should continue for as long as clinical benefit is evident, or until unacceptable toxicity occurs. Following discontinuation of therapy, the natural course of the disease, i.e. progression, can be expected**.** In Study CABL001X2101 all patients discontinued from the study 30 days after discontinuation of treatment hence, persistence effect could not be assessed.

No studies have been conducted to assess withdrawal and rebound effects.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

The FDA's Assessment:

Not applicable. In addition, PRO endpoints may not be interpretable in trials without a control arm.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

No additional analysis other than those described in the study report were performed.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.1.6. Integrated Review of Effectiveness

The FDA's Assessment:

The primary efficacy results are from Study A2301. Supportive efficacy results are from Study X2101.

Study A2301 was a randomized, open-label trial of asciminib vs. bosutinib in subjects with CML-CP, previously treated with at least 2 prior TKIs. The primary endpoint of MMR at 24 weeks was considered appropriate as it reflects an endpoint reasonably likely to predict longer term disease control and survival, and represents an acceptable depth and duration of response in this setting. FDA agrees that the open-label design is appropriate given the primary endpoint was assessed by central lab determined BCR-ABL1 levels and therefore not likely to be subject to measurement bias. Study X2101 was a single-arm trial of asciminib in subjects with CML or Ph+ ALL. This trial provided evidence of efficacy for subjects with Ph+ CML-CP harboring the T315I mutation. In this trial, efficacy was based on a subgroup of 45 patients with Ph+ CML-CP harboring the T315I mutation who received asciminib at a dose of 200 mg twice daily. FDA has previously accepted single-arm trials to support the approval of treatment of relapsed or intolerant CML.

From a statistical point of view, FDA agreed that:

1) Study A2301 showed that MMR at 24 week in the asciminib arm was higher than that in the bosutinib arm (Table 25) and met the pre-specified threshold for statistical significance. In addition, Study A2301 showed that the MMR rate at 48 weeks was higher than that in bosutinib. With a median duration of follow-up of 20 months (range: 1 day to 36 months), the median duration of response had not yet been reached for patients who achieved MMR at any time.
2) In Study X2101, the MMR rate by 24 weeks for the two dose cohorts in Table 32 were 16% (95% CI: 4.5, 36) for asciminib 40 mg BID cohort and 29% (95% CI: 8.4, 58) for asciminib 80 mg QD cohort. The overall MMR rate by 24 weeks was 23% (95% CI: 15, 34).
3) Study X2101 showed that 42% (19/45, 95% CI: 28% to 58%) and 49% (22/45, 95% CI: 34% to 64%) of the CML-CP patients harboring T35I mutation treated with asciminib achieved by 24 weeks and by 96 weeks, respectively.

Of note, the key secondary endpoint of Study A2301, the MMR rate at 96 weeks was not analyzed due to immaturity of the data. Instead, the MMR rate at 48 weeks was assessed.

8.1.7. Assessment of Efficacy Across Trials

Primary End Points

The Applicant's Position:

There was no pooling done for efficacy analysis. Data from studies A2301 and X2101 are presented separately for each indication CML-CP with at least 2 prior TKI and CML CP harboring T315I mutation respectively.

The FDA's Assessment:

FDA confirms the Applicant's position. Also, please refer to Sections 8.1.2 and 8.1.4 – 8.1.6.

Secondary and Other Endpoints

The FDA's Assessment:

The secondary endpoints such as MMR rate at 48 weeks in Study CABL001A2301 and MMR rate by 96 weeks in Study CABL001X2101 were analyzed. Results from these analyses were in line with those from the primary endpoints in the two studies. Also, please refer to Sections 8.1.2 and 8.1.4 – 8.1.6.

Subpopulations

The FDA's Assessment:

For the subgroup of Ph+ CML-CP harboring the T315I mutation, efficacy was based on 45 patients with Ph+ CML-CP harboring the T315I mutation who received asciminib at a dose of 200 mg twice daily in the Study CABL001X2101. Results from these analyses showed that MMR rate with corresponding DOR was consistent with those from the analyses of the primary endpoints in primary populations for studies CABL001A2301 and CABL001X2101, with numerically higher MMR rate in this subgroup. Also, please refer to Sections 8.1.2 and 8.1.4 – 8.1.6.

Additional Efficacy Considerations

The Applicant's Position

Data from Study CABL001A2301 (described in section 8.1.2) supported by data from subset of patients with CML-CP not harboring the T315I mutation in the Phase I study (Study CABL001X2101 described in section 8.1.4) provide evidence of the efficacy of asciminib single-agent in Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) previously treated with two or more tyrosine kinase inhibitors.

The FDA's Assessment:

FDA confirms the Applicant's position.

8.1.8. Integrated Assessment of Effectiveness

The Applicant's Position:

Patients with Ph+ CML-CP previously treated with two or more TKIs

Results from the Study CABL001A2301 and Study CABL001X2101 provide compelling evidence supporting the efficacy claim of asciminib 40 mg BID in adult patients with Ph+ CML-CP, previously treated with two or more TKIs. Further, the efficacy-response analyses demonstrated the anti-leukemic activity of asciminib single agent regardless of dose levels (i.e. total daily dose of 20 to 400 mg) and number of prior lines of therapy received (i.e. 1 to 5 prior lines). The exposure-efficacy analysis of BCR-ABL1 ratio time course showed a slightly positive exposure-response relationship over the complete wide dose range tested regardless of PK metrics (daily AUC, Cmax and Cmin) used.

Study CABL001A2301 met its primary objective; superiority was demonstrated for asciminib 40 mg BID relative to bosutinib 500 mg QD for the primary endpoint of MMR at Week 24. The MMR rate at Week 24 was 25.5% in the asciminib arm (nearly twice as high) compared to 13.2% in the bosutinib arm. The treatment difference in the MMR rate was both statistically significant and clinically meaningful in this heavily pretreated population: 12.2% (95% CI: 2.19, 22.30, two-sided

p-value: 0.029) (per the Cochran–Mantel–Haenszel two-sided test, stratified by the MCyR status at baseline).

Multiple subgroup and sensitivity analyses in Study CABL001A2301 demonstrated the observed treatment benefit to be robust and consistent. Consistent treatment benefit (MMR at Week 24) was observed with asciminib compared to bosutinib irrespective of the number of previous lines of treatment with TKIs. The MMR rate at Week 24 was higher in patients on asciminib regardless of the detection of BCR-ABL1 mutations at baseline. As shown by the logistic regression models, imbalances at baseline between treatment arms based on sex (less females on asciminib), reason of discontinuation from last TKI (more intolerant patients on asciminib) and number of prior lines of TKI therapy (patients on asciminib less pre-heavily treated) did not have any significant impact on the primary analysis.

The efficacy of asciminib was further demonstrated by other secondary endpoints of the Study CABL001A2301. Superior and sustained results with asciminib treatment were observed for MMR/CCyR at and by all-time points. However, no long-term efficacy data with the exception of those presented in the preceding sections are available at the time of this application.

In Study CABL001A2301, at Week 24, there was a two-fold increase in the percentage of patients with BCR ABL1 IS ≤ 1% on asciminib compared to those on bosutinib (44.4% vs. 20.8%) (when only patients with BCR-ABL1 IS >1% at baseline were included in the analysis) which is considered clinically relevant.

A higher proportion of patients achieved deep molecular response (MR4 or better) in the asciminib arm as compared with the bosutinib arm (10.8% vs 5.3%). Of note, in contrast to bosutinib, the majority of patients on asciminib achieving MR4 also achieved MR4.5 (8.9% vs. 1.3%).

Among patients who achieved MMR, median time to MMR was 12.7 weeks asciminib arm and 14.3 weeks in bosutinib arm. The majority of patients who achieved MMR continued to have MMR (51/54; 94.4%) in the asciminib arm. The KM estimated proportion of patients maintaining their MMR for 24 weeks was 95.4% (95% CI: 82.8, 98.8) in the asciminib arm vs 100.0% (95% CI: NE, NE) in the bosutinib arm.

In addition to the efficacy data from Study CABL001A2301, Study CABL001X2101 provided supportive evidence of the efficacy of asciminib. A clinically meaningful and durable MMR rate was observed across asciminib dose levels ≥ 40 mg total daily dose and across all lines of therapy. Among the 86 MMR evaluable patients, 50 (58.1%) patients achieved MMR. The cumulative MMR rate by Week 24 was 23.3% (same as MMR rate at Week 24).

Among the 50 patients who achieved MMR in Study CABL001X2101, 46 patients maintained this response or improved it to a deeper level of response up to the cut-off date. The responses achieved were highly durable given the median duration of exposure of 183.4 weeks. The KM estimated proportion of patients maintaining their MMR for 96 weeks was 93% (95% CI: 85.7, 100.0). The KM estimated median time to MMR was not reached. The median time to MMR

among responders was 38.3 weeks.

The efficacy of asciminib in patients with Ph+ CML-CP previously treated with two or more TKIs is durable as demonstrated by the duration of first MMR in Study CABL001A2301 and Study CABL001X2101. In addition to the primary analysis in pivotal Study CABL001A2301, MMR rate at and by Week 96 analyses, PFS and OS update analyses at the end of 5-year follow-up are planned and would provide further data to ascertain the durability of response.

Patients with Ph+ CML-CP harboring the T315I mutation

Results from Study CABL001X2101 show clinically meaningful efficacy of asciminib 200 mg BID in patients with CML in CP harboring the T315I mutation. The information to support this indication is from a subset of 48 patients with CML-CP harboring T315I mutation receiving asciminib 200 mg BID enrolled in Study CABL001X2101.

Within Study CABL001X2101, for the 48 patients with T315I mutation the median duration of exposure was 69.8 weeks, including 40 patients (83.3%) who were exposed to study treatment for at least 24 weeks. This duration was considered sufficient to draw the efficacy results in these patients. Of 48 patients, 45 patients were included for efficacy analysis and 3 patients were excluded as these patients had atypical/unknown transcripts.

In 45 patients in the T315I mutation analysis set, MMR was achieved by 22 (48.9%) patients and the cumulative MMR rate by Week 24 was 42.2% (95% CI: 27.7, 57.8). The median time to MMR was 12.2 weeks and up to the time of cut-off date, 2 of 22 patients (one each from ponatinib pretreated and ponatinib-naive group) had lost MMR. The KM estimated proportion of patients maintaining their MMR for at least 96 weeks was 86.0%.

The results from the sensitivity analysis including patients with the expression of BCR ABL atypical/unknown transcripts as non-responders, showed a similar MMR rate by Week 24 of 39.6%.

The results from ponatinib-naive and ponatinib pre-treated population were generally consistent with the overall results, with higher MMR rates observed in ponatinib-naive patients compared to ponatinib pre-treated patients. In 19 ponatinib naïve patients, 13 (68.4%) patients achieved MMR. The cumulative MMR rate by Week 24 was 57.9% (90% CI: 36.8%, 77.0%). In 26 ponatinib pre-treated patients, MMR was achieved by 9 (34.6%) patients overall, the cumulative MMR rate by Week 24 was 30.8% (90% CI: 16.3, 48.7).

Among all 22 responders, 20 patients maintained this response or improved it to a deeper level of response up to the cut-off date. The KM estimated proportion of patients maintaining their MMR for 96 weeks was 86.0% (95% CI: 65.9, 100.0). The KM estimated median time to MMR was not reached. The median time to MMR among responders was 12.2 weeks.

The cumulative MMR rate in patients harboring T315I mutation supports the clinical benefit of asciminib in this subset of patients with poor prognosis. Efficacy was seen even in patients who

failed previous treatment with ponatinib, the only approved TKI for patients harboring the T315I mutation.

Results of the exposure-efficacy analyses indicated that a dose of 200 mg BID in patients harboring T315I mutation is considered as the optimal dose based on the totality of clinical data, asciminib exposure achieved at 200 mg BID and the model-derived EC95 value.

The FDA's Assessment:

Please refer to the FDA's Assessment in Sections 8.1.6 and 8.1.7.

8.2. Review of Safety

The Applicant's Position:

The safety evaluation of asciminib monotherapy is based on data from 356 patients with CML-CP/-AP in two clinical studies (Study CABL001A2301 and Study CABL001X2101) and 310 healthy volunteers (including 8 subjects with renal impairment and 24 subjects with hepatic impairment) in 9 clinical pharmacology studies. The data from these studies allow for a comprehensive and robust assessment of the safety profile of asciminib monotherapy and an evaluation of the overall benefit-risk balance in patients with Ph+ CML-CP. This safety population is considered appropriate for characterization of common AEs thus providing guidance on toxicity management in the intended population. Based on the mechanism of action, the safety profile of asciminib was expected to be similar between patients with CML-CP harboring and not harboring T315I mutation. Therefore, patients harboring the T315I mutation were included in the Safety Pool of Study CABL001A2301 and Study CABL001X2101.

The indications and the respective sources for safety information are presented below:

For "Patients with Ph+ CML-CP previously treated with ≥ 2 TKIs": The safety evaluation of asciminib monotherapy in patients with Ph+ CML-CP is based primarily on the data from the primary analysis (data cut-off date: 25-May-2020) of the pivotal Study CABL001A2301 (asciminib group; N=156 and bosutinib group; N=76). The safety data from the Study CABL001X2101 (data cutoff date: 02-Apr-2020) provides supportive evidence of asciminib safety in patients with CML-CP, including patients with CML-CP harboring the T315I mutation.

Pooled data provide the possibility of a more comprehensive analysis of the safety profile of asciminib treatment at different doses and different treatment regimens. Safety pools are defined as follows:

- Pool A (asciminib All patients Safety Pool; N=356): Data from all patients treated with asciminib in the Study CABL001A2301 (N=156) along with data from all patients with CML-CP/-AP (regardless of T315I mutation) treated with single agent asciminib at any dose from Study CABL001X2101 (N=200).
- Pool B (N=195): Data from all patients treated with asciminib in the Study CABL001A2301 (N=156) along with the data from patients with CML-CP/-AP/-BP and Ph+ ALL (regardless of

T315I mutation) treated with a starting dose of single agent asciminib 40 mg BID in Study CABL001X2101 (N=39).

- Pool C (asciminib 40 mg BID Safety Pool; N=187): Data from all patients treated with asciminib in the Study CABL001A2301 (N=156) along with data from patients with CML-CP (regardless of T315I mutation) treated with a starting dose of single agent asciminib 40 mg BID in Study CABL001X2101 (N= 31).
- Pool D (N=310): Data from all healthy volunteers participated in the nine clinical pharmacology studies (including hepatic and renal impairment subjects).

For "Patients with Ph+ CML-CP harboring the T315I mutation": The safety evaluation is based primarily on the data from 48 patients in Study CABL001X2101 who received single agent asciminib 200 mg BID, which is the recommended dose regimen. Further, data from 70 patients with CML-CP harboring the T315I mutation who received single agent asciminib at any dose regimen in the Study CABL001X2101 are provided as supportive information.

The FDA's Assessment:

We agree with the Applicant's position of the safety database for asciminib. In the asciminib All Patients Safety Pool (N=356), they pooled safety data from all patients treated with asciminib in Study CABL001A2301 (N=156) and from all patients with CML-CP / -AP treated with single-agent asciminib in study CABL001X2101 (N=200). Doses ranged from 10 mg bid to 200 mg bid and 80 mg daily to 200 mg daily.

The analyses in this review are based on Study CABL001A2301 with a data cut-off date of 25 May 2020 and Study CABL001X2101 with a data cut-off date of 02 April 2020. The Applicant submitted a 30-day Safety Update with a data cut-off date of 06 Jan 2021 for both studies. The safety analyses for purposes of the USPI will be presented from the data cut-off date of 06 Jan 2021. In this review, full safety analyses at the most recent timepoint conducted by the FDA will not be presented, but areas of significant differences in the timepoints will be noted.

8.2.1. Safety Review Approach

The Applicant's Position:

Safety data for "patients with Ph+ CML previously treated with two or more TKIs" are based on the results of two studies, Study CABL001A2301 and Study CABL001X2101. Safety data for "patients with Ph+ CML-CP harboring the T315I mutation" is based on a subset of patients with Ph+ CML-CP harboring T315I mutation who received asciminib at 200 mg BID in Study CABL001X2101. The adverse events of special interest (AESIs) are identified by grouping AEs that are of scientific and medical concern specific to asciminib and/or are related to class risks of other TKIs. All safety analyses were performed on Safety set of Study CABL001A2301 and Study CABL001X2101, which included all patients who received at least one dose of study treatment.

The FDA's Assessment:
Because asciminib All patients Safety Pool (N=356) provides a larger patient population to describe the safety of single agent asciminib, Warnings and Precautions section of the prescribing information will describe adverse events of special interest in this patient population. Otherwise, safety data in this review and the USPI will be mostly based on the patient populations in Study CABL001A2301 and the T315I arm of CABL001X2101 independently.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 35: Duration of exposure – Study CABL001A2301, Study CABL001X2101, and asciminib Safety Pools (Safety set)

	Study CABL001A2301		Study CABL001X2101	Safety Pool	
	Bosutinib 500 mg QD N=76	**Asciminib 40 mg BID N=156**	**Asciminib 80 mg QD (CP) N=18**	**Asciminib 40 mg BID (CP) N=187**	**Asciminib All patients N=356**
Duration of exposure (weeks)					
n	76	156	18	187	356
Mean (SD)	33.66 (26.414)	49.38 (31.486)	150.98 (57.242)	69.06 (65.506)	95.14 (81.017)
Median	29.21	43.36	173.43	49.14	65.07
Q1-Q3	17.14-38.79	27.29-69.21	112.57-189.14	28.14-84.00	31.07-144.86
Min-Max	1.0-117.0	0.1-129.9	15.1-211.4	0.1-295.3	0.1-302.1
Duration of exposure categories -n (%)					
<8 weeks	10 (13.2)	12 (7.7)	0	14 (7.5)	24 (6.7)
8 to < 16 weeks	6 (7.9)	5 (3.2)	1 (5.6)	5 (2.7)	11 (3.1)
16 to < 24 weeks	11 (14.5)	11 (7.1)	0	13 (7.0)	23 (6.5)
24 to < 48 weeks	36 (47.4)	57 (36.5)	1 (5.6)	59 (31.6)	77 (21.6)
48 to < 96 weeks	8 (10.5)	55 (35.3)	0	58 (31.0)	85 (23.9)
96 to < 144 weeks	5 (6.6)	16 (10.3)	4 (22.2)	18 (9.6)	46 (12.9)
144 to < 192 weeks	0	0	9 (50.0)	2 (1.1)	33 (9.3)
≥ 192 weeks	0	0	3 (16.7)	18 (9.6)	57 (16.0)
Patient-Treatment-Years	**49.0**	**147.6**	**52.1**	**247.5**	**649.1**

Patient-Treatment-Years (PTY) is the sum of each patient's treatment exposure in years.
Source: Novartis ABL001A Summary of clinical safety-Table 5-1

The Applicant's Position:

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

Exposure to asciminib in Study CABL001A2301 and Study CABL001X2101 was considered appropriate to allow for an adequate assessment of safety of asciminib in patients who are representative of the intended target population (Table 33).

Patients with Ph+ CML-CP harboring the T315I mutation

In Study CABL001X2101, among 70 patients with Ph+ CML-CP harboring the T315I mutation who received at least one dose of asciminib at any dose regimen, 48 patients were treated at the starting dose of 200 mg BID, which is the recommended dose regimen in this population. The median duration of exposure in patients with Ph+ CML-CP harboring the T315I mutation at the 200 mg BID dose was 69.8 weeks; 37.5% of the patients were exposed to treatment for ≥ 96 weeks and 12.5% for ≥ 144 weeks.

The FDA's Assessment:

Considering that the primary endpoint of Study CABL001A2301 is MMR at 24 weeks, the duration of exposure to asciminib is adequate. The 30-day Safety Update with a data cut-off date of 06 Jan 2021 provided about 7.5 months of additional follow-up for patients in Study A2301 and about 9 months of additional follow-up for patients in Study CABL001X2101.

Relevant characteristics of the safety population:

The Applicant's Position:

Includes safety data for "patients with Ph+ CML previously treated with two or more TKIs" based on the results of two studies, Study CABL001A2301 (registration study) and Study CABL001X2101 (supportive study).

Safety data for "patients with Ph+ CML-CP harboring the T315I mutation" is based on a subset of patients with Ph+ CML-CP harboring T315I mutation who received asciminib at 200 mg BID dose in Study CABL001X2101.

The FDA's Assessment:

The safety population was nearly identical to the efficacy population. Baseline characteristics of the efficacy population are described in section 8.1 and they represent the safety population in Study CABL001A2301 and Study CABL001X2101.

Adequacy of the safety database:

The Applicant's Position:

The evaluation of safety is based on safety data from the two clinical studies (Study CABL001A2301 and Study CABL001X2101), which were pooled to form asciminib Safety

Pools to support the target indication in patients previously treated with ≥ 2 TKIs. All safety analyses were performed on Safety set of Study CABL001A2301 and Study CABL001X2101, which included all patients who received at least one dose of study treatment. The inclusion of the asciminib Safety Pools enabled the following:

- Evaluation of the impact of different doses and different treatment regimens from Study CABL001X2101.
- An informed assessment of the safety profile of asciminib
- Judgment of the overall benefit-risk of the drug in the treatment of Ph+ CML-CP.
- Robust safety evaluation based on a larger pool of patients with longer duration of follow-up.

The FDA's Assessment:
The size of the safety database is adequate to provide a reasonable estimate of adverse reactions, and the duration of treatment is adequate to allow assessment of adverse reactions over time for the indicated population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted data sets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported; data in the CRFs and adverse event databases were consistent.

The FDA's Assessment:
The quality of the safety data submitted was adequate to allow substantial primary review.

Categorization of Adverse Event

The Applicant's Position:

The safety of asciminib was evaluated based on:

- Frequency, type, and severity of AEs (graded as per NCI CTCAE version 4.03) and reported causal relationship to treatment of AEs (Note: Grade 5 events were collected only in Study CABL001A2301 and were derived for Study CABL001X2101 based on events with fatal outcome, and incorporated in the asciminib Safety Pool).
- Frequency of deaths, SAEs, and AESIs
- Changes in laboratory parameters, with particular attention to Grade 3 or 4 laboratory abnormalities (graded in accordance with the NCI's CTCAE, version 4.03)

- ECG changes and vital signs

The nature and timing of the clinical monitoring of AEs was considered adequate for the expected toxicities associated with asciminib. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 for data in individual studies (Study CABL001A2301 and Study CABL001X2101, and version 23.1 for the pooled data. The use of successive MedDRA versions had no significant impact on the analysis.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. Adverse events were assessed by frequency (i.e., events per patient). Additional group terms were evaluated based on common related terms (see Appendix 19.5). The grouped terms are included in safety analyses throughout the review and will be indicated with an "*" or "(GT)" in safety tables and the text of the review. The same grouped terms were used for safety analyses throughout the label.

Routine Clinical Tests

The Applicant's Position:

Data from all sources (central and local laboratories) were combined. The summaries included all laboratory assessments collected no later than 30 days after study treatment discontinuation. The clinical monitoring of patient safety was considered adequate for the expected toxicities associated with the study treatment. Patients were questioned about AEs at each clinic visit. In addition, AEs could also be detected when reported by the patients during or between visits or through physical examination, laboratory test results, or other assessments. Further to the standard safety evaluations outlined above, AE categories expected to be associated with asciminib were also analyzed. These AESIs were selected based on the mechanism of action of asciminib as well as nonclinical and early clinical observations.

The FDA's Assessment:
FDA agrees with the Applicant's position. The frequency of clinical assessments is adequate to assess the risks of serious safety signals.

8.2.4. Safety Results

Deaths

Data:

Table 36: Summary of deaths – Study CABL001A2301, Study CABL001X2101 and asciminib Safety Pools (Safety set)

	Study CABL001A2301		Study CABL001X2101	Safety Pool	
Category Preferred term	Bosutinib 500 mg QD N=76 n (%)	Asciminib 40 mg BID N=156 n (%)	Asciminib 80 mg QD (CP) N=18 n (%)	Asciminib 40 mg BID (CP) N=187 n (%)	Asciminib All patients N=356 n (%)
Total deaths	1 (1.3)	4 (2.6)	1 (5.6)	4 (2.1)	12 (3.4)
Within 30 days after last dose	1 (1.3)	2 (1.3)	1 (5.6)	2 (1.1)	8 (2.2)
Primary reason: Study indication	0	0	0	0	3 (0.8)
Primary reason: Other	1 (1.3)	2 (1.3)	1 (5.6)	2 (1.1)	5 (1.4)
Embolism arterial	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Ischaemic stroke	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Cardiac arrest	0	0	1 (5.6)	0	1 (0.3)
Completed suicide	0	0	0	0	1 (0.3)
General physical condition abnormal	0	0	0	0	1 (0.3)
Septic shock	1 (1.3)	0	0	0	0

MedDRA version 23.1.
Source: Novartis ABL001A Clinical overview Table 5-4

The Applicant's Position:

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

Overall, 3 on-treatment deaths were reported in Study CABL001A2301: 2 patients in the asciminib group (arterial embolism and ischemic stroke; confounding factors were present in both cases and neither was suspected to be related study treatment) and 1 patient (septic shock; suspected) in the bosutinib group. One on-treatment death in the 80 mg QD dose group was reported in Study CABL001X2101, due to cardiac arrest, which was not suspected to be related to study treatment (Table 36).

No additional on-treatment deaths were reported in the asciminib Safety pool C (40 mg BID) to those already observed in the asciminib treatment group in Study CABL001A2301. In the asciminib Safety pool A (All patients), there were 8 on-treatment deaths: 3 cases were due to the study indication, 2 cases were already mentioned above (in Study CABL001A2301), and the remaining 3 cases were attributed to cardiac arrest (mentioned above in Study CABL001X2101 80 mg QD dose group), completed suicide, and general physical condition deterioration.

Patients with Ph+ CML-CP harboring the T315I mutation

No on treatment deaths were reported in patients with Ph+ CML-CP harboring the T315I mutation and receiving the asciminib 200 mg BID dose regimen in Study CABL001X2101. Two on-treatment deaths were reported in patients treated at any dose regimen, one due to underlying disease in the 160 mg BID group and other was suicide (not suspected to be related to study treatment) in the 80 mg BID group.

The FDA's Assessment:
FDA agrees with the Applicant's assessment based on the investigator's assessment of causality of death due to AE. FDA analysis showed that of the 4 deaths in the asciminib arm of study CABL001A2301, the 2 deaths due to CML occurred 30 days after last dose of asciminib. The two deaths within 30 days after last dose of asciminib were caused by embolism arterial and ischemic stroke. Both of these patients had predisposing risk factors for arterial occlusive events. FDA assesses that based on the death narratives provided the causality between asciminib and deaths seems to be possible. In both Study CABL001A2301 and Study ABL001X2101, no excess mortality within 30 days of initiation of treatment was observed with asciminib. Cardiovascular toxicity including cardiovascular toxicity, cardiac failure and arrhythmia was added as a new section in Warnings & Precautions of the label.

Table showing deaths in Study A2301 and X2101

	Study A2301	
USUBJID	**Preferred term for death**	**Summary of death narrative**
CABL001A2301 (b) (6)	Ischemic stroke (asciminib 40 mg bid)	At screening patient had left atrial abnormality, left ventricular hypertrophy, inverted T waves, and depressed ST segment on initial ECG. On Day 56, he had ischemic stroke and died on Day 60. The relationship is evaluated as being possible.
CABL001A2301 (b) (6)	Embolism arterial (asciminib 40 mg bid)	At screening, patient's ECG showed left anterior hemiblock. The patient discontinued asciminib on Day 245 because of lack of efficacy and started treatment with ponatinib. 15 days after last dose of asciminib, and 7 days after starting ponatinib, the patient had mesenteric arterial thromboembolism. She denied surgical intervention and died 17 days after last dose of asciminib. The relationship is evaluated as being possible.
CABL001A2301	Chronic Myeloid	Asciminib was permanently discontinued on Day

(b) (6)	Leukemia (asciminib 40 mg bid)	199 due to lack of efficacy and the patient received the last dose on Day 182. Later, he was treated with hydroxycarbamide and he died 78 days after the last dose of asciminib due to CML. The relationship is evaluated as being not related.
CABL001A2301 (b) (6)	Chronic Myeloid Leukemia (asciminib 40 mg bid)	Asciminib was permanently discontinued due to neutropenia on Day 49. The patient died due to CML 283 days after the last dose of asciminib. The relationship is evaluated as being not related.
	Study X2101	
CABL001X2101 (b) (6)	General physical condition abnormal (asciminib 80 mg bid)	Patient had history of bladder cancer and urostomy. On Day 246, he was hospitalized with sepsis, renal failure, liver disorder, acute kidney injury. Blood culture revealed E. Coli. He developed right pleural effusion on Day 365. On Day 408, he presented with abnormal physical condition and asciminib was discontinued on Day 409. He died 2 days after last dose of asciminib. The relationship is evaluated as being unlikely related.
CABL001X2101 (b) (6)	Completed suicide (asciminib 80 mg bid)	Patient had depression and sleep disorder and was using olanzapine and lorazepam. Patient's asciminib dose was increased to 160 mg bid on Day 1093 due to lack of efficacy. On Day 1424, patient's depression worsened and asciminib was temporarily interrupted. Patient received the last dose of asciminib on Day 1441 and committed suicide on Day 1444. The relationship is evaluated as being unlikely related.
CABL001X2101 (b) (6)	Cardiac arrest (asciminib 80 mg qd)	Patient had history of hypercholesterolemia, carotid artery stenosis, and carotid endarterectomy. She had hypertension and abnormal non-clinically significant ST-depression on ECG on the first day of treatment. On Day 646, she developed left index third phalange ischemia while using asciminib 200 mg qd. On

		Day 681, she was diagnosed with myocardial ischemia and 3 days later, two stents were placed. On Day 860, she had acute cardiac failure. On Day 930, she developed systemic scleroderma. On Day 1013, she had recurrence of acute cardiac failure. She died of cardiac arrest on Day 1325. The relationship is evaluated as being possible.
CABL001X2101 (b) (6)	COVID-19 pneumonia (asciminib 200 mg bid)	Patient had hypertension, sleep apnea syndrome, chronic kidney disease, dyslipidemia. On Day 910, patient was hospitalized with fever and diagnosed with COVID-19 pneumonia and on Day 916 developed respiratory distress and died one day later. The relationship is evaluated as being possible.
CABL001X2101 (b) (6)	Leukemia (asciminib 160 mg bid)	The patient had neutropenia, anemia, thrombocytopenia, ALT, AST increases, hypocalcemia while using asciminib. On Day 77, asciminib was permanently discontinued due to disease progression. The patient was then treated with multi-agent chemotherapy. 22 days after last dose of asciminib, he had multiple organ dysfunction syndrome and septic shock. He died 24 days after last dose of asciminib. The relationship is evaluated as being not related.
CABL001X2101 (b) (6)	Leukemia (asciminib 200 mg qd)	Patient had hyperglycemia, coronary artery disease, and alcohol use. Screening ECG showed intraventricular conduction defect and first-degree AV block with heart rate of 52 bpm. On Day 42, the patient presented with rapid recurrent atrial fibrillation. On Day 50, patient had atrial fibrillation and the arrhythmogenic focus was ablated. Asciminib was discontinued on Day 130 due to disease progression. Patient died 71 days after last dose of asciminib due to disease progression. Although the relationship between asciminib and disease progression is evaluated as being not related, the relationship between asciminib and atrial fibrillation is

		evaluated as being possible.
CABL001X2101 (b) (6)	Leukemia (asciminib 150 mg bid)	The patient had CML-AP and had used all approved TKIs. The patient had several episodes of anemia and neutropenia while on asciminib. On Day 235, she developed a cerebral infarction and 3 days later asciminib was permanently discontinued because of disease progression. Although the relationship between asciminib and disease progression is evaluated as being not related, the relationship between asciminib and cerebral infarction is evaluated as being possible.
CABL001X2101 (b) (6)	Pneumonia (asciminib 200 mg bid)	Patient had hypertension, degenerative aortic and mitral valve disease, surgery for schwannoma, hypercholesterolemia, obesity, grade 1 pleural effusion since (b) (6). On Day 888, she developed COVID-19 pneumonia, had atrial fibrillation and acute respiratory distress syndrome later. On Day 917, she had cerebrovascular accident. She died on Day 927, 40 days after last dose of asciminib. Although the relationship between asciminib and COVID-19 pneumonia is evaluated as being not related, the relationship between asciminib and atrial fibrillation and cerebrovascular accident is evaluated as being possible.
CABL001X2101 (b) (6)	Pneumonia aspiration (asciminib 20 mg bid)	The patient had history of coronary artery disease, hypertension, Sjogren's syndrome, Type II DM, and hypertriglyceridemia. On Day 372, he developed peripheral arterial occlusive disease. On Day 414, he had a bypass graft. On Day 436, the patient had artery bypass occlusion. On Day 474, 64 days after interruption of asciminib, he had aspiration pneumonia and died. Although the relationship between asciminib and aspiration pneumonia is evaluated as being unlikely related, the relationship between asciminib and peripheral arterial occlusive disease is evaluated as being possible.
CABL001X2101 (b) (6)	Leukemia (asciminib 150 mg bid)	The patient initially used asciminib 40 mg bid and dasatinib 100 mg qd from (b) (6) to (b) (6)

		(b) (6). The patient was re-enrolled into the study on (b) (6) and on Day 57, dose of asciminib was increased to 200 mg bid and on day 115, asciminib was permanently discontinued because of lack of efficacy. Ten days after last dose of asciminib, patient was diagnosed with tumor lysis syndrome and upper GI hemorrhage. The patient had three episodes of circulatory collapse and died. The relationship is evaluated as being not related.

Serious Adverse Events

Data

Table 37: Serious adverse events by preferred term and grading irrespective of study treatment relationship[1] – Study CABL001A2301, Study CABL001X2101 and asciminib Safety Pools (Safety set)

	Study CABL001A2301				Study CABL001X2101		Safety Pool			
	Bosutinib 500 mg QD N=76		Asciminib 40 mg BID N=156		Asciminib 80 mg QD (CP) N=18		Asciminib 40 mg BID (CP) N=187		Asciminib All Patients N=356	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of patients with at least one event	**14 (18.4)**	**12 (15.8)**	**21 (13.5)**	**16 (10.3)**	**8 (44.4)**	**7 (38.9)**	**32 (17.1)**	**24 (12.8)**	**100 (28.1)**	**75 (21.1)**
Pneumonia	0	0	0	0	1 (5.6)	1 (5.6)	2 (1.1)	2 (1.1)	7 (2.0)	7 (2.0)
Pyrexia	0	0	2 (1.3)	2 (1.3)	0	0	3 (1.6)	3 (1.6)	5 (1.4)	3 (0.8)
Non-cardiac chest pain	0	0	1 (0.6)	1 (0.6)	0	0	2 (1.1)	1 (0.5)	4 (1.1)	3 (0.8)
Vomiting	1 (1.3)	0	1 (0.6)	0	1 (5.6)	1 (5.6)	1 (0.5)	0	4 (1.1)	3 (0.8)
Atrial fibrillation	1 (1.3)	1 (1.3)	0	0	0	0	1 (0.5)	1 (0.5)	3 (0.8)	3 (0.8)
Cardiac failure congestive	1 (1.3)	1 (1.3)	0	0	1 (5.6)	1 (5.6)	1 (0.5)	1 (0.5)	3 (0.8)	3 (0.8)
Cataract	0	0	0	0	1 (5.6)	1 (5.6)	1 (0.5)	1 (0.5)	3 (0.8)	3 (0.8)
Acute kidney injury	1 (1.3)	1 (1.3)	0	0	1 (5.6)	1 (5.6)	0	0	2 (0.6)	1 (0.3)

	Study CABL001A2301				Study CABL001X2101		Safety Pool			
	Bosutinib 500 mg QD		Asciminib 40 mg BID		Asciminib 80 mg QD (CP)		Asciminib 40 mg BID (CP)		Asciminib All Patients	
	N=76		N=156		N=18		N=187		N=356	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Cardiac failure	0	0	1 (0.6)	1 (0.6)	1 (5.6)	1 (5.6)	1 (0.5)	1 (0.5)	2 (0.6)	2 (0.6)
Haematuria	0	0	0	0	1 (5.6)	0	0	0	2 (0.6)	1 (0.3)
Myocardial ischaemia	0	0	1 (0.6)	0	1 (5.6)	1 (5.6)	1 (0.5)	0	2 (0.6)	1 (0.3)
Acute coronary syndrome	1 (1.3)	1 (1.3)	0	0	0	0	0	0	1 (0.3)	1 (0.3)
Atypical pneumonia	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Bone pain	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Cardiac arrest	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Cardiac failure acute	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Cardiovascular disorder	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Colitis	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Dehydration	1 (1.3)	0	1 (0.6)	1 (0.6)	0	0	1 (0.5)	1 (0.5)	1 (0.3)	1 (0.3)
Fibromyalgia	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Gastritis	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Haemolytic anaemia	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Hemiparesis	1 (1.3)	1 (1.3)	0	0	0	0	1 (0.5)	1 (0.5)	1 (0.3)	1 (0.3)
Kidney infection	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
May-Thurner syndrome	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Osteonecrosis	0	0	0	0	1 (5.6)	0	0	0	1 (0.3)	0
Peripheral ischaemia	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Pulmonary embolism	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Respiratory failure	1 (1.3)	1 (1.3)	0	0	0	0	0	0	1 (0.3)	1 (0.3)
Septic shock	1 (1.3)	1 (1.3)	0	0	0	0	0	0	1 (0.3)	1 (0.3)
Visual impairment	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)

	Study CABL001A2301				Study CABL001X2101		Safety Pool			
	Bosutinib 500 mg QD N=76		Asciminib 40 mg BID N=156		Asciminib 80 mg QD (CP) N=18		Asciminib 40 mg BID (CP) N=187		Asciminib All Patients N=356	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Pleural effusion	0	0	0	0	0	0	1 (0.5)	1 (0.5)	8 (2.2)	4 (1.1)
Decreased appetite	1 (1.3)	0	0	0	0	0	0	0	0	0
Dermatitis allergic	1 (1.3)	1 (1.3)	0	0	0	0	0	0	0	0
Diffuse large B-cell lymphoma	1 (1.3)	1 (1.3)	0	0	0	0	0	0	0	0
Drug eruption	1 (1.3)	1 (1.3)	0	0	0	0	0	0	0	0
Pancytopenia	1 (1.3)	1 (1.3)	0	0	0	0	0	0	0	0
Rash	2 (2.6)	2 (2.6)	0	0	0	0	0	0	0	0
Respiratory tract infection	1 (1.3)	1 (1.3)	0	0	0	0	0	0	0	0
Rib fracture	1 (1.3)	0	0	0	0	0	0	0	0	0
Squamous cell carcinoma	1 (1.3)	1 (1.3)	0	0	0	0	0	0	0	0
Stomatitis	1 (1.3)	1 (1.3)	0	0	0	0	0	0	0	0

[1]With at least 0.5% incidence in Study CABL001A2301 or asciminib Safety Pool or at least 1% incidence in Study CABL001X2101
Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 23.1, CTCAE version 4.03.
Source: Novartis ABL001A Summary of clinical safety-Table 2-13

The Applicant's Position:

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

The proportion of patients with SAEs was lower in the asciminib group compared to the bosutinib group (13.5% vs. 18.4%) in Study CABL001A2301; few had SAEs that were suspected to be treatment related (2.6% vs. 9.2%). The incidence of individual SAEs was low in both groups. In the asciminib group, all individual SAEs except pyrexia (two patients), were reported in not more than one patient (Table 35).

In Study CABL001X2101 80 mg QD dose group, SAEs were reported as single occurrences in 8 (44.4%) patients. One patient had SAEs that were suspected to be treatment-related; the SAEs

reported by this patient were bone pain, fibromayalgia (both Grade 3) and osteonecrosis (Grade 2).

The incidence of SAEs was low with the occurrence of either SAE in ≤ 2% of patients in the asciminib Safety pool A (all patients).

In the asciminib 40 mg BID Safety Pool, no additional suspected SAEs were reported to those already reported in the asciminib treatment group in Study CABL001A2301.

Patients with Ph+ CML-CP harboring the T315I mutation

SAEs occurred in 10 out of 48 patients with CML-CP harboring the T315I mutation and receiving asciminib 200 mg BID, including one patient who had SAEs suspected to be treatment-related. With exception of abdominal pain, pneumonia and vomiting (each reported in two patients); all other SAEs were reported as single occurrences. One patient had SAEs (non-cardiac chest pain and IIIrd nerve paralysis, both in same patient and Grade 3) which were suspected to be study treatment related (per investigator's assessment).

The FDA's Assessment:

FDA performed an analysis of all-grade treatment-emergent SAEs and events occurring in > 1% in the asciminib arm which are presented in the table below for A2301. For study A2301, SAEs > 1% in the bosutinib arm were not included in the table as any SAE occurring in one patient is 1.3% resulting in many SAEs above this threshold and their inclusion would not help in interpretation of the safety of asciminib. AEs regarding whole blood count (e.g. neutropenia or neutrophil count decreased) are excluded here and evaluated in the laboratory section or AESI where relevant. Analysis of SAEs appears similar to the Applicant's analysis. The Applicant used preferred terms, and the FDA groups preferred terms that describe the same concept. However, the Applicant's SAE data in both studies is acceptable because the differences are not thought to affect the safety profile of asciminib. The overall rate of SAEs was lower in the asciminib arm than in the bosutinib arm and the two drugs seemed to have different overall safety profiles.

Serious AEs (>1%) in Study CABL001A2301

	A2301	
	Asciminib N=156 (%)	**Bosutinib N=76 (%)**
Any SAE	13	18
Cardiovascular Disorder*	1.9	2.6
Pyrexia*	1.9	0
Cardiac Failure Congestive*	1.3	0
Source: FDA analysis using adae.xpt, adsl.xpt *Grouped term (see Appendix 19.5)		

FDA also performed an analysis of all-grade treatment-emergent SAEs and events occurring in > 4% in Study X2101. Analysis of SAEs appears similar to the Applicant's analysis except with different grouped terms. With the higher dose of asciminib in Study X2101, SAEs were more frequent and the types of SAEs were different than in Study A2301.

Serious AEs (>4%) in Study CABL001X2101

	X2101
	Asciminib 200 mg BID N= 48 (%)
Any SAE	21
Gastrointestinal Toxicity*	6.3
Abdominal pain*	4.2
Pneumonia*	4.2
Source: FDA analysis using adae.xpt, adsl.xpt *Grouped term (see Appendix 19.5)	

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 38: Adverse events leading to study treatment discontinuation by preferred term and grading - Study CABL001A2301, Study CABL001X2101 and asciminib Safety Pools (Safety set)

	Study CABL001A2301				**Study CABL001X2101**		**Safety Pool**			
	Bosutinib 500 mg QD		**Asciminib 40 mg BID**		**Asciminib 80 mg QD (CP)**		**Asciminib 40 mg BID (CP)**		**Asciminib All Patients**	
	N=76		**N=156**		**N=18**		**N=187**		**N=356**	
	All grades	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of patients with at least one event	**16 (21.1)**	**12 (15.8)**	**9 (5.8)**	**8 (5.1)**	**3 (16.7)**	**1 (5.6)**	**12 (6.4)**	**10 (5.3)**	**29 (8.1)**	**23 (6.5)**
Lipase increased	0	0	0	0	0	0	1 (0.5)	1 (0.5)	4 (1.1)	4 (1.1)
Thrombocytopenia	1 (1.3)	1 (1.3)	3 (1.9)	3 (1.9)	0	0	3 (1.6)	3 (1.6)	4 (1.1)	4 (1.1)
Amylase increased	0	0	1 (0.6)	0	0	0	2 (1.1)	0	3 (0.8)	1 (0.3)
Platelet count decreased	0	0	2 (1.3)	2 (1.3)	0	0	2 (1.1)	2 (1.1)	3 (0.8)	3 (0.8)
Neutropenia	3 (3.9)	3 (3.9)	2 (1.3)	2 (1.3)	0	0	2 (1.1)	2 (1.1)	2 (0.6)	2 (0.6)

	Study CABL001A2301				Study CABL001X2101		Safety Pool			
	Bosutinib 500 mg QD		Asciminib 40 mg BID		Asciminib 80 mg QD (CP)		Asciminib 40 mg BID (CP)		Asciminib All Patients	
	N=76		N=156		N=18		N=187		N=356	
Preferred term	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Neutrophil count decreased	0	0	2 (1.3)	2 (1.3)	0	0	2 (1.1)	2 (1.1)	2 (0.6)	2 (0.6)
Thrombocytosis	0	0	0	0	1 (5.6)	0	0	0	2 (0.6)	0
Acute coronary syndrome	0	0	0	0	0	0	0	0	1 (0.3)	0
Acute kidney injury	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Blast crisis in myelogenous leukaemia	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.3)
Bronchospasm	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.3)
Cardiac arrest	0	0	0	0	1 (5.6)	1 (5.6)	0	0	1 (0.3)	1 (0.3)
Cholecystitis acute	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.3)
Completed suicide	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.3)
Cyanosis	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.3)
Dyspnoea	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.3)
Ejection fraction decreased	0	0	1 (0.6)	1 (0.6)	0	0	1 (0.5)	1 (0.5)	1 (0.3)	1 (0.3)
General physical condition abnormal	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.3)
Hypersensitivity	0	0	0	0	0	0	0	0	1 (0.3)	0
Ischaemic stroke	0	0	1 (0.6)	1 (0.6)	0	0	1 (0.5)	1 (0.5)	1 (0.3)	1 (0.3)
Leukocytosis	0	0	0	0	1 (5.6)	0	0	0	1 (0.3)	0
Non-cardiac chest pain	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.3)
Pancreatitis	0	0	0	0	0	0	1 (0.5)	1 (0.5)	1 (0.3)	1 (0.3)
Pancreatitis acute	0	0	0	0	0	0	1 (0.5)	0	1 (0.3)	0
Pancytopenia	0	0	0	0	0	0	0	0	1 (0.3)	1 (0.3)
Rash	1 (1.3)	1 (1.3)	0	0	0	0	0	0	1 (0.3)	0
Urticaria	0	0	0	0	0	0	0	0	1 (0.3)	0
Alanine aminotransferase increased	4 (5.3)	3 (3.9)	0	0	0	0	0	0	0	0

	Study CABL001A2301				Study CABL001X2101		Safety Pool			
	Bosutinib 500 mg QD		Asciminib 40 mg BID		Asciminib 80 mg QD (CP)		Asciminib 40 mg BID (CP)		Asciminib All Patients	
	N=76		N=156		N=18		N=187		N=356	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Aspartate aminotransferase Increased	2 (2.6)	1 (1.3)	0	0	0	0	0	0	0	0
Blood creatinine increased	1 (1.3)	0	0	0	0	0	0	0	0	0
Diarrhoea	2 (2.6)	1 (1.3)	0	0	0	0	0	0	0	0
Diffuse large B-cell lymphoma	1 (1.3)	1 (1.3)	0	0	0	0	0	0	0	0
Drug eruption	1 (1.3)	0	0	0	0	0	0	0	0	0
Hydrothorax	1 (1.3)	1 (1.3)	0	0	0	0	0	0	0	0
Squamous cell carcinoma	1 (1.3)	1 (1.3)	0	0	0	0	0	0	0	0

Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 23.1, CTCAE version 4.03.
Source: Novartis ABL001A Summary of clinical safety-Table 2-15

The Applicant's Position:

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

The frequency of AEs leading to study treatment discontinuation reported was substantially lower in the asciminib group compared to the bosutinib group (5.8% vs. 21.1%) in Study CABL001A2301. Majority of these AEs were Grade ≥ 3 (asciminib 5.1% vs. bosutinib 15.8%). The incidence of individual AEs leading to study treatment discontinuation was low in the asciminib group; except thrombocytopenia in 3 patients, all other AEs occurred in not more than 2 patients (Table 36).

In Study CABL001X2101 80 mg QD dose group, AEs leading to study treatment discontinuation were reported as single occurrences in 3/18 patients.

The incidence of AEs leading to study treatment discontinuation was low in the asciminib Safety pool C (40 mg BID) (6.4%) and the asciminib Safety pool A (all patients) (8.1%) and consistent with that reported in the asciminib treatment group in Study CABL001A2301. No specific AE predominated.

Patients with Ph+ CML-CP harboring the T315I mutation

Among patients with CML-CP harboring the T315I mutation receiving 200 mg BID asciminib, single occurrence of AEs that lead to study treatment discontinuation were reported in 6/70 patients; of whom 3/48 patients had AEs (lipase increased, pancytopenia and thrombocytosis each in 1 patient) who received asciminib at 200 mg BID.

The FDA's Assessment:
FDA agrees with the Applicant's assessment for study CABL001A2301 except for some minor points. The percentage of patients who discontinued in the asciminib arm for all grade AEs was 5.8% compared to 23.7% in the bosutinib arm. Particular AEs leading to discontinuation did not occur in more than 2% of patients in study CABL001A2301 in the asciminib arm. AEs which led to discontinuation in more than 2% of subjects in the bosutinib arm were alanine aminotransferase increased, neutropenia, aspartate aminotransferase increased, diarrhea, rash (GT), and thrombocytopenia.

FDA agrees with the Applicant's assessment in patients with CML-CP harboring the T315I mutation treated at 200 mg bid. Discontinuation rate was 6% which was similar to the rate in Study CABL001X2101. Patients discontinued because of lipase increased, pancytopenia and thrombocytosis (one patient each).

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 39: Adverse events, leading to dose interruption or adjustment, by preferred term and grading occurring in at least 2 patients in either of the treatment groups- (Study CABL001A2301) (Safety set)

	Bosutinib N=76		Asciminib N=156	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of patients with at least one event	**46 (60.5)**	**37 (48.7)**	**59 (37.8)**	**53 (34.0)**
Neutropenia	8 (10.5)	7 (9.2)	23 (14.7)	22 (14.1)
Thrombocytopenia	6 (7.9)	5 (6.6)	23 (14.7)	23 (14.7)
Platelet count decreased	1 (1.3)	1 (1.3)	7 (4.5)	7 (4.5)
Lipase increased	2 (2.6)	2 (2.6)	6 (3.8)	6 (3.8)
Neutrophil count decreased	2 (2.6)	2 (2.6)	6 (3.8)	6 (3.8)
Blood bilirubin increased	1 (1.3)	0	3 (1.9)	0
Hypertension	0	0	3 (1.9)	3 (1.9)
Nausea	8 (10.5)	0	3 (1.9)	1 (0.6)
Vomiting	4 (5.3)	0	3 (1.9)	1 (0.6)

	Bosutinib N=76		Asciminib N=156	
Preferred term	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Amylase increased	0	0	2 (1.3)	1 (0.6)
Blood creatine phosphokinase increased	0	0	2 (1.3)	2 (1.3)
Diarrhoea	14 (18.4)	7 (9.2)	2 (1.3)	0
Menorrhagia	0	0	2 (1.3)	0
White blood cell count decreased	1 (1.3)	1 (1.3)	2 (1.3)	2 (1.3)
Alanine aminotransferase increased	10 (13.2)	10 (13.2)	1 (0.6)	1 (0.6)
Anaemia	3 (3.9)	3 (3.9)	1 (0.6)	1 (0.6)
Aspartate aminotransferase increased	8 (10.5)	5 (6.6)	1 (0.6)	1 (0.6)
Constipation	2 (2.6)	0	0	0
Decreased appetite	2 (2.6)	0	0	0
Fatigue	2 (2.6)	1 (1.3)	0	0
Hypophosphataemia	2 (2.6)	2 (2.6)	0	0
Pruritus	2 (2.6)	1 (1.3)	0	0
Pyrexia	2 (2.6)	0	0	0
Rash	4 (5.3)	2 (2.6)	0	0

A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 23.0, CTCAE version 4.03.
Source: Novartis ABL001A Summary of clinical safety-Table 2-16

The Applicant's Position:

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

In Study CABL001A2301, the proportion of patients with AEs requiring dose interruption or adjustment was lower in the asciminib treatment group (37.8%) relative to the bosutinib treatment group (60.5%). The most frequently (≥ 10%) occurring AEs requiring dose adjustment and/or interruption were thrombocytopenia and neutropenia in the asciminib treatment group; and diarrhea, ALT increase, neutropenia, nausea and AST increase in the bosutinib treatment group (Table 37).

The AEs requiring dose interruption or adjustment that occurred with at least a 5% lower incidence in the asciminib treatment group relative to the bosutinib treatment group were diarrhea (-17.1%), ALT increase (-12.6%), AST increase (-9.9%), nausea (-8.6%), and rash (-5.3%).

The AEs requiring dose interruption or adjustment that occurred with at least a 5% higher incidence in the asciminib treatment group relative to bosutinib was thrombocytopenia (+6.8%).

Patients with Ph+ CML-CP harboring the T315I mutation

AEs leading to dose interruption or adjustment of study treatment for patients with Ph+ CML-CP harboring the T315I mutation and receiving asciminib 200 mg BID in Study CABL001X2101 tended to be similar with all patients with Ph+ CML-CP harboring the T315I mutation in Arm 1 of Study CABL001X2101 irrespective of the dose administered. No new findings that would affect the safety profile of asciminib were reported.

Overall, in patients with Ph+ CML-CP harboring the T315I mutation and receiving asciminib 200 mg BID, 35.4% of the patients had AEs leading to dose adjustment/interruptions; 27.1% of the patients had AEs that led to study treatment interruption or adjustment which were suspected to be study treatment related (per investigator assessment). Except for lipase increase (n=4 patients; 8.3%) and thrombocytopenia (n=3 patients; 6.3%), all other AEs leading to dose interruption/adjustments were reported in either 1 or 2 patients. These observations were consistent with the observations made in all patients with Ph+ CML-CP harboring the T315I mutation in Arm 1 of Study CABL001X2101 irrespective of the dose administered.

The FDA's Assessment:

FDA analysis of AEs leading to dose interruption of asciminib in study CABL001A2301 occurred in 37% of patients in asciminib arm compared to 54% of patients in bosutinib arm. FDA analysis also showed that dose reduction occurred in 5% of patients in asciminib arm and 26% of patients in the bosutinib arm. The majority of dose modifications (dose interruptions and dose reductions) were dose interruptions. The most frequent causes for dose interruption in the asciminib arm were neutropenia (15%) and thrombocytopenia (14%). Other AEs which led to dose interruption were platelet count decreased (4.5%), neutrophil count decreased (3.8%), and lipase increased (3.8%). The only AE > 2% which led to dose reduction in the asciminib arm was thrombocytopenia (3.2%).

FDA analysis of AEs leading to temporary interruption of asciminib in Study CABL001X2101 occurred in 25% of patients with T315I mutations treated at 200 mg bid. AEs > 4% which led to temporary interruption of asciminib were thrombocytopenia (6%), lipase increased (6%), and pneumonia (GT) (4.2%). According to FDA analysis, dose reduction of asciminib occurred in 23% of patients in Study CABL001X2101 and the most frequent causes were lipase increased (8%), abdominal pain (GT) (4.2%), and amylase increased (4.2%). All other AEs which led to dose adjustment of asciminib were seen in only one patient.

Significant Adverse Events

The Applicant's Position:

The severity of adverse events in discussed in the "Treatment Emergent Adverse Events and Adverse Reactions" section below.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 40: Adverse events (at least 5% in Study CABL001A2301 and asciminib Safety Pool and at least 15% in Study CABL001X2101[1]) (Safety set)

	Study CABL001A2301				Study CABL001X2101		Safety Pool			
	Bosutinib 500 mg QD		Asciminib 40 mg BID		Asciminib 80 mg QD (CP)		Asciminib 40 mg BID (CP) (Pool C)		Asciminib All Patients (Pool A)	
	N=76		N=156		N=18		N=187		N=356	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of patients with at least one event	**73 (96.1)**	**46 (60.5)**	**140 (89.7)**	**79 (50.6)**	**18 (100)**	**14 (77.8)**	**171 (91.4)**	**103 (55.1)**	**340 (95.5)**	**214 (60.1)**
Thrombocytopenia	10 (13.2)	5 (6.6)	35 (22.4)	27 (17.3)	5 (27.8)	2 (11.1)	41 (21.9)	29 (15.5)	78 (21.9)	51 (14.3)

	Study CABL001A2301				Study CABL001X2101		Safety Pool			
	Bosutinib 500 mg QD		Asciminib 40 mg BID		Asciminib 80 mg QD (CP)		Asciminib 40 mg BID (CP) (Pool C)		Asciminib All Patients (Pool A)	
	N=76		N=156		N=18		N=187		N=356	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Headache	10 (13.2)	0	25 (16.0)	3 (1.9)	5 (27.8)	2 (11.1)	33 (17.6)	4 (2.1)	77 (21.6)	7 (2.0)
Fatigue	7 (9.2)	1 (1.3)	16 (10.3)	0	7 (38.9)	0	29 (15.5)	0	74 (20.8)	3 (0.8)
Nausea	35 (46.1)	0	18 (11.5)	1 (0.6)	4 (22.2)	0	24 (12.8)	1 (0.5)	70 (19.7)	3 (0.8)
Diarrhoea	54 (71.1)	8 (10.5)	18 (11.5)	0	4 (22.2)	0	27 (14.4)	0	69 (19.4)	2 (0.6)
Arthralgia	2 (2.6)	0	16 (10.3)	0	4 (22.2)	1 (5.6)	24 (12.8)	0	66 (18.5)	3 (0.8)
Hypertension	3 (3.9)	3 (3.9)	18 (11.5)	9 (5.8)	5 (27.8)	4 (22.2)	27 (14.4)	13 (7.0)	61 (17.1)	31 (8.7)
Lipase increased	5 (6.6)	3 (3.9)	8 (5.1)	6 (3.8)	4 (22.2)	3 (16.7)	22 (11.8)	13 (7.0)	60 (16.9)	35 (9.8)
Vomiting	20 (26.3)	0	11 (7.1)	2 (1.3)	3 (16.7)	1 (5.6)	18 (9.6)	3 (1.6)	53 (14.9)	8 (2.2)
Neutropenia	13 (17.1)	9 (11.8)	28 (17.9)	23 (14.7)	4 (22.2)	2 (11.1)	32 (17.1)	26 (13.9)	52 (14.6)	40 (11.2)
Rash	18 (23.7)	3 (3.9)	11 (7.1)	0	3 (16.7)	0	20 (10.7)	0	52 (14.6)	0
Abdominal pain	11 (14.5)	1 (1.3)	7 (4.5)	0	4 (22.2)	0	17 (9.1)	0	44 (12.4)	4 (1.1)
Pain in extremity	5 (6.6)	0	10 (6.4)	1 (0.6)	3 (16.7)	0	16 (8.6)	1 (0.5)	44 (12.4)	2 (0.6)
Pruritus	5 (6.6)	1 (1.3)	8 (5.1)	0	2 (11.1)	0	12 (6.4)	0	43 (12.1)	1 (0.3)
Upper respiratory tract infection	4 (5.3)	0	11 (7.1)	1 (0.6)	8 (44.4)	0	17 (9.1)	1 (0.5)	42 (11.8)	1 (0.3)
Anaemia	6 (7.9)	3 (3.9)	15 (9.6)	2 (1.3)	3 (16.7)	0	21 (11.2)	6 (3.2)	41 (11.5)	17 (4.8)

	Study CABL001A2301				Study CABL001X2101		Safety Pool			
	Bosutinib 500 mg QD		Asciminib 40 mg BID		Asciminib 80 mg QD (CP)		Asciminib 40 mg BID (CP) (Pool C)		Asciminib All Patients (Pool A)	
	N=76		N=156		N=18		N=187		N=356	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Back pain	1 (1.3)	1 (1.3)	10 (6.4)	1 (0.6)	3 (16.7)	1 (5.6)	15 (8.0)	1 (0.5)	40 (11.2)	4 (1.1)
Cough	4 (5.3)	0	10 (6.4)	0	2 (11.1)	0	17 (9.1)	0	39 (11.0)	0
Nasopharyngitis	2 (2.6)	0	15 (9.6)	0	0	0	19 (10.2)	0	39 (11.0)	0
Constipation	4 (5.3)	0	8 (5.1)	0	4 (22.2)	0	13 (7.0)	0	38 (10.7)	0
Dizziness	2 (2.6)	0	10 (6.4)	0	4 (22.2)	0	15 (8.0)	0	38 (10.7)	1 (0.3)
Amylase increased	4 (5.3)	0	9 (5.8)	1 (0.6)	2 (11.1)	0	16 (8.6)	4 (2.1)	36 (10.1)	8 (2.2)
Myalgia	2 (2.6)	0	7 (4.5)	0	1 (5.6)	0	11 (5.9)	0	33 (9.3)	2 (0.6)
Alanine aminotransferase increased	21 (27.6)	11 (14.5)	6 (3.8)	1 (0.6)	1 (5.6)	1 (5.6)	7 (3.7)	1 (0.5)	31 (8.7)	9 (2.5)
Oedema peripheral	2 (2.6)	0	9 (5.8)	0	1 (5.6)	0	15 (8.0)	0	30 (8.4)	2 (0.6)
Pyrexia	6 (7.9)	0	5 (3.2)	2 (1.3)	0	0	9 (4.8)	3 (1.6)	29 (8.1)	3 (0.8)
Abdominal pain upper	5 (6.6)	1 (1.3)	7 (4.5)	0	2 (11.1)	0	10 (5.3)	0	27 (7.6)	0
Dyspnoea	2 (2.6)	0	5 (3.2)	0	3 (16.7)	0	10 (5.3)	0	27 (7.6)	2 (0.6)
Insomnia	1 (1.3)	0	8 (5.1)	0	0	0	12 (6.4)	0	27 (7.6)	2 (0.6)

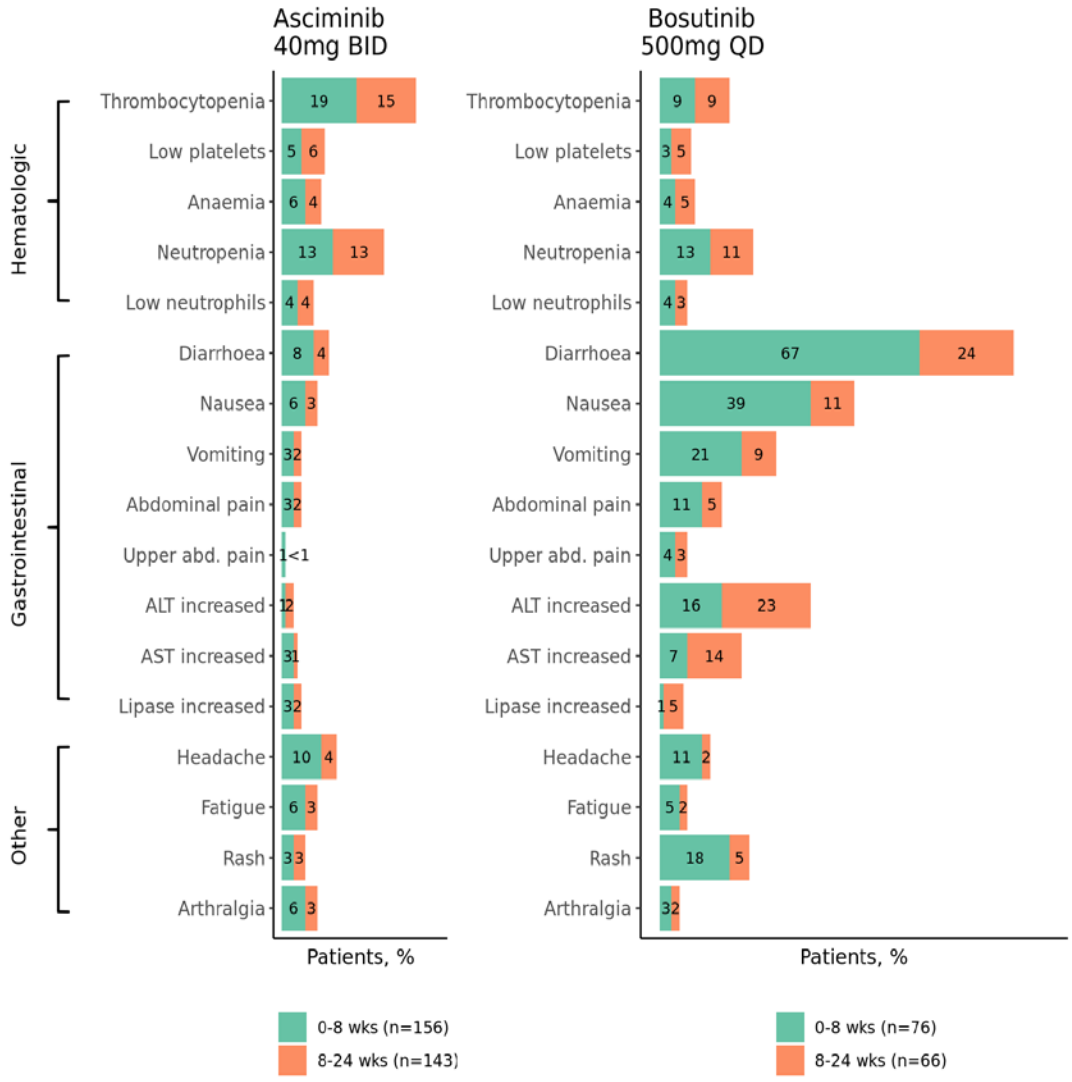
	Study CABL001A2301				Study CABL001X2101		Safety Pool			
	Bosutinib 500 mg QD		Asciminib 40 mg BID		Asciminib 80 mg QD (CP)		Asciminib 40 mg BID (CP) (Pool C)		Asciminib All Patients (Pool A)	
	N=76		N=156		N=18		N=187		N=356	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Aspartate aminotransferase increased	16 (21.1)	5 (6.6)	6 (3.8)	1 (0.6)	1 (5.6)	0	7 (3.7)	2 (1.1)	26 (7.3)	5 (1.4)
Hyperuricaemia	2 (2.6)	0	5 (3.2)	2 (1.3)	3 (16.7)	2 (11.1)	6 (3.2)	3 (1.6)	24 (6.7)	6 (1.7)
Decreased appetite	6 (7.9)	0	6 (3.8)	0	0	0	7 (3.7)	0	23 (6.5)	1 (0.3)
Hypertriglyceridaemia	1 (1.3)	0	3 (1.9)	2 (1.3)	4 (22.2)	2 (11.1)	7 (3.7)	2 (1.1)	23 (6.5)	7 (2.0)
Dyspepsia	3 (3.9)	0	8 (5.1)	0	1 (5.6)	0	8 (4.3)	0	22 (6.2)	0
Muscle spasms	0	0	7 (4.5)	1 (0.6)	1 (5.6)	0	12 (6.4)	1 (0.5)	22 (6.2)	1 (0.3)
Non-cardiac chest pain	1 (1.3)	0	6 (3.8)	1 (0.6)	2 (11.1)	0	9 (4.8)	1 (0.5)	22 (6.2)	3 (0.8)
Anxiety	1 (1.3)	0	5 (3.2)	1 (0.6)	2 (11.1)	1 (5.6)	7 (3.7)	1 (0.5)	21 (5.9)	3 (0.8)
Bone pain	1 (1.3)	0	2 (1.3)	0	2 (11.1)	1 (5.6)	7 (3.7)	0	20 (5.6)	1 (0.3)
Hyperglycaemia	0	0	5 (3.2)	3 (1.9)	3 (16.7)	1 (5.6)	8 (4.3)	3 (1.6)	20 (5.6)	6 (1.7)
Oropharyngeal pain	1 (1.3)	0	5 (3.2)	0	4 (22.2)	0	7 (3.7)	0	20 (5.6)	0
Blood creatinine increased	3 (3.9)	0	5 (3.2)	0	0	0	7 (3.7)	0	19 (5.3)	0

	Study CABL001A2301				Study CABL001X2101		Safety Pool			
	Bosutinib 500 mg QD		Asciminib 40 mg BID		Asciminib 80 mg QD (CP)		Asciminib 40 mg BID (CP) (Pool C)		Asciminib All Patients (Pool A)	
	N=76		N=156		N=18		N=187		N=356	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Gamma-glutamyltransferase increased	0	0	1 (0.6)	1 (0.6)	1 (5.6)	1 (5.6)	3 (1.6)	2 (1.1)	19 (5.3)	7 (2.0)
Platelet count decreased	4 (5.3)	2 (2.6)	10 (6.4)	7 (4.5)	1 (5.6)	0	13 (7.0)	10 (5.3)	19 (5.3)	14 (3.9)
Dry eye	1 (1.3)	0	3 (1.9)	0	1 (5.6)	0	6 (3.2)	0	18 (5.1)	0
Dry skin	6 (7.9)	0	3 (1.9)	0	2 (11.1)	0	4 (2.1)	0	18 (5.1)	0
Hyperhidrosis	0	0	2 (1.3)	0	3 (16.7)	0	3 (1.6)	0	18 (5.1)	0
Hypophosphataemia	4 (5.3)	3 (3.9)	2 (1.3)	1 (0.6)	0	0	4 (2.1)	2 (1.1)	18 (5.1)	5 (1.4)
Neutrophil count decreased	4 (5.3)	3 (3.9)	7 (4.5)	6 (3.8)	0	0	9 (4.8)	8 (4.3)	17 (4.8)	15 (4.2)
Migraine	0	0	0	0	3 (16.7)	2 (11.1)	0	0	5 (1.4)	3 (0.8)
Asthenia	1 (1.3)	0	9 (5.8)	0	1 (5.6)	0	10 (5.3)	0	16 (4.5)	0

	Study CABL001A2301				Study CABL001X2101		Safety Pool			
	Bosutinib 500 mg QD		Asciminib 40 mg BID		Asciminib 80 mg QD (CP)		Asciminib 40 mg BID (CP) (Pool C)		Asciminib All Patients (Pool A)	
	N=76		N=156		N=18		N=187		N=356	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

[1] At least 5% incidence in Study CABL001A2301 and asciminib Safety Pool and at least 15% incidence in Study CABL001X2101 (due to small sample size of 80 mg QD dose group).
Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 23.1, CTCAE version 4.03.
The change in MedDRA version 23.0 to 23.1 changed PT of musculoskeletal pain to arthralgia, PT of bone marrow to and myelosuppression and PT of eye burns to thermal burns of eye for 17, 3 and 2 reported AEs respectively in both the studies.
CP: Chronic Phase
Source: Novartis ABL001A Clinical overview-Table 5-2

Figure 8: Adverse events over time – (Study ABL011A2301) (Safety Set)



Adverse events over time: proportion of patients with on-treatment AEs occurring during the first 8 weeks of treatment, and newly occurring between weeks 8-24 of treatment. Denominators are the number of patients on treatment at the beginning of the indicated time interval. A patient with multiple occurrences of an AE with the same preferred term within the same time interval is counted only once in that time interval.
Source: Novartis ABL001A Summary of Clinical Safety-Figure 2-1

The Applicant's Position:

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

Most frequent AEs by preferred term

Study CABL001A2301: The proportion of patients who had at least one AE in Study CABL001A2301 was lower in the asciminib group compared to the bosutinib group (89.7% vs. 96.1%). Thrombocytopenia, neutropenia, headache, diarrhea, hypertension, nausea, and fatigue were the most frequently reported AEs associated with asciminib therapy, with each

occurring in ≥ 10% of patients. Adverse events that were reported more frequently in the asciminib group (with a ≥ 5% difference relative to the bosutinib group) were thrombocytopenia (+9.2%), arthralgia (+7.7%), hypertension (+7.6%), nasopharyngitis (+7.0%), and back pain (+5.1%) (Table 38).

Occurrence of AEs by time interval**:** The majority of the AEs reported in the asciminib and bosutinib groups (76.9% vs. 85.5%) occurred within the first 2 months of start of the treatment Figure 8 (). The incidence rate of AEs decreased over time (post 8 weeks and up to 24 weeks) with the exception of incidence of hematological AEs that remained the same, and a higher incidence of ALT/AST increase in the bosutinib group.

Severity of AEs: Except thrombocytopenia, neutropenia and hypertension, all other Grade ≥ 3 AEs were reported in <5% of patients in the asciminib group. Grade ≥ 3 thrombocytopenia (+10.7% difference relative to bosutinib group) was reported more frequently in the asciminib group.

Treatment-related AEs: Thrombocytopenia (19.9% vs. 13.2%), and neutropenia (14.7% vs. 14.5%) were the most frequent treatment-related AEs (>10%) reported in the asciminib group compared to the bosutinib group; however the difference in the incidence of these AEs was <10% between the two treatment groups. Of note, the frequency of treatment-related diarrhea (-65.2%), nausea (-31.8%), increased ALT (-27.0%), vomiting (-20.5%), rash (-17.1%), and increased AST (17.8%) were considerably lower in the asciminib group relative to bosutinib group.

Study CABL001X2101 80 mg QD dose group: All patients who were treated with asciminib 80 mg QD had at least one AE, and in majority of patients (88.9%) AEs reported were treatment-related. Upper respiratory tract infection (44.4%; 8 patients) and fatigue (38.9%; 7 patients) were the most frequently reported AEs in >5 patients; all these events were Grade 1 or 2.

Severity of AEs: Except for hypertension (22.2%; 4 patients) and lipase increased (16.7%; 3 patients), all Grade ≥ 3 AEs were reported infrequently in either 1 or 2 patients.

Asciminib safety pools: Except for lipase increased (+11.8%) and fatigue (+10.5%) that were more frequently reported in the asciminib All Patients Safety Pool, the type and frequency of AEs in both the asciminib Safety pool C (40 mg BID) and the asciminib Safety pool A (all patients) were largely consistent (difference of ≤ 10%) with those from the asciminib treatment group in Study CABL001A2301. No remarkable difference was observed in the incidence of treatment-related AEs in the Safety Pools and the asciminib group in the Study CABL001A2301.

Consistent with the asciminib group in the Study CABL001A2301, most of the AEs in the asciminib All patients Safety Pool occurred within the first 8 weeks after the start of study treatment, and the incidence remained same or decreased over time.

Patients with Ph+ CML-CP harboring the T315I mutation

Table 41: Adverse events, regardless of study treatment relationship occurring in 10% of patients by preferred term and asciminib treatment in patients with Ph+ CML-CP harboring T315I mutation at screening – Study CABL001X2101 (Safety set)

	Asciminib 200 mg BID N=48		All patients N=70	
Dictionary-derived term	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with at least one event	**48 (100)**	**27 (56.3)**	**70 (100)**	**41 (58.6)**
Fatigue	14 (29.2)	1 (2.1)	17 (24.3)	1 (1.4)
Nausea	13 (27.1)	0	16 (22.9)	0
Arthralgia	7 (14.6)	0	14 (20.0)	1 (1.4)
Diarrhoea	10 (20.8)	1 (2.1)	14 (20.0)	1 (1.4)
Headache	8 (16.7)	1 (2.1)	14 (20.0)	1 (1.4)
Alanine aminotransferase increased	7 (14.6)	3 (6.3)	12 (17.1)	5 (7.1)
Pain in extremity	6 (12.5)	0	12 (17.1)	0
Vomiting	9 (18.8)	3 (6.3)	12 (17.1)	3 (4.3)
Aspartate aminotransferase increased	6 (12.5)	1 (2.1)	11 (15.7)	4 (5.7)
Lipase increased	10 (20.8)	8 (16.7)	11 (15.7)	9 (12.9)
Rash	4 (8.3)	0	11 (15.7)	0
Thrombocytopenia	8 (16.7)	7 (14.6)	11 (15.7)	8 (11.4)
Pruritus	6 (12.5)	0	10 (14.3)	0
Pyrexia	4 (8.3)	0	10 (14.3)	0
Back pain	6 (12.5)	1 (2.1)	9 (12.9)	1 (1.4)
Hypertension	5 (10.4)	3 (6.3)	9 (12.9)	5 (7.1)
Myalgia	4 (8.3)	0	9 (12.9)	1 (1.4)
Abdominal pain	7 (14.6)	3 (6.3)	8 (11.4)	3 (4.3)
Constipation	4 (8.3)	0	8 (11.4)	0
Cough	6 (12.5)	0	8 (11.4)	0
Anaemia	4 (8.3)	2 (4.2)	7 (10.0)	5 (7.1)
Dyspnoea	3 (6.3)	0	7 (10.0)	0
Gamma-glutamyltransferase increased	4 (8.3)	2 (4.2)	7 (10.0)	3 (4.3)

	Asciminib 200 mg BID N=48		All patients N=70	
Dictionary-derived term	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Hyperuricaemia	4 (8.3)	0	7 (10.0)	0
Hypophosphataemia	1 (2.1)	1 (2.1)	7 (10.0)	3 (4.3)
Musculoskeletal pain	6 (12.5)	0	7 (10.0)	0
Amylase increased	5 (10.4)	2 (4.2)	5 (7.1)	2 (2.9)

Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 23.0 , CTCAE version 4.03.
Source: Novartis ABL001A Clinical overview Table 5-3

The Applicant's Position:

All patients with CML-CP treated with 200 mg BID dose of asciminib single agent had at least one AE regardless of study treatment relationship (Table 39: Adverse events, regardless of study treatment relationship occurring in 10% of patients by preferred term and asciminib treatment in patients with Ph+ CML-CP harboring T315I mutation at screening – Study CABL001X2101 (Safety set).

Fatigue, nausea, diarrhea, headache, vomiting, lipase increase, thrombocytopenia were the most frequent AEs reported (>15%) in patients treated at 200 mg BID. Most of these AEs were of ≤ Grade 2 and the most frequently (>10%) reported Grade ≥3 events were lipase increased and thrombocytopenia were reported as in 16.7% and 14.6% of patients, respectively.

The occurrence of AE incidence rates over time was considerably reduced > 8 weeks after treatment start compared to that occurred in the first 8 weeks, with the exception of thrombocytopenia; however the number of patients was small for making any definitive conclusion.

Adverse Drug Reactions

Numerical screening for candidates for ADRs was performed by flagging adverse events showing any excess cumulative incidence proportion ≥ 2% vs. bosutinib (all grades and Grade ≥ 3), by weeks 8, 24, 48 and overall in Study CABL001A2301 (as well as any similar increase between these timepoints in the asciminib arm). In addition, all labeled ADRs for bosutinib, core safety topics for asciminib captured in the case retrieval strategy (CRS) of the safety risk profile, and designated medical events (DMEs) were considered as ADR candidates regardless of the aforementioned numerical screening rule.

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

Number of patients with at least one ADR in Study CABL001A2301 was lower in asciminib treatment group (80.1%) compared to bosutinib treatment group (90.8%). Number of patients with at least one Grade ≥ 3 ADR was lower in asciminib (41.7%) treatment group compared to bosutinib (50.0%) (Table 42). The most frequent ADRs occurring in asciminib treatment group with an incidence rate of ≥ 20% were thrombocytopenia (28.8%), neutropenia (21.8%), and upper respiratory tract infection (21.2%). The most frequent Grade ≥ 3 ADRs, with an incidence rate of ≥ 5%, were thrombocytopenia (21.8%), neutropenia (17.9%), and hypertension (5.8%).
In Study CABL001X2101 asciminib 80 mg QD dose group, all patients experienced at least one ADR and 13 patients experienced at least one Grade ≥ 3 ADR. The most frequent ADRs (all grades) occurring in asciminib treatment group with an incidence rate of ≥ 20% were upper respiratory tract infection and fatigue (each 44.4%), thrombocytopenia and dyslipidemia (each 33.3%), headache, hypertension, abdominal pain and pancreatic enzyme increase (each 27.8%), neutropenia, anemia, dizziness, nausea, diarrhea, rash, arthralgia (each 22.2%).
In the asciminib safety pools, the incidence of majority of the ADRs was similar to the ADRs observed in Study CABL001A2301, the ADRs with a higher incidence of ≥ 20% were musculoskeletal pain (34.6%), thrombocytopenia (27.2%), upper respiratory tract infection (25.6%), fatigue (24.2%), headache (21.6%) and pancreatic enzyme increase (20.2%).

Patients with Ph+ CML-CP harboring the T315I mutation

Except two patients, all (95.8%) the patients with Ph+ CML-CP harboring T315I mutation and treated with asciminib 200 mg BID experienced at least one ADR with 25 patients (52.1%) experiencing at least one Grade ≥ 3 ADRs (Table 43). The most frequent ADRs occurring with an incidence rate of ≥ 20% were musculoskeletal pain (37.5%), fatigue (31.3%), nausea (27.1%), pancreatic enzymes increase (25.0%), and diarrhea (20.8%). The most frequent Grade ≥ 3 ADRs, with an incidence rate of ≥ 5%, were pancreatic enzyme increase (18.8%), thrombocytopenia (16.7%), neutropenia (12.5%), hepatic enzyme increased (8.3%), abdominal pain, vomiting and hypertension (each 6.3%).

Table 42: Frequency and frequency category of adverse drug reactions by SOC and ADR for Core Data Sheet – Study CABL001A2301, Study CABL001X2101 & Pool A (Safety set)

	Study CABL001A2301				Study CABL001X2101		Asciminib Safety Pool		
	Asciminib 40 mg BID N=156 n (%)		Bosutinib 500 mg QD N=76 n (%)		Asciminib 80 mg QD N=18 n (%)	Asciminib 80 mg QD N=18 n (%)	Asciminib Pool A N=356 n (%)		
Adverse Drug Reaction	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grades ≥ 3	Frequency category Pool A N=356 All Grades
No of patients with at least one ADR	**125 (80.1)**	**65 (41.7)**	**69 (90.8)**	**38 (50.0)**	**18 (100)**	**13 (72.2)**	**322 (90.4)**	**182 (51.1)**	
Infections and infestations									
Upper respiratory tract infection	33 (21.2)	1 (0.6)	6 (7.9)	0	8 (44.4)	0	91 (25.6)	1 (0.3)	Very common
Lower respiratory tract infection	4 (2.6)	0	2 (2.6)	0	2 (11.1)	1 (5.6)	24 (6.7)	7 (2.0)	Common
Influenza	5 (3.2)	0	2 (2.6)	0	1 (5.6)	0	16 (4.5)	1 (0.3)	Common
Blood and lymphatic system disorders									
Thrombocytopenia	45 (28.8)	34 (21.8)	14 (18.4)	7 (9.2)	6 (33.3)	2 (11.1)	97 (27.2)	65 (18.3)	Very common
Neutropenia	34 (21.8)	28 (17.9)	16 (21.1)	11 (14.5)	4 (22.2)	2 (11.1)	65 (18.3)	53 (14.9)	Very common
Anaemia	15 (9.6)	2 (1.3)	7 (9.2)	3 (3.9)	4 (22.2)	0	43 (12.1)	17 (4.8)	Very common
Febrile neutropenia	1 (0.6)	1 (0.6)	0	0	0	0	3 (0.8)	3 (0.8)	Uncommon
Metabolism and nutrition disorders									
Dyslipidaemia	6 (3.8)	4 (2.6)	2 (2.6)	0	6 (33.3)	2 (11.1)	33 (9.3)	9 (2.5)	Common

	Study CABL001A2301				Study CABL001X2101		Asciminib Safety Pool		
	Asciminib 40 mg BID N=156 n (%)		Bosutinib 500 mg QD N=76 n (%)		Asciminib 80 mg QD N=18 n (%)	Asciminib 80 mg QD N=18 n (%)	Asciminib Pool A N=356 n (%)		
Adverse Drug Reaction	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grades ≥ 3**	**Frequency category Pool A N=356 All Grades**
Decreased appetite	6 (3.8)	0	6 (7.9)	0	0	0	23 (6.5)	1 (0.3)	Common
Nervous system disorders									
Headache	25 (16.0)	3 (1.9)	10 (13.2)	0	5 (27.8)	2 (11.1)	77 (21.6)	7 (2.0)	Very common
Dizziness	10 (6.4)	0	2 (2.6)	0	4 (22.2)	0	38 (10.7)	1 (0.3)	Very common
Eye disorders									
Dry eye	3 (1.9)	0	1 (1.3)	0	1 (5.6)	0	18 (5.1)	0	Common
Vision blurred	4 (2.6)	0	0	0	2 (11.1)	0	17 (4.8)	0	Common
Cardiac disorders									
Palpitations	4 (2.6)	0	0	0	0	0	15 (4.2)	0	Common
Vascular disorders									
Hypertension	18 (11.5)	9 (5.8)	3 (3.9)	3 (3.9)	5 (27.8)	4 (22.2)	62 (17.4)	31 (8.7)	Very common
Respiratory, thoracic and mediastinal disorders									
Cough	10 (6.4)	0	4 (5.3)	0	2 (11.1)	0	39 (11.0)	0	Very common
Dyspnoea	5 (3.2)	0	2 (2.6)	0	3 (16.7)	0	27 (7.6)	2 (0.6)	Common

	Study CABL001A2301				Study CABL001X2101		Asciminib Safety Pool		
	Asciminib 40 mg BID N=156 n (%)		Bosutinib 500 mg QD N=76 n (%)		Asciminib 80 mg QD N=18 n (%)	Asciminib 80 mg QD N=18 n (%)	Asciminib Pool A N=356 n (%)		
Adverse Drug Reaction	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grades ≥ 3**	**Frequency category Pool A N=356 All Grades**
Non-cardiac chest pain	6 (3.8)	1 (0.6)	1 (1.3)	0	2 (11.1)	0	22 (6.2)	3 (0.8)	Common
Pleural effusion	2 (1.3)	0	0	0	0	0	15 (4.2)	5 (1.4)	Common
Gastrointestinal disorders									
Pancreatic enzymes increased	13 (8.3)	6 (3.8)	7 (9.2)	3 (3.9)	5 (27.8)	3 (16.7)	72 (20.2)	40 (11.2)	Very common
Nausea	18 (11.5)	1 (0.6)	35 (46.1)	0	4 (22.2)	0	70 (19.7)	3 (0.8)	Very common
Diarrhoea	18 (11.5)	0	54 (71.1)	8 (10.5)	4 (22.2)	0	69 (19.4)	2 (0.6)	Very common
Abdominal pain	13 (8.3)	0	16 (21.1)	2 (2.6)	5 (27.8)	0	65 (18.3)	4 (1.1)	Very common
Vomiting	11 (7.1)	2 (1.3)	20 (26.3)	0	3 (16.7)	1 (5.6)	53 (14.9)	8 (2.2)	Very common
Pancreatitis	0	0	0	0	1 (5.6)	0	9 (2.5)	4 (1.1)	Common
Hepatobiliary disorders									
Hepatic enzyme increased	8 (5.1)	1 (0.6)	23 (30.3)	13 (17.1)	2 (11.1)	1 (5.6)	47 (13.2)	12 (3.4)	Very common
Blood bilirubin increased	3 (1.9)	0	1 (1.3)	0	1 (5.6)	0	12 (3.4)	1 (0.3)	Common
Skin and subcutaneous tissue disorders									
Rash	18 (11.5)	0	19 (25.0)	4 (5.3)	4 (22.2)	0	66 (18.5)	0	Very common

	Study CABL001A2301				Study CABL001X2101		Asciminib Safety Pool		
	Asciminib 40 mg BID N=156 n (%)		Bosutinib 500 mg QD N=76 n (%)		Asciminib 80 mg QD N=18 n (%)	Asciminib 80 mg QD N=18 n (%)	Asciminib Pool A N=356 n (%)		
Adverse Drug Reaction	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grades ≥ 3**	**Frequency category Pool A N=356 All Grades**
Urticaria	2 (1.3)	0	2 (2.6)	0	1 (5.6)	0	12 (3.4)	0	Common
Musculoskeletal and connective tissue disorders									
Musculoskeletal pain	25 (16.0)	2 (1.3)	10 (13.2)	1 (1.3)	8 (44.4)	2 (11.1)	123 (34.6)	9 (2.5)	Very common
Arthralgia	16 (10.3)	0	2 (2.6)	0	4 (22.2)	1 (5.6)	66 (18.5)	3 (0.8)	Very common
General disorders and administration site conditions									
Fatigue	22 (14.1)	0	8 (10.5)	1 (1.3)	8 (44.4)	0	86 (24.2)	3 (0.8)	Very common
Pruritus	8 (5.1)	0	5 (6.6)	1 (1.3)	2 (11.1)	0	43 (12.1)	1 (0.3)	Very common
Oedema	10 (6.4)	0	2 (2.6)	0	2 (11.1)	0	32 (9.0)	2 (0.6)	Common
Pyrexia	5 (3.2)	2 (1.3)	7 (9.2)	0	0	0	29 (8.1)	3 (0.8)	Common
Investigations									
Blood creatine phosphokinase increased	2 (1.3)	2 (1.3)	3 (3.9)	1 (1.3)	0	0	11 (3.1)	3 (0.8)	Common
Electrocardiogram QT prolonged	2 (1.3)	1 (0.6)	0	0	0	0	2 (0.6)	1 (0.3)	Uncommon

	Study CABL001A2301				Study CABL001X2101		Asciminib Safety Pool		
	Asciminib 40 mg BID N=156 n (%)		Bosutinib 500 mg QD N=76 n (%)		Asciminib 80 mg QD N=18 n (%)	Asciminib 80 mg QD N=18 n (%)	Asciminib Pool A N=356 n (%)		Frequency category Pool A N=356
Adverse Drug Reaction	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grades ≥ 3**	**All Grades**

A patient with multiple occurrences of an ADR under one treatment is counted only once in the ADR category for that treatment.
A patient with multiple adverse drug reactions is counted only once in the total row.
ADRs with a start date up to 30 days after the last study treatment date are included.
No fatal adverse drug reactions were observed.
MedDRA version 23.1, CTCAE version 4.03, Case Retrieval Strategy version released 25-Feb-2021
Frequency category is based on the following convention: very common (=1/10); common (=1/100 to <1/10); uncommon (=1/1,000 to <1/100); rare (=1/10,000 to <1/1,000); very rare (<1/10,000)
Source: Novartis ABL001A Summary of Safety-Table 2-35

Table 43: Frequency and frequency category of adverse drug reactions by SOC and ADR for Core Data Sheet (CDS) – Study CABL001X2101 & Pool A: single agent asciminib in CML CP patients with CML-CP harboring the T315I mutation at screening (Safety set)

	Study CABL001X2101		Asciminib Safety Pool		
	Asciminib 200 mg BID N=48 n (%)		Asciminib Pool A N=356 n (%)		
Adverse Drug Reaction	All grades	Grade ≥ 3	All grades	Grade ≥ 3	Frequency category All Grades
No of patients with at least one ADR	**46 (95.8)**	**25 (52.1)**	**322 (90.4)**	**182 (51.1)**	
Infections and infestations					
Upper respiratory tract infection	5 (10.4)	0	91 (25.6)	1 (0.3)	Very common
Lower respiratory tract infection	4 (8.3)	2 (4.2)	24 (6.7)	7 (2.0)	Common
Influenza	1 (2.1)	0	16 (4.5)	1 (0.3)	Common
Blood and lymphatic system disorders					
Thrombocytopenia	9 (18.8)	8 (16.7)	97 (27.2)	65 (18.3)	Very common
Neutropenia	7 (14.6)	6 (12.5)	65 (18.3)	53 (14.9)	Very common
Anaemia	4 (8.3)	2 (4.2)	43 (12.1)	17 (4.8)	Very common
Febrile neutropenia	0	0	3 (0.8)	3 (0.8)	Uncommon
Metabolism and nutrition disorders					
Dyslipidaemia	2 (4.2)	1 (2.1)	33 (9.3)	9 (2.5)	Common
Decreased appetite	2 (4.2)	0	23 (6.5)	1 (0.3)	Common
Nervous system disorders					
Headache	8 (16.7)	1 (2.1)	77 (21.6)	7(2.0)	Very common
Dizziness	3 (6.3)	0	38 (10.7)	1(0.3)	Very common
Eye disorders					
Dry eye	1 (2.1)	0	18 (5.1)	0	Common
Vision blurred	1 (2.1)	0	17 (4.8)	0	Common
Cardiac disorders					
Palpitations	2 (4.2)	0	15 (4.2)	0	Common
Vascular disorders					
Hypertension	5 (10.4)	3(6.3)	62 (17.4)	31 (8.7)	Very common
Respiratory, thoracic and mediastinal disorders					
Cough	6 (12.5)	0	39 (11.0)	0	Very common
Dyspnoea	3 (6.3)	0	27 (7.6)	2 (0.6)	Common
Non-cardiac chest pain	3 (6.3)	1(2.1)	22 (6.2)	3 (0.8)	Common
Pleural effusion	1 (2.1)	1(2.1)	15 (4.2)	5 (1.4)	Common
Gastrointestinal disorders					

	Study CABL001X2101		Asciminib Safety Pool		
	Asciminib 200 mg BID N=48 n (%)		Asciminib Pool A N=356 n (%)		
Adverse Drug Reaction	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**Frequency category All Grades**
Pancreatic enzymes increased	12 (25.0)	9(18.8)	72 (20.2)	40 (11.2)	Very common
Nausea	13 (27.1)	0	70 (19.7)	3 (0.8)	Very common
Diarrhoea	10 (20.8)	1(2.1)	69 (19.4)	2 (0.6)	Very common
Abdominal pain	7 (14.6)	3(6.3)	65 (18.3)	4 (1.1)	Very common
Vomiting	9 (18.8)	3(6.3)	53 (14.9)	8 (2.2)	Very common
Pancreatitis	1 (2.1)	0	9 (2.5)	4 (1.1)	Common
Hepatobiliary disorders					
Hepatic enzyme increased	9 (18.8)	4(8.3)	47 (13.2)	12 (3.4)	Very common
Blood bilirubin increased	3 (6.3)	0	12 (3.4)	1 (0.3)	Common
Skin and subcutaneous tissue disorders					
Rash	7 (14.6)	0	66 (18.5)	0	Very common
Urticaria	1 (2.1)	0	12 (3.4)	0	Common
Musculoskeletal and connective tissue disorders					
Musculoskeletal pain	18 (37.5)	1(2.1)	123 (34.6)	9 (2.5)	Very common
Arthralgia	8 (16.7)	0	66 (18.5)	3 (0.8)	Very common
General disorders and administration site conditions					
Fatigue	15 (31.3)	1(2.1)	86 (24.2)	3 (0.8)	Very common
Pruritus	6 (12.5)	0	43 (12.1)	1 (0.3)	Very common
Oedema	4 (8.3)	2(4.2)	32 (9.0)	2 (0.6)	Common
Pyrexia	4 (8.3)	0	29 (8.1)	3 (0.8)	Common
Investigations					
Blood creatine phosphokinase increased	2 (4.2)	0	11 (3.1)	3 (0.8)	Common
Electrocardiogram QT prolonged	0	0	2 (0.6)	1 (0.3)	Uncommon

A patient with multiple occurrences of an ADR under one treatment is counted only once in the ADR category for that treatment.
A patient with multiple adverse drug reactions is counted only once in the total row.
ADRs with a start date up to 30 days after the last study treatment date are included.
No fatal adverse drug reactions were observed.
MedDRA version 23.1, CTCAE version 4.03, Case Retrieval Strategy version released 25-Feb-2021
Frequency category is based on the following convention: very common (=1/10); common (=1/100 to <1/10); uncommon (=1/1,000 to <1/100); rare (=1/10,000 to <1/1,000); very rare (<1/10,000).
Source" Novartis Summary of clinical safety-Table 2-36

The FDA's Assessment:
FDA agrees with the Applicant's assessment of all grade TEAEs in Study A2301.

FDA agrees with the Applicant's assessment of all grade AEs in study CABL001X2101 except that arthralgia (16.7%) is missing as one of the most frequent TEAEs in the text although it is included to be present in 14.6% of patients in Table 41. It is assumed that it was not included in the text as its percentage was less than < 15% in the Applicant's analysis. In this review, the FDA grouped term of musculoskeletal pain includes arthralgia.

The upper table shows the TEAEs ≥ 10%, all grade and grade 3-4, in Study CABL001A2301 and the lower table shows TEAEs ≥ 10% in CABL001X2101 in patients with T315I treated at 200 mg bid. These tables include laboratory investigations which are generally underreported as AEs and will be reported separately in labeling and are reviewed in the laboratory section below. Items in bold in the upper table (musculoskeletal pain, thrombocytopenia, and hypertension) are TEAEs which are ≥ 5% higher in asciminib arm vs. bosutinib arm. Items in bold in the lower table (lipase increased, thrombocytopenia, amylase increased, vomiting, and abdominal pain) are Grade 3-4 in > 5% patients.

TEAEs ≥ 10% in A2301

	Asciminib N=156 (%)		**Bosutinib N=76 (%)**	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Any TEAE	90	50	96	61
Musculoskeletal Pain*	**24**	**1.9**	**17**	**1.3**
Thrombocytopenia	**22**	**17**	**17**	**9**
Neutropenia	18	15	22	16
Headache*	16	1.9	14	0
Rash*	15	0.6	32	8
Fatigue*	14	0	11	1.3
Diarrhea*	12	0	71	11
Nausea	12	0.6	47	0
Hypertension*	**12**	**6.5**	**3.9**	**3.9**
Abdominal Pain*	9	0	22	2.6
Vomiting*	7	1.3	26	0
Alanine aminotransferase increased	3.9	0.6	28	14
Aspartate aminotransferase increased	3.9	0.6	21	7

Source: FDA analysis using adae.xpt, adsl.xpt (25 May 2021)
* Indicates grouped terms, see Appendix 19.5.

TEAEs ≥ 10% in CABL001X2101

	Asciminib 200 mg BID N=48 (%)	
	Any Grade	**Grade 3-4**
Any TEAE	100	47
Musculoskeletal pain*	50	4
Fatigue*	31	2.1
Nausea	27	0
Rash*	25	0
Lipase increased	**21**	**17**
Diarrhea*	21	2.1
Thrombocytopenia	**17**	**15**
Vomiting*	**19**	**6**
Headache*	19	2.1
Abdominal pain*	**17**	**8**
Hemorrhage*	15	2.1
Alanine aminotransferase increased	**15**	**6**
Aspartate aminotransferase increased	13	2.1
Pruritus	13	0
Cough*	13	0
Hypertension*	10	6
Amylase increased	10	4.2

Source: FDA analysis using adae.xpt, adsl.xpt (25 May 2021)
* Indicates grouped terms, see Appendix 19.5.

We agree with the Applicant's assessment of all grade AEs and grade ≥ 3 AEs in Study CABL001X2101 in Table 41.

The Applicant proposed select TEAEs that should not be considered ADRs above in Table 25. The Agency will consider any TEAEs with ≥ 10% incidence and occurring ≥ 2% more frequent on the treatment arm an ADR. FDA used custom queries and PTs to test for adverse drug reactions in study CABL001A2301. We do not agree with the Applicant's inclusion of some ADRs in Table 42. The TEAEs which should be listed as ADRs are upper respiratory tract infection (GT), thrombocytopenia, hypertension (GT), musculoskeletal pain (GT) (which does not include the PT of arthralgia), arthralgia, and fatigue (GT).

In addition, the frequencies of all grades and grade ≥ 3 thrombocytopenia and neutropenia were found to be higher in the bosutinib arm. The frequencies of upper respiratory tract infection (GT), lower respiratory tract infection (GT) and rash (GT) as assessed by the FDA were higher than in the Applicant's analyses in both arms because the FDA used grouped terms,

however the Applicant did not. These differences were thought not to influence the safety profile of asciminib.

FDA used custom queries and PTs to test for adverse drug reactions in study CABL001X2101. Based on the Applicant's definition of ADRs, we agree with the Applicant's assessment of Table 43 in general except that hemorrhage (GT), neuropathy peripheral (GT), and pneumonia (GT) should also be included as their frequencies are ≥ 5%. In addition, the frequency of rash (GT) was 25% in FDA assessment. The differences in frequencies of upper respiratory tract infection (GT), lower respiratory tract infection (GT) and musculoskeletal pain (GT) as reported by the Applicant and as assessed by the FDA are not thought to influence the safety profile of asciminib.

Laboratory Findings

The Applicant's Position:

Hematology

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

In Study A2301 asciminib 40 mg BID dose, the new or worsened post-baseline any grade hematological laboratory abnormalities, which occurred in:

- At least 10% lower proportion of patients in the asciminib treatment group relative to the bosutinib treatment group were: Hemoglobin decrease (-17.3%) and Lymphocytes decrease (-15.8%).
- At least 10% higher proportion of patients in the asciminib treatment group relative to bosutinib treatment group were Leukocytes decrease (+19.4%).

In Study A2301, the incidences of new or worsened grade 3 hematologic laboratory abnormalities were similar (difference < 5%) in both the treatment groups. Incidence of grade 4 were higher (difference > 5%) in the asciminib treatment group for platelets decrease (+6.5%) and neutrophils decrease (+6.1%) relative to the bosutinib treatment group.

In Study X2101 asciminib 80 mg dose group most frequently (≥ 40%) noted new or worsened hematologic laboratory abnormalities (all grades) were lymphocytes decrease (50%) and platelets decrease (44.4%). The incidence of grade 3 or 4 hematologic abnormalities was low (either 1 or 2 patients).

Asciminib Safety Pools: All the post-baseline hematologic laboratory abnormalities in both the asciminib 40 mg BID Safety Pool and the asciminib All Patients Safety Pool were consistent with those in the asciminib treatment group in Study CABL001A2301, with the exception of lymphocytes decrease; 17.1% in the asciminib treatment group in Study A2301 and 38.6% in the asciminib All Patients Safety Pool.

Patients with Ph+ CML-CP harboring the T315I mutation

The worst post-baseline hematologic laboratory abnormalities in patients with Ph+ CML-CP harboring the T315I mutation and receiving asciminib 200 mg BID dose in Study X2101 were consistent with all patients with Ph+ CML-CP harboring the T315I mutation in Arm 1 of Study CABL001X2101 receiving asciminib at any dose.

Although the incidence of any grade hematology abnormalities ranged between (33.3% to 68.8%) in patients with Ph+ CML-CP harboring the T315I mutation and receiving asciminib 200 mg BID dose, the incidence of grade ≥ 3 abnormalities was low (< 15%).

Biochemistry

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

In Study A2301 asciminib 40 mg BID, the most frequently (≥ 20%) noted new or worsened post-baseline (any grade) biochemical laboratory abnormalities in either of the treatment groups which also occurred in at least a 10% lower proportion of patients in the asciminib treatment group relative to the bosutinib treatment group were ALT increase (-31.3%) and AST increase (-30.6%). Triglycerides increase (+14.1%) was the lab abnormality which occurred in higher proportions of patients in the asciminib treatment group relative to the bosutinib treatment group (at least a 10% relative difference). Triglycerides increase was noted in >50% of patients in both the treatment groups (70.5% vs. 53.9% in the asciminib and bosutinib treatment group respectively) and these increases were predominantly of grade 1 or 2. Glucose increases were noted in 83.3% and 68.4% of the patients in asciminib and bosutinib treatment groups respectively and results indicate that the higher frequency of increases of glucose in the asciminib arm were not sustained over time. The incidence of most of the grade 3 and grade 4 biochemistry parameters was similar in both the treatment groups. A lower incidence (difference of >5%) of grade 3 biochemistry parameters was observed in asciminib treatment group compared to bosutinib treatment group for ALT increase (-15.2%) and AST increase (-6.0%).

The most frequently (≥ 40%) noted new or worsened post-baseline biochemical laboratory abnormalities (all grades) in patients receiving 80 mg QD dose were pancreatic lipase increase, phosphate decrease (each 55.6%), triglycerides increase (52.9%), and potassium increase (50.0%). Except for grade 3 phosphate decrease and grade 4 urate increase each (16.7%; n=3), new or worsened post-baseline biochemical laboratory abnormalities grade ≥ 3 were only seen in either 1 or 2 patients.

The majority of the post-baseline biochemical laboratory abnormalities in both the asciminib 40 mg BID. Safety Pool and the asciminib All Patients Safety Pool were consistent (difference of < 10%) with those in the asciminib treatment group in Study A2301. The biochemical laboratory abnormalities which were noted with ≥ 10% higher incidence in the asciminib All Patients Safety Pool compared to asciminib treatment group in Study A2301 were pancreatic lipase increase (+19%), potassium increase (+17.9%), phosphate decrease (+17.4%), ALT increase (+13.1%), albumin decrease (+12.6%) AST increase (+11.3%), calcium corrected decrease (+11.2%) and amylase increase (+11%). The higher frequency of pancreatic lipase increase and other

biochemistry parameters in the asciminib safety pool might be attributable to the longer exposure to asciminib treatment in Study X2101 than in Study A2301.

Pooling was not performed for hepatic function parameters, hence results for individual studies are presented. In Study CABL001A2301, increases in ALT or AST > 3×ULN were noted in lower numbers of patients in the asciminib treatment group (3.8%) compared to in the bosutinib treatment group (30.3%). In the asciminib treatment group, 1 patient had BILI increase of > 2×ULN. In both treatment groups, the majority of hepatic laboratory elevations (of AST and/or ALT and/or TBL) were noted as isolated increases. No concurrent elevations of ALT or AST > 3×ULN and total bilirubin > 2×ULN and ALP < 2×ULN meeting Hy's law biochemical criteria were observed in either of the treatment groups. In Study X2101 no concurrent elevations of ALT or AST > 3 × ULN and total bilirubin > 2 × ULN and ALP < 2 × ULN meeting the Hy's law biochemical criteria was observed among patients with ALT/AST and bilirubin levels within normal ranges at baseline.

Patients with Ph+ CML-CP harboring the T315I mutation

In Study X2101, the worst post-baseline biochemistry laboratory abnormalities in patients with Ph+ CML-CP harboring the T315I mutation and receiving asciminib 200 mg BID tended to be similar to that of all patients with Ph+ CML-CP harboring the T315I mutation in Arm 1 of Study X2101 irrespective of the dose administered.

The most frequently (≥ 30% of patients) noted biochemistry laboratory abnormalities in patients with Ph+ CML-CP harboring the T315I mutation and receiving asciminib 200 mg BID dose were triglycerides increase (64.6%), ALT increase (54.2%), urate increase (50.0%), GGT increase (47.9%), AST increase and potassium increase (each 45.8%), pancreatic lipase increase (43.8%), phosphate decrease and calcium corrected decrease (each 41.7%), and creatinine increase (37.5%). The majority of these abnormalities were of grade 1 or 2 intensity, with the exception of pancreatic lipase increase (18.8%), none of the grade ≥ 3 biochemistry abnormalities were noted in >10% of patients.

Hepatic function parameter results for patients with Ph+ CML-CP harboring the T315I mutation and receiving asciminib 200 mg BID dose, tended to be consistent with all patients with Ph+ CML-CP harboring the T315I mutation irrespective of the dose administered.

In the 200 mg BID cohort, post-baseline elevation in transaminases (ALT or AST) > 3 × ULN were noted in 7 patients (14.6%). Total bilirubin > 2 × ULN was reported in 1 patient (2.1%). No concurrent elevations of ALT or AST > 3 × ULN and total bilirubin > 2 × ULN and ALP < 2 × ULN meeting Hy's law biochemical criteria were observed among patients with ALT/AST and bilirubin levels within normal ranges at baseline. One patient with ALT/AST and/or total bilirubin above normal range at baseline met the Hy's law biochemical criteria during study and DILI was excluded upon assessment.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of hematology parameters. Myelosuppression resulting in leukopenia, anemia, and thrombocytopenia are known direct effects of tyrosine

kinase inhibitors. In Study A2301, myelosuppression of all grades and grades 3-4 were similar in asciminib vs. bosutinib arms. In Study X2101, myelosuppression was encountered at a lower rate than in Study A2301. Neutropenia and thrombocytopenia accounted for the most common causes of interruption of asciminib in Study A2301. Thrombocytopenia was the most common reason for dose reduction of asciminib in Study A2301. In Study X2101, thrombocytopenia was one of the most common causes of temporary interruption of asciminib. However, hemorrhage (GT) was less frequent in asciminib arm compared to bosutinib arm.
FDA agrees with the Applicant's assessment of biochemistry parameters. Triglycerides increase and glucose increase were more frequent in asciminib arm in Study A2301. Amylase increase and lipase increase were similar in both arms in Study A2301; however, they occurred at a much higher frequency in Study X2101. Although ALT increase and AST increase were less frequent with asciminib in Study A2301, bilirubin increase was 12% with asciminib compared to 8% with bosutinib. ALT increase, AST increase, and bilirubin increase were more frequent in Study X2101 compared to Study A2301. Updated results of laboratory abnormalities for Study A2301 and X2101 will be reflected separately for each study in the label. The Applicant will include uric acid increased, calcium corrected decreased, creatinine increased, and potassium decreased in Table 4 of the USPI for Study A2301 and in Table 6 of the USPI for Study X2101.

Vital Signs

The Applicant's Position:

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

In Study CABL001A2301, higher incidence of hypertension as AE was reported in patients on asciminib (11.5% vs. 3.9% bosutinib) with a similar proportion of events across periods overtime periods of 8, 24 and 48 weeks during the first year on treatment within the asciminib group. Despite this difference, notable changes on systolic (SBP values ≥ 180 mmHg together with an increase ≥ 20 mmHg; 3.2% vs. 1.3%) and diastolic (DBP values ≥ 105 mmHg together with an increase ≥ 15 mmHg; 4.5% vs. 5.3%) blood pressures were relatively similar between both treatment groups. None of the patient discontinued treatment due to hypertension events in either of the treatment groups.

In Study CABL001X2101, overall, no clinically meaningful changes in vital signs from baseline were noted. The most frequent (≥ 10% of all patients) notable changes observed was increase pulse rate (≥ 100 bpm and increase >25%) in 35/200 (17.5%) patients, increased weight in 27/200 (13.5%) patients, and decreased weight in 20/200 (10.0%) patients.

Notable systolic blood pressure (≥ 180 mmHg and increase ≥ 20 mmHg) and diastolic pressure (≥ 105 mmHg and increase ≥ 15 mm Hg) were reported in 10/200 (5.0%) patients each which was added to align information on hypertension in this study as presented for Study CABL001A2301.

Patients with Ph+ CML-CP harboring the T315I mutation

In Study CABL001X2101, no clinically meaningful changes in vital signs from baseline were noted in patients with Ph+ CML-CP harboring the T315I mutation and receiving asciminib 200 mg BID. The most frequent (≥ 10% of all patients) notable change observed were, increased pulse rate (≥ 100 bpm and increase of > 25%) in 7 patients (14.6%), increased weight in 5 patients (10.4%).

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Electrocardiograms (ECGs)

The Applicant's Position:

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

In Study CABL001A2301, while a higher proportion of patients in the asciminib treatment group had notable Fridericia corrected QT intervals (QTcF) compared to the bosutinib treatment group,

1 patient (0.6%) in the asciminib treatment group was noted with a new > 500 ms QTcF value; observed concomitantly with a > 60 ms increase from baseline. This was a single occurrence on Week 1 Day 1. On Day 2, the event reduced to grade 2, asciminib was interrupted and after patient recovered restarted at a reduced dose of 20 mg BID. Thirteen patients (8.3%) in the asciminib treatment group had new > 450 ms to ≤ 480 ms QTcF values compared to 2 patients (2.7%) in the bosutinib treatment group.

In Study CABL001X2101, the ECG changes were not clinically meaningful. QTcF increases >60 ms and absolute QTcF > 500 ms were observed in 2 patients (2.0%) and 3 (1.5%) patients, respectively. Increases of > 30 ms to ≤ 60 ms from baseline in QTcF were reported in 24 of 199 patients (12.1%).

Patients with Ph+ CML-CP harboring the T315I mutation

Overall, ECG changes were not clinically meaningful in patients with Ph+ CML-CP harboring the T315I mutation and receiving asciminib at 200 mg BID dose. In these patients, QTcF increase > 60 ms and absolute QTcF > 500 ms were observed in 2 patients (4.2%) each. An increase > 30 ms to ≤ 60 ms from baseline in QTcF was reported in 5 of 48 patients (10.4%).

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

QT

The Applicant's Position:

No dedicated QT studies were conducted for asciminib, as was agreed with the Agency upon receipt of the Thorough QT Study Wavier (26-Sep-2019). Preclinical studies indicated no risk of an electrophysiological effect with asciminib. Comprehensive evaluation of the potential of asciminib to affect the ECG intervals based on the data from Study CABL001X2101, indicate a low likelihood of repolarization risk with asciminib as a single agent at 40 mg BID or 80 mg QD in patients with CML not harboring the T315I mutation, and 200 mg BID asciminib in patients with CML harboring the T315I mutation. Although few patients had QTc prolongation, there was no associated clinical symptoms observed. Concentrations-QT analyses based on Study CABL001X2101 data (across a wide range of doses (10 to 280 mg), in two different dosing regimens (QD and BID)) showed that the estimated mean and upper bound of the 90% CIs ΔQTcF at 40 mg BID, 80 mg QD, 200 mg BID and at the HCRE (which is the worst case scenario for Cmax at 200 mg BID) were below 10 ms, which is the threshold that is considered clinically significant according to the regulatory guidance. Overall, the integrated assessment of QT/QTc prolongation data suggests that asciminib has no clinically relevant effect on QTc prolongation.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. According to the QT-IRT consult, "the AE data do not suggest a proarrhythmic risk due delayed cardiac repolarization. There were, however, a

few subjects with treatment related prolonged QTc interval." (b) (4)

In the safety dataset for asciminib monotherapy, there were 3 patients (0.8%) with QTc prolongation, including 1 (0.3%) with grade 3. This is included in the Cardiovascular Toxicity W&P.

Immunogenicity

The Applicant's Position:

Not applicable as this was assessed nor expected.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

Adverse events of special interest (AESI) are groupings of AEs that are of scientific and medical concern specific to asciminib and/or are related to class risks of other TKIs. These groupings are defined using MedDRA terms, SMQs, and preferred terms.

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

In the Study CABL001A2301 40 mg BID asciminib group including patients with Ph+ CML-CP previously treated with 2 or more TKIs, there were no cases of phototoxicity and hepatitis B virus reactivation. The AESIs, which had comparable incidence (difference of < 2%) across both the treatment groups, were myelosuppression (except for thrombocytopenia), pancreatic toxicity, hemorrhage, ischemic heart and CNS conditions, QTc prolongation, cardiac failure edema and fluid retention and reproductive toxicity. The AESI with at least a 15% lower incidence in the asciminib treatment group relative to bosutinib treatment group were.

- GI toxicity (-47.5%)
- Hepatotoxicity (including laboratory terms) (-22.0%)
- Hypersensitivity (-16.3)

In the asciminib 80 mg QD dose group the most frequently (> 30%) AESI observed were GI toxicity (55.6%), myelosuppression (44.4%), and hypersensitivity (33.3%)

The incidence of the majority of AESIs in both the asciminib 40 mg BID Safety Pool and asciminib All Patients Safety Pool were consistent with the asciminib treatment group in Study CABL001A2301. A higher incidence of at least 10% was observed in the asciminib All Patients Safety Pool compared to asciminib treatment group for following AESIs categories.

- GI toxicity: 47.8% and 31.4%

- Hypersensitivity: 29.5% and 17.9%
- Pancreatic toxicity: 21.3% and 8.3%

8.2.5.1 Pancreatic toxicity

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

Pancreatic enzyme increase and pancreatitis events were reported in the clinical development program. Pancreatic toxicity is an important identified risk. In non-clinical study, pancreatic acinar atrophy was observed in dogs at AUC exposures below to those achieved in patients at the 40 mg BID or 80 mg QD or 200 mg BID dose. There was a correlation between the presence of increased serum amylase and lipase activities and the presence of pancreatic acinar cell damage at necropsy. In Study CABL001A2301, no events of pancreatitis were reported in either treatment group. The pancreatic toxicity events corresponded to the laboratory terms amylase increased and lipase increased. Pancreatic toxicity events occurred in similar proportions of patients in the asciminib treatment group (8.3% all grades; Grade 3, 3.2%; Grade 4, 0.6%) and in the bosutinib treatment group (9.2% all grades; Grade 3, 3.9%; Grade 4, 0%). None of these events was serious or had fatal outcome. Except one patient discontinuing treatment in the asciminib group, most of these events were managed without any treatment intervention, and dose interruptions.
In Study CABL001X2101 80 mg QD dose group, five (27.8%) of 18 patients had pancreatic toxicity related events including 3 patients with Grade 3 events. Except one case of pancreatitis, other events were pancreatic enzyme increases. No Grade 4 events were reported. None of these events led to study treatment discontinuation nor were fatal.
The incidence of pancreatic toxicity events was higher (> 5%) in the asciminib safety pool compared to the asciminib treatment group in Study CABL001A2301. The incidences were 15.5% and 21.3% in the asciminib 40 mg BID. Safety Pool and the asciminib All Patients Safety Pool respectively and 8.3% in the asciminib treatment group in Study CABL001A2301. The cumulative incidence of pancreatic toxicity events at all the time points was higher (by at least 4.5%) in both the Safety Pools, compared to the asciminib treatment group in Study CABL001A2301. The most frequently observed events were lipase increase and amylase increase. The number of patients with pancreatitis, hyperlipasemia and pancreatitis acute were 2 patients, 2 patients and 1 patient in asciminib 40 mg BID safety pool and 7 patients, 4 patients and 2 patients in asciminib All patients safety pool, respectively.

Patients with Ph+ CML-CP harboring the T315I mutation

Pancreatic toxicity events were noted in 25% (n=12) of the patients with Ph+ CML-CP harboring the T315I mutation and receiving asciminib 200 mg BID and the pancreatic events were lipase increase (20.8%), amylase increase (10.4%), hyperlipasemia and pancreatitis (each in 1 patient). Grade 3 events were reported in 14.6% (n=7) and Grade 4 events in 4.2% (n=2) of patients receiving asciminib 200 mg BID. None of these events were SAEs. Although, the incidence of pancreatic toxicity (including Grade ≥ 3 events) was high, these events were reversible. These events were manageable with dose reduction/dose interruption.

8.2.5.2 Myelosupression

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

Myelosuppression was not evident in nonclinical studies with asciminib, however, as with other TKIs for CML, myelosuppressive events, including those of higher severity (Grade ≥ 3), are prevalent in the CML patient population. Additionally, normal hematopoiesis is suppressed because of CML cells having a competitive advantage and when CML cells are cleared, it takes time for normal hematopoiesis to recover.

In Study CABL001A2301, the overall incidence of myelosuppression was similar in both treatment groups (37.2% vs. 35.5% in the asciminib and bosutinib groups respectively). The myelosuppression events were primarily thrombocytopenia (22.4% vs. 13.2%) and neutropenia (17.9% vs. 17.1%) in asciminib and bosutinib treatment groups respectively. Despite a higher frequency of thrombocytopenia in the asciminib group, the frequency of hemorrhage (increased risk of thrombocytopenia) was similar between asciminib and bosutinib (10.3% vs 9.2%).

Grade 4 events were more frequent in the asciminib treatment group (15.4% vs. 5.3% in the bosutinib group); this was predominantly due to cases of Grade 4 thrombocytopenia (10.3% vs. 2.6% in the bosutinib group). The proportion of patients with SAEs was low (1.3%) and none of the SAEs were fatal. These events were successfully managed by dose interruptions, and additional therapies. Treatment discontinuation due to myelosuppression was low and similar between the two treatment groups (3.8% vs. 5.3%).

In Study CABL001X2101 80 mg QD dose group, 8 (44.4%) of 18 patients had myelosuppression related events including 3 patients with Grade ≥ 3 events. None of these events led to study treatment discontinuation nor was fatal.

The incidence of myelosuppressive events in the asciminib 40 mg BID Safety Pool and the asciminib All Patients Safety Pool were consistent (difference of < 2%) with that in the asciminib treatment group in Study CABL001A2301. The cumulative incidence of myelosuppression events at Week 8 was lower in the asciminib All Patients Safety Pool compared to asciminib treatment group in Study CABL001A2301, and were comparable at Week 24 and 48 in both the Safety Pools, and asciminib treatment group in Study CABL001A2301.

The incidence and type of myelosuppression events in the safety pools were consistent with that observed in the asciminib treatment group in Study CABL001A2301. None of the myelosuppression events reported had fatal outcome.

Patients with Ph+ CML-CP harboring the T315I mutation

Myelosuppressive events were noted in 22.9% of the patients; and thrombocytopenia (16.7%) was the primary event in these patients with Ph+ CML-CP harboring the T315I mutation and receiving asciminib 200 mg BID. Grade 3 events were reported in 4.2% (n=3) and Grade 4 events in 14.6% (n=7) of patients receiving asciminib 200 mg BID. None of these events was SAEs. The

majority of myelosuppression events occurred within first 8 weeks of the start of the asciminib treatment. Dose adjustments and dose interruption each were needed in 3 patients (6.3%) and 4 patients (8.3%) respectively and 1 patient had discontinued the study treatment due to these events.

8.2.5.3 Hypersensitivity

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

Hypersensitivity is a known risk with existing TKIs and hence the patients with known or/suspected hypersensitivity were excluded from the Study CABL001A2301. Most of the events related to hypersensitivity were related to skin reactions. Hypersensitivity events occurred in 17.9% of patients in asciminib and 34.2% with bosutinib in Study CABL001A2301. Though these events were common with asciminib, most of these were mild to moderate in severity. In the asciminib treatment group, none of these events was serious and no patient discontinued treatment. Few patients required dose modification; and the proportion of patients managed with concomitant medications was asciminib: 9.0% and bosutinib: 28.9%. Events were reversible indicating that management in accordance with routine clinical practice guidelines was effective.

In Study CABL001X2101 asciminib 80 mg QD dose group, 6 of 18 patients had events related to hypersensitivity with 1 patient having Grade 3 event of circulatory collapse, which event was not related to hypersensitivity reaction this patient had medical history of heart failure (Grade 2) and hypertension. None of the events was SAEs and none required study treatment discontinuation/ interruption/dose adjustments.

The incidence of hypersensitivity events was similar in the asciminib 40 mg BID Safety Pool and the asciminib treatment group in Study CABL001A2301. However, a higher incidence (+11.6%) primarily due to rash was observed in the asciminib All Patients Safety Pool (29.5%), relative to that reported in Study CABL001A2301 (17.9%). In the asciminib All Patients Safety Pool, the incidence of individual hypersensitivity events was low with the exception of rash (14.6%). Two cases resulted in permanent discontinuation of asciminib in Study CABL001X2101: one event of hypersensitivity (in a patient receiving 40 mg BID starting dose) and another patient due to event of bronchospasm (in a patient receiving 200 mg BID starting dose).

Patients with Ph+ CML-CP harboring the T315I mutation

Hypersensitivity including rashes occurred in 25.0% (12 patients) of the patients with Ph+ CML-CP harboring the T315I mutation and receiving asciminib 200 mg BID. Rash and rash maculopapular (each in 8.3%; n=4) were the primarily reported hypersensitivity events. None of these events were of Grade ≥ 3 and none of them was a SAE. None of the patients required dose adjustment/interruption and/or study treatment discontinuation.

8.2.5.4 QTc prolongation

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

Moderate cardiovascular effects were seen in nonclinical studies; however, QTc prolongation was not observed.

In Study CABL001A2301, QTc prolongation related events were reported in 4 patients in the asciminib group and 1 patient in the bosutinib group. No Grade 4 events were reported and none of the events led to study discontinuation. In the asciminib group, two cases of ECG QTc prolonged were reported as AEs; one of these patients experienced QTcF > 500 ms with > 60 ms increase – the event resolved with dose interruption and did not reoccur after asciminib was resumed at the reduced dose of 20 mg BID. The higher frequency of QTcF increases per ECG on asciminib did not translate to clinical events. Dose interruption due to a QT prolongation AE was reported in 1 patient. In all other patients, no dose adjustment needed.

In the asciminib 80 mg QD dose group, 3 of 18 patients had events related to QTc prolongation, including 1 patient who discontinued study treatment due to the event (cardiac arrest with a fatal outcome that occurred one day after the patient was hospitalized due to acute kidney injury).

Overall, the concentration-effect analysis demonstrated that at therapeutic doses, asciminib does not have a relevant effect on cardiac repolarization as the estimated mean and upper bound of the 90% CIs ΔQTcF at 40 mg BID, 80 mg QD, 200 mg BID and at the HCRE (which is the worst case scenario for Cmax at 200 mg BID) were below 10 ms, which is the threshold that is considered clinically significant according to the regulatory guidance.

The incidence of events related to QTc prolongation in both the asciminib 40 mg BID Safety Pool and the asciminib All Patients Safety Pool were consistent (difference of <1%) with the incidence observed in the asciminib treatment group in Study CABL001A2301. One fatal event (cardiac arrest) was noted in the asciminib All Patients Safety Pool (80 mg QD cohort); this event was not suspected to be study treatment related (by the investigator) and was not related to ECG QT prolongation.

Patients with Ph+ CML-CP harboring the T315I mutation

One patient (in Study CABL001X2101) with Ph+ CML-CP harboring the T315I mutation and receiving asciminib 200 mg BID dose had a QTc prolongation event (ventricular tachycardia, grade 3, SAE) 29 days after study treatment discontinuation. This patient discontinued the study treatment (after 209 days of asciminib treatment) due to physician's decision (lack of efficacy) and had opted for stem cell transplant. This event was managed by providing medication/therapy and the patient had recovered from the event of ventricular tachycardia by the data cut-off date.

8.2.5.5 Hepatotoxicity

Patients with Ph+ CML-CP previously treated with 2 or more TKIs

Hepatic enzyme elevations were observed in the non-clinical and early clinical studies of asciminib. In Study CABL001A2301, hepatotoxicity events (including laboratory terms) were reported in a lower proportion of patients in the asciminib treatment group (8.3%) compared to

the bosutinib treatment group (30.3%). In the asciminib group, most of these AEs were Grade 1 or 2, were reversible, and not considered to be clinically relevant; in contrast, in the bosutinib treatment group, 17.1% of patients had Grade 3 events and 5.3% of patients discontinued treatment due to hepatotoxicity. Further, at the time of data cut-off in the bosutinib group hepatotoxicity events were ongoing in 14.5% of patients.

Based on the laboratory values, ALT/AST increase > 3 × ULN were noted in 3.8% of patients in the asciminib treatment group compared with 30.3% of patients in the bosutinib treatment group. The majority of liver events presented as isolated AST and/or ALT increases and none was associated with combined bilirubin elevation, and no Hy's law case was reported.

In Study CABL001X2101 asciminib 80 mg QD dose group, 3 of 18 patients had hepatotoxicity events with 1 patient having Grade ≥ 3 event (ALT and GGT increase in same patient). Increases of ALT and AST were noted in 7 and 5 patients respectively; of this 1 patient had Grade 3 ALT increase. No event was a SAE and none led to discontinuation of study treatment.

The incidence of hepatotoxicity events in both the asciminib Safety pool (40 mg BID) and the All patients asciminib Safety pool was consistent (difference < 10%) with those observed in the asciminib treatment group in Study CABL001A2301.

No concurrent elevations of ALT or AST > 3×ULN and total bilirubin > 2×ULN and ALP < 2×ULN meeting Hy's law biochemical criteria were observed either in Study CABL001A2301, Study CABL001X2101 80 mg dose group and in overall asciminib Safety Pool among patients with ALT/AST and bilirubin levels within normal ranges at baseline. However, in asciminib 'All Patients Safety Pool', 1 patient had an increase in transaminases concomitant with increase in total bilirubin at baseline and was assessed for potential drug-induced liver injury (DILI).

Patients with Ph+ CML-CP harboring the T315I mutation

Hepatic enzymes/bilirubin elevations occurred in 25% of patients (12 patients) receiving asciminib 200 mg BID. No Grade 4 events were reported and Grade 3 events were reported in 10.4% (n=5). None of the events was a SAE. There were no life threatening AEs, no Hy's law case, and no evidence of progressive or irreversible liver damage. Two patients required dose adjustment and 1 patient required drug interruption; no patient required permanent discontinuation due to hepatotoxicity events. The majority of hepatotoxicity events occurred within first 8 weeks of the start of the asciminib treatment.

The FDA's Assessment:

FDA performed analysis of all GTs including AESI in study A2301, X2101, and in the safety pool of 356 patients. The Warnings and Precautions of the label includes myelosuppression, pancreatic toxicity, hypertension, hypersensitivity, cardiovascular toxicity and embryo-fetal toxicity sections. Myelosuppression, especially of Grades 3-4 is common in CML patients. Myelosuppression usually takes the form of thrombocytopenia and neutropenia and these are usually manageable. Pancreatic toxicity usually becomes manifest as pancreatic enzyme increase and pancreatitis. Nonclinical models also showed pancreatic acinar atrophy in dogs.

Hypertension might be seen with use of tyrosine kinase inhibitors and its frequency was ≥ 10 % in both trials. Hypersensitivity is also a known risk factor of tyrosine kinase inhibitors and frequent in patients using this group of drugs.

Although cardiovascular toxicity was not noted to be an AESI, it was also added as a W & P in the label. FDA suggested that the Applicant add a section on Arteriovascular Events in W&P which would include the OOD's list of preferred terms for arteriovascular events. The Applicant suggested excluding the preferred terms of creatine kinase increased and noncardiac chest pain as these were not directly associated with arteriovascular events. This was found acceptable by FDA. They also included MedDRA version 23.1 narrow SMQs of Ischemic Central Nervous System Vascular Conditions, Ischemic Heart Disease (narrow), and Embolic and thrombotic events, arterial. The resultant section called Cardiovascular Toxicity includes three main adverse reactions which are cardiovascular toxicity, cardiac failure and arrhythmia. Cardiovascular toxicity was added to draw attention to this adverse event and to follow up patients with cardiovascular factors more closely.

FDA agrees with the Applicant's general assessment of submission-specific safety issues. In addition, AESI which had at least a 5% higher incidence in asciminib arm in study A2301 were musculoskeletal pain (GT), and hypertension (GT), respectively, 23.7% vs. 17.1% and 12.2 vs. 3.9%.

FDA agrees with the Applicant's assessment of pancreatic toxicity (GT). Pancreatic toxicity (GT) was usually evident as increased amylase or increased lipase levels. Pancreatic toxicity (GT) was more frequent in Study X2101 than in Study A2301.

FDA agrees with the Applicant's analysis of myelosuppression. Refer to the above section on laboratory findings for an analysis of myelosuppression.

The most frequent hypersensitivity event in the 356 patient safety pool was rash (GT) (25%) and its frequency is higher than in Applicant's analysis as a GT was used. However, this is not thought to affect the overall safety profile of asciminib.

FDA agrees with the Applicant's analysis of hepatotoxicity (GT). As stated, both all grade and grades 3-4 hepatotoxicity were more frequent in Study X2101 than in Study A2301. Hepatotoxicity is not included in W&P section of the label as the AEs were generally of lower grades and transient.

In addition, the GT of cardiovascular toxicity in the updated dataset of 356 patients in the asciminib safety pool showed a frequency of 13%. Grade 3 cardiovascular toxicity was diagnosed in 3.4% of patients and grade 4 cardiovascular toxicity in 0.6% of patients. Three of the cardiovascular toxicities (0.8%) were fatal. Three patients (0.8%) permanently discontinued asciminib because of cardiovascular toxicity. In addition, cardiac failure congestive (GT) was seen in 2.2% of the 356 patient asciminib safety set. It was grade 3 in 1.1% of patients. One

patient (0.3%) discontinued asciminib because of cardiac failure. Arrhythmia (GT), including QTc prolongation was diagnosed in 7% patients and it was grade 3 in 2% of patients. There was QTc prolongation in 3 (0.8%) patients and it was grade 3 in one (0.3%) patient.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:
Overall, compared to bosutinib, treatment with asciminib was associated with better improvement in disease-related symptoms and health-related quality of life (as assessed by MDASI CML, PGIC along with EQ-5D-5L); and in work productivity and activity impairment (as assessed by WPAI-CML). No specific patient outcome assessments describing safety or tolerability was performed.

The FDA's Assessment:
Patient-reported outcomes were evaluated as an exploratory endpoint in Study A2301. Evaluation provided by the Applicant was not confirmed by FDA. While these results may show better clinical outcome assessments with asciminib, this was limited by the possibility of bias in an open-label study and differences in treatment duration between arms.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:
Subgroup analyses were conducted to identify potential safety issues that were limited to subpopulations; these typically demonstrated a pattern of events consistent with that reported for the respective overall populations except for few differences.

Patients with Ph+ CML-CP previously treated with two or more TKIs

Age
In Study CABL001A2301, in the asciminib treatment group, except for headache, the incidence of all AEs in both the age subgroups were consistent (difference of < 10%). In the bosutinib treatment group, higher incidence of ALT increase (+15.2%) and platelet decrease (+13.3%) was observed in ≥ 65 years age category compared to 18 to < 65 years age category; the incidence of all other Grade ≥ 3 AEs in both the age subgroups were consistent (difference of < 10%).
In Study CABL001X2101 asciminib 80 mg QD dose group, the incidence of AEs in all AEs category was similar in all the age categories, however due to overall low number of patients these results should be interpreted with caution.
The AE (all grades) results observed in the asciminib 40 mg BID Safety Pool and asciminib All Patients Safety Pool was consistent with the results observed in the asciminib treatment group in Study CABL001A2301. In the asciminib All Patients Safety Pool grade ≥ 3 hypertension was observed in 16.7% of the patients in ≥ 65 years age category compared to 6.3% patients in 18 to < 65 years age category.
Gender

The overall safety was similar for both genders in the asciminib and bosutinib treatment groups in Study CABL001A2301. However, in the asciminib treatment group higher incidence of AEs suspected to be treatment related was observed in females (74.7%) compared to males (53.1%) and higher incidence of AEs requiring additional therapy was observed in females (74.7%) compared to males (58.0%); whereas for the AEs (grade ≥ 3) males (55.6%) had a higher frequency compared to females (45.3%). In the bosutinib treatment group, females had higher incidence of Grade ≥ 3 treatment related AEs compared to males (55.6% vs. 41.9%).
In Study CABL001X2101 asciminib 80 mg QD dose group, the incidence of AEs in all categories of AEs was similar in both the genders, however due to overall low number of patients (10 female and 8 male patients) these results should be interpreted with caution.
In the asciminib 40 mg BID Safety Pool, compared to males, females had a higher incidence of AEs suspected to be, treatment related (77.3% vs. 59.6%). Overall, similar safety results were observed between both the asciminib Safety pool C (40 mg BID) and the asciminib All Patients Safety Pool, and the asciminib treatment group in Study CABL001A2301 for the gender subgroups.

Race

No clinically relevant differences were observed amongst ethnic sub-groups across Study CABL001A2301, Study CABL001X2101 80 mg and Asciminib Safety pool. However, due to small sub-group size the data should be interpreted with caution.

Renal Impairment

In Study CABL001A2301, based on the aGFR at baseline, in the bosutinib treatment group, there were 41 subjects with normal renal function, 31 patients with mild renal impairment and 4 patients with moderate renal impairment and in the asciminib treatment group, there were 82 subjects with normal renal function, 60 patients with mild and 10 patients with moderate renal impairment. As the number of patients with moderate renal impairment is small in both the treatment groups (4 and 10 patients), this group has not been considered for comparison across various AEs categories.
In Study CABL001A2301, the asciminib treatment group none of the AEs (all grades) were noted with a higher incidence (of ≥ 10%) in mild renal impairment group compared to normal renal function group. In the bosutinib treatment group, the AEs where higher incidence (of ≥ 10%) was observed in mild renal impairment group compared to normal renal function group were headache (7.3% vs. 19.4%), thrombocytopenia (7.3% vs. 22.6%), diarrhea (68.3% vs. 80.6%), fatigue (4.9% vs. 16.1%), vomiting (19.5% vs. 35.5%) and platelet count decrease (0% vs. 12.9%).

In Study CABL001X2101, based on the aGFR at baseline, there were 8 normal patients, 7 patients with mild and 3 patients with moderate renal impairment who were treated with asciminib 80 mg QD dose. Due to small number of patients these results should be interpreted with caution.

The results of overall AEs categories observed in the asciminib 40 mg BID Pool and asciminib All Patient Pool was consistent with the results observed in the asciminib treatment group in Study CABL001A2301.

Patients with Ph+ CML-CP harboring the T315I mutation

Overall, subgroup analysis did not show unexpected finding that would affect the safety profile of asciminib in a specific subgroup. Considering the low number of patients with CML-CP harboring the T315I mutation who received asciminib 200 mg BID and the differences in the number of patients between subgroups, results to be interpreted with caution.

The FDA's Assessment:
FDA agrees with the Applicant's assessment in general. The T315I group in Study CABL001X2101 received a 5 times higher dose than patients in Study CABL001A2301. Some common TEAEs like rash, lipase increased, and diarrhea were more frequent in Study CABL001X2101. In addition, AESI of pancreatic toxicity, hepatotoxicity and hypersensitivity were more frequent with the higher dose of asciminib in Study CABL001X2101. Therefore, the differences in safety are likely related to the dose of asciminib used and not the demographics and disease characteristics.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
Not applicable as no such clinical studies were planned.

The FDA's Assessment:
FDA confirms the Applicant's position.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Position:
Carcinogenicity studies have not been conducted with asciminib.

The FDA's Assessment:
FDA confirms the Applicant's position.

Human Reproduction and Pregnancy
The Applicant's Position:

Based on findings in animal studies, asciminib could cause fetal harm when administered to a pregnant woman.

A single case of pregnancy has been reported in Study CABL001X2101 and this female patient was treated with combination of asciminib 40 mg and imatinib 400 mg. The patient discontinued treatment. No adverse event (AE) was reported because of this exposure, and the patient delivered a full term normal neonate.

In Study CABL001A2301 among patients who received asciminib 40 mg, one patient had maternal exposure during pregnancy and spontaneous abortion. Dose was interrupted due to maternal exposure during pregnancy. Both the events resolved. Two patients (1 each in asciminib

and bosutinib group) were diagnosed (after informed consent form [ICF]) with congenital cardiovascular anomaly. None of these events were serious or suspected to be related to study treatment by the Investigator.
There is no data on the effects of asciminib on the breastfed child or on milk production.

The FDA's Assessment:
FDA confirms the Applicant's position.

Pediatrics and Assessment of Effects on Growth
The Applicant's Position:
Not applicable as no pediatric trial has started yet to enroll. Studies are planned to assess the effects on growth.

The FDA's Assessment:
FDA confirms the Applicant's position. PREA PMR for pediatric PK study has been requested.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There is limited experience with overdose with asciminib in clinical setting. In clinical studies, asciminib has been administered with a wide dose range from 10 mg BID up to 280 mg BID with no evidence of increasing toxicity. In case of suspected overdose, patients should be closely monitored for signs or symptoms and symptomatic treatment initiated in case of suspected overdose.

No studies have been conducted to assess withdrawal and rebound effects and withdrawal and rebound effects were not reported in clinical studies.

Safety in healthy volunteers treated with asciminib
The overall safety results in the Healthy Volunteer Pool were consistent with those observed in patients in the target indication, with obvious lower incidences and intensities in the healthy subject population. These favorable safety results were also applicable for laboratory parameters, vital signs, and ECG analyses. No new additional safety finding was observed in the Healthy Volunteer Pool to the already known safety profile of asciminib.

The FDA's Assessment:
FDA confirms the Applicant's position. Asciminib does not have abuse potential because of its toxicity profile.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified through Postmarket Experience

The Applicant's Position:

Not applicable (asciminib is not currently registered [or approved] in the US or in any other part of the world).

The FDA's Assessment:
FDA confirms the Applicant's position.

Expectations on Safety in the Postmarket Setting
The Applicant's Position:

Toxicities appear to have been adequately represented in Study CABL001A2301. Potential safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

The FDA's Assessment:
FDA agrees with the Applicant's position. The overall safety in the post-market setting is expected to be similar to that observed in the clinical trials in this Application. A PMR for 2-year follow-up about safety and efficacy for Study A2301 has been requested.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

Patients with Ph+ CML-CP previously treated with two or more TKIs

Asciminib administered at 80 mg daily total dose (taken as 80 mg QD or 40 mg BID) demonstrated favorable safety profile in the treatment of patients with Ph+ CML-CP previously treated with ≥ 2 TKIs.

The safety of asciminib in patients with Ph+ CML CP, previously treated with ≥ 2 BCR-ABL1 ATP-competitive TKIs has been well characterized. The safety evaluation of asciminib was primarily based on the data from the Study CABL001A2301. It was complemented with pooled data from studies CABL001X2101 and CABL001A2301. The patients enrolled into these studies are expected to adequately represent the target population. The safety assessments performed are appropriate and considered adequate for the safety evaluation of asciminib in the target indication.

In Study CABL001A2301, the median duration of exposure to study treatment was longer in the asciminib arm (43.4 weeks vs. 29.2 weeks) compared to the bosutinib arm.

The most commonly reported AEs in the asciminib treatment group (in ≥ 10% of patients) in Study CABL001A2301 included the followings: thrombocytopenia (22.4%), neutropenia (17.9%), headache (16%), diarrhea (11.5%), hypertension (11.5%), nausea (11.5%), and fatigue (10.3%). The most commonly reported AEs in the bosutinib treatment group (in ≥ 10% of patients)

included: diarrhea (71.1%), nausea (46.1%), ALT increased (27.6%), vomiting (26.3%), rash (23.7%), AST increased (21.1%), neutropenia (17.1%), abdominal pain (14.5%), headache (13.2%), and thrombocytopenia (13.2%).

Overall, 3 on-treatment deaths were reported in Study CABL001A2301: 2 patients in the asciminib group (arterial embolism and ischemic stroke; confounding factors were present in both cases and neither was suspected to be related to study treatment) and 1 patient (septic shock; suspected) in the bosutinib group. The incidence of individual SAEs was low for both treatment groups. The most commonly occurring SAEs were pyrexia (n = 2; 1.3%) in the asciminib treatment group and rash (n = 2; 2.6%) in the bosutinib treatment group; all other SAEs were reported as single cases. The proportion of patients with AEs leading to treatment discontinuation was markedly lower in the asciminib treatment group compared to the bosutinib treatment group (5.8% vs. 21.1%).

The hematological laboratory abnormalities in Study CABL001A2301 were consistent with the observed hematologic AE profile for the study drugs. Glucose increase and triglycerides increase were noted >50% of patients in both the treatment groups with a higher frequency in patients on asciminib: glucose - increase 83.3% asciminib vs 68.4% bosutinib, triglycerides - increase 70.5% asciminib vs 53.9% bosutinib. These were predominantly Grade 1 and 2. However, worsening of glycosylated hemoglobin elevated (≥ 6.5%) during the study was less frequently observed in patients on asciminib (4.9%) as compared to patients on bosutinib (5.8%).

The incidence of AESIs that were considered to be of scientific and medical concern specific to asciminib and/or related to class risks of other TKIs was similar between the asciminib and bosutinib groups in Study CABL001A2301. Patients experiencing myelosuppression AESIs (erythropenia, leucopenia, thrombocytopenia, cytopenias affecting more than one lineage) was similar in the asciminib (37.2% all grades, 26.3% Grade ≥ 3 events) and bosutinib treatment groups (35.5% all grades, 23.7% Grade ≥ 3 events), with thrombocytopenia were more frequently reported in patients on asciminib than on bosutinib (any Grade 22.4% vs. 13.2% and Grade ≥ 3 17.3% vs. 6.6% respectively). However, these events were manageable with dose reduction/dose interruption; and treatment discontinuation due to myelosuppression was low and similar between the two treatment groups (3.8% vs. 5.3%). Of note, treatment discontinuation due to thrombocytopenia AESIs was also low in both the treatment groups. Despite a higher frequency of thrombocytopenia events in the asciminib group, the frequency of hemorrhage was similar between asciminib and bosutinib (10.3% vs 9.2%).

The proportion of patients with gastrointestinal toxicity, hepatotoxicity and hypersensitivity AESIs were substantially lower in the asciminib treatment group compared to the bosutinib treatment group (both all grades and Grade ≥ 3). Comparable proportion of patients with pancreatic enzyme increase was seen without clinical events of pancreatitis in both treatment groups.

The hematological laboratory abnormalities were consistent with the observed hematologic AE profile for the study drugs.

No substantial difference in the safety findings were observed in the asciminib 80 mg QD group of Study CABL001X2101 compared to the safety pool of 40mg BID and the pool of 356 patients.

In summary, the asciminib safety profile was favorable relative to that of bosutinib as indicated by lower incidences of AEs, AEs with lesser severity, fewer AEs requiring dose adjustments and treatment discontinuations with asciminib. The majority of the AEs were tolerable and manageable with the predefined management guidelines. These results were strengthened by the results from the asciminib Safety Pools where longer-term treatment continued to be associated with a tolerable safety profile in patients with CML-CP previously treated with ≥ 2 TKIs.

Patients with Ph+ CML-CP harboring the T315I mutation

Asciminib administered at 200 mg BID in Study CABL001X2101 demonstrated favorable safety profile in the treatment of patients with CML-CP harboring the T315I mutation. Importantly, the safety profile of the asciminib 200 mg BID regimen is consistent with that observed in Study CABL001A2301 and the Safety Pools with no specific safety finding in this group of patients.

Asciminib has been administered across a wide dose range of dose regimen from 10 mg BID to 200 mg BID and 80 mg QD to 200 mg QD in Study CABL001X2101, with no evidence of increasing toxicity. A dose of 200 mg BID in patients harboring T315I mutation is considered as the optimal dose based on the totality of clinical data, asciminib exposure achieved at 200 mg BID and the model-derived EC95 value.

Adverse events reported in patients treated at 200 mg BID are consistent with those reported in patients treated at any dose. No on-treatment deaths were reported. Treatment discontinuations due to AEs was low indicating asciminib was well tolerable.

The most commonly reported AEs (≥ 20%) were fatigue (29.2%); nausea (27.1%), diarrhea and lipase increase (both 20.8%). Grade ≥ 3 events were reported in 56.3% of patients; lipase increase (16.7%) and thrombocytopenia (14.6%) were reported most frequently (≥ 10%).

No untoward effects (new or unexpected safety findings) that led to alterations of the safety profile were observed with the asciminib 200 mg BID regimen in patients with Ph+ CML-CP harboring the T315I mutation. Overall, safety results were consistent with all patients with Ph+ CML-CP harboring the T315I mutation irrespective of dose in Arm 1 of Study CABL001X2101.

The FDA's Assessment:

Overall safety summary performed by FDA differed in various aspects from the summary provided by the Applicant above. FDA's analysis for Study CABL001A2301 revealed musculoskeletal pain (GT) and rash (GT) to be among the most common (≥10%) AEs in the asciminib arm, and musculoskeletal pain (GT) and fatigue to be among the most common AEs in the bosutinib arm. TEAEs of Grade 3-4 which were > 5% in the asciminib arm in Study CABL001A2301 were thrombocytopenia, neutropenia, and hypertension (GT). For the label, the Applicant used the grouped terms suggested by FDA. Therefore, the safety information in the label matches with FDA's analyses.

The W&P section of the label contains the sections of Myelosuppression, Pancreatic Toxicity, Hypertension, Hypersensitivity, Cardiovascular Toxicity, and Embryo-Fetal Toxicity.
According to the updated dataset included in the label, serious adverse reactions > 1% in the asciminib arm included pyrexia (1.9%), cardiac failure congestive (1.3%), thrombocytopenia (GT) (1.3%) and urinary tract infection (GT) (1.3%).

FDA's analysis for Study CABL001A2101 also revealed musculoskeletal pain (GT) and rash (GT) to be among the most common (≥20%) AEs in T315I (+) patients. TEAEs of Grade 3-4 which were > 5% in Study CABL001X2101 were lipase increased, thrombocytopenia, abdominal pain (GT), vomiting, and hypertension (GT), and alanine aminotransferase increased.
Based on the updated dataset included in the label, serious adverse reactions > 1% with asciminib 200 mg bid included abdominal pain (GT) (4.2%), vomiting (GT) (4.2%), pneumonia (GT) (4.2%), musculoskeletal pain (GT) (2.1%), headache (GT) (2.1%), hemorrhage (GT) (2.1%), constipation (2.1%), arrhythmia (GT) (2.1%), and pleural effusion (2.1%)..

Concerning AESI using the updated safety dataset, myelosuppression was more frequent in Study CABL001A2301 than in Study CABL001X2101 (38% vs. 25%) while pancreatic toxicity, hepatotoxicity, and hypersensitivity were less frequent in Study CABL001A2301 than in Study CABL001X2101, respectively, 8% vs. 31%, 10% vs. 25%, and 19% vs. 29%. Cardiovascular toxicity (GT) was also less frequent in Study CABL001A2301 than in Study CABL001X2101, respectively, 6% vs. 10%).

FDA requested the Applicant to add neuropathy peripheral, constipation, urinary tract infection, hemorrhage, arrhythmia, cardiac failure congestive, dry skin, insomnia, and anxiety in the USPI as clinically relevant adverse reactions in < 10% of patients treated with asciminib in Study A2301. All of them except dry skin, insomnia, and anxiety were added as these three are usually seen at lower grades, were manageable, and were unlikely to be related to asciminib.

In addition, FDA requested the Applicant to add neuropathy peripheral, constipation, arrhythmia, cardiac failure congestive, dry skin, insomnia, and anxiety in the USPI as clinically relevant adverse reactions in < 10% of patients treated with asciminib in Study X2101. As per the Agency's request, neuropathy peripheral, constipation, arrhythmia, and cardiac failure congestive were included in the label.

Safety summary, CABL001A2301 and CABL001X2101

	A2301		**X2101**
	Asciminib 40 mg BID N=156 N (%)	**Bosutinib N=76 N (%)**	**Asciminib 200 mg BID N=48 N (%)**
All Grade TEAEs	140 (90)	73 (96)	48 (100)
Grade ≥ 3 TEAEs	79 (51)	47 (62)	27 (56)

Grade 3 TEAEs	45 (29)	40 (53)	18 (38)
Grade 4 TEAEs	32 (21)	6 (8)	9 (19)
Grade 5 (Deaths due to TEAEs)	2 (1.3)	1 (1.3)	0 (0)
Serious TEAEs (SAEs)	21 (13)	14 (18)	10 (21)
Drug Withdrawn - due to AEs	9 (6)	18 (24)	3 (6)
Drug Interrupted – due to AEs	58 (37)	41 (54)	12 (25)
Dose Reduced – due to AEs	8 (5)	20 (26)	11 (23)
Source: FDA analysis using adae.xpt, adsl.xpt for each study			

In the FDA assessment, the submitted evidence has provided substantial evidence for the safe use of asciminib for both indications. Safety events increased over time and were more frequent with the higher dose of asciminib in Study CABL001X2101. Overall, single-agent asciminib was well tolerated for the treatment of refractory/intolerant CML-CP patients. Patients who have used 2 or more prior TKIs or have the T315I mutation have poor prognosis as the disease progresses to advanced stages and there are limited treatment options. The level of toxicity described with single-agent asciminib is acceptable for the clinical benefit observed.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:
No major statistical issues were identified. The submitted clinical data from studies CABL001A2301 (phase 3) and CABL001X2101 (phase 1) yielded the following results:

1. In Study CABL001A2301, the MMR rate at Week 24 in the asciminib arm was 25% (95% CI: 19, 33) compared to that in the bosutinib arm 13% (95% CI: 6.5, 23). The treatment difference in MMR rate at Week 24 was 12% (95% CI: 2.2, 22; two-sided p-value: 0.029 per the Cochran–Mantel–Haenszel test, stratified by the MCyR status at baseline).
2. In Study CABL001X2101, the MMR rate by 24 weeks for the two dose cohorts in above Table 30 were 16% (95% CI: 4.5, 36) for asciminib 40 mg BID cohort and 29% (95% CI: 8.4, 58) for asciminib 80 mg QD cohort. The overall MMR rate by 24 weeks was 23% (95% CI: 15, 34).
3. In Study CABL001X2101, the MMR rate by 24 weeks and by 96 weeks for the 45 patients with Ph+ CML-CP harboring the T315I mutation who received asciminib at a dose of 200 mg twice daily in the Study CABL001X2101 were 42% (95% CI: 28 to 58) and 49% (95% CI: 34 to 64), respectively.

Of note, the key secondary endpoint of MMR rate at Week 96 for Study CABL001A2301 was not analyzed due to immaturity of the data.

8.4. Conclusions and Recommendations

The FDA's Assessment:
The review team was able to verify or clarify the efficacy and safety endpoints as provided by the Applicant. The review team recommends approval of the NDA.

The FDA approach toward approval in CML in CP the R/I population is to grant accelerated approval when at least 24 weeks (6 months) of efficacy and safety data is available. For conversion to regular approval, the FDA requires 96-weeks (2 years) of efficacy and safety information. Follow up to the later timepoint is required only from the study-drug treatment arm in the case of an active-controlled study to demonstrate benefit with use of the study drug. In this submission, the Applicant provided efficacy and safety information from study A2301 to 48 weeks; however, more than 30% had not reached the 96-week evaluation. Therefore, the data from A2301 supports accelerated approval in patients with CML in CP in patients treated with at least 2 prior TKIs. The study includes a key secondary endpoint for MMR at 96 weeks, and a PMR will be issued to obtain this information. Patients may continue on study for up to 5 years.

For the treatment of patients with T315I mutations, only 6 of 48 patients who remain on treatment have not yet reached their 96-week evaluation. With almost 90% of patients having their 96-week assessment or discontinuing prior to that date, a later data cutoff would likely have similar efficacy and safety information. The durability of MMR responses and safety in this population supports regular approval for this indication.

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
This Application was not presented to the Oncologic Drug Advisory Committee or any other external consultants because the application did not raise significant safety or efficacy issues.

10 Pediatrics

The Applicant's Position:

On September 16, 2020, Novartis received an Agreed Initial Pediatric Study Plan (iPSP) Agreement letter from the Agency, which included a partial waiver and deferral for asciminib for the treatment of Pediatric Philadelphia chromosome positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP), previously treated with one or more tyrosine kinase inhibitors.

The FDA's Assessment:

FDA agrees with the Applicant's position. Their proposed pediatric indication in the agreed iPSP is "Pediatric Philadelphia chromosome positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP), previously treated with one or more tyrosine kinase inhibitors." They are requesting a partial waiver for the pediatric age group < 1 year old with Ph+ CML-CP from requirements to conduct pediatric assessments because of: 1) the rarity of the disease in infants, 2) the various available therapies, and 3) the targeted study population treated with at least one previous TKI.

Their development program in children ≥ 1 years old to (b) (4) years old with Ph+ CML-CP will be separate from their Phase 3 program and they requested deferrals for: 1) development of an age-appropriate formulation (mini-tablets), 2) completion of the pediatric PK study (CABL001I12201), and 3) physiologically based PK (PBPK) modeling and simulation.

Study CABL001I12201 will be an open-label trial to evaluate PK, safety, and acceptability / tolerability of asciminib in children ≥ 1 years old to < 18 years old with Ph+ CML-CP, previously treated with one or more TKIs. The main goal will be to establish the dose(s) for pediatric CML patients aged ≥ 1 years old to < 18 years old that will provide comparable exposure to adult patients in Study CABL001A2301. They will extrapolate the efficacy of asciminib from the adult Phase III Study CABL001A2301 and the dose in pediatric patients will be matched to the exposure in adults. Study CABL001I12201 is planned to be initiated in September 2021 and completed in January 2026. The agency issued a PMR under the FDARA amendment to PREA for Study CABL001I12201.

11 Labeling Recommendations

The table below summarizes select changes to the proposed United States Prescribing Information (USPI). See the final approved USPI for SCEMBLIX (asciminib) accompanying the approval letter for more information.

Section	Applicant's proposed Labeling	FDA's proposed Labeling
Highlights of Prescribing Information	N/A	Waiver for requirement for ½ page for HL to be granted.
Section 1 Indications and Usage	(b) (4)	FDA modified to indicate that the indication for: • Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs) will be approved under accelerated approval based on major molecular response. The indication for: • Ph+ CML in CP with the T315I mutation will have regular approval.
Section 2 Dosage and Administration	Included (b) (4)	FDA modified this section to conform to current labeling practices (b) (4) information about duration of treatment was included in subsection 2.1. In subsection 2.4 Table 1 modified for clarity and Table 2 modified to include CTCAE grading for non-hematologic ARs.
Section 5 Warnings and Precautions (W&P)	Included W&P for: Myelosuppression Pancreatic Toxicity (b) (4) Hypertension Hypersensitivity (b) (4)	FDA deleted the W&Ps (b) (4) A new W&P for Cardiovascular

	Embryo-Fetal Toxicity	Toxicity were added.
Section 6 Adverse Reactions		FDA included a pooled population of 356 patients for the W&P. Revisions made throughout this section to align with OOD preferred approach for the presentation of safety data.
Section 7 Drug Interactions	7.1 Included recommendations for strong CYP3A4 inhibitors (b) (4) 7.2 Included recommendations for CYP3A4 substrates with narrow therapeutic index, CYP2C9 substrates (b) (4)	In section 7.1, FDA deleted (b) (4) A recommendation to avoid coadministration with itraconazole oral solution containing Hydroxypropyl-β-cyclodextrin was added because asciminib exposure is significantly decreased with the concomitant use of itraconazole oral solution. In section 7.2. FDA added recommendations to avoid coadministration of ASEMBLIX at 200 mg twice daily with sensitive CYP2C9 substrates and certain CYP2C9 substrates; if coadministration cannot be avoided, a recommendation was added to consider alternative therapy with non-CYP2C9 substrate. FDA added a subsection recommending close monitoring for adverse reactions in patients treated with SCEMBLIX at all recommended doses with concomitant use of P-gp substrates.
Section 8 Use in Specific Populations	Included recommendations for 8.6 renal and 8.7 hepatic impairment	FDA updated section 8 throughout to align with current labeling practices. FDA added eGFR classification to renal impairment in section 8.6.

		FDA changed the description of hepatic impairment to the NCI classification to align with current labeling practice in section 8.7.
[redacted] (b) (4)		
Section 12 Clinical Pharmacology	Included information on mechanism of action, pharmacodynamics, and pharmacokinetics	In 12.1, FDA revised to remove potentially promotional language; added exposure-response relationships. In 12.2, FDA revised the cardiac electrophysiology to note that asciminib does not cause a large mean increase in the QTc interval at the maximum recommended clinical dosage. Section 12.3 was revised throughout to align with current practices for the display of pharmacokinetic data; FDA updated the PK parameters based on its independent PopPK analysis.
Section 13 Nonclinical Toxicology	In section 13.1, included a statement [redacted] (b) (4)	FDA modified section 13.1 to: • Describe that carcinogenicity studies have not been conducted with asciminib; • Describe that asciminib was not genotoxic in an in vitro bacterial mutagenicity assay, an in vitro micronucleus assay in human peripheral blood lymphocytes, nor in an in vivo rat peripheral blood reticulocyte micronucleus assay. • Describe animal studies [redacted] (b) (4)
Section 14 Clinical Studies	Included section 14.1 Ph+ CML-	FDA modified these sections to align

	CP, Previously Treated with Two or More TKIs and section 14.2 Ph+ CML-CP harboring the T315I mutation	with current labeling practices for the description of clinical studies, including updating race based on the FDA guidance "Collection of Race and Ethnicity Data in Clinical Trials". FDA removed (b) (4)

The FDA's Assessment:
The FDA modified sections of the USPI as described in the table above. See the review of the patient labeling (PPI) conducted by the Division of Medical Policy Programs for more information.

12 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position:
No REMS is recommended.

The FDA's Assessment:
The risks associated with asciminib can be adequately managed in the post-market setting through product presentation and labeling. There are no additional risk management strategies required beyond the recommended packaging and labeling.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

PMR#1 is to conduct clinical study CABL001A2301 (ASCEMBL), A Phase 3, Multi-center, Open-label, Randomized Study of Oral ABL001 Versus Bosutinib in Patients With Chronic Myelogenous Leukemia in Chronic Phase (CML-CP), Previously Treated With 2 or More Tyrosine Kinase Inhibitors and provide the interim report with at least 24 months (96 weeks) follow-up of all patients to describe and confirm the clinical benefit of asciminib. The rationale is that data cutoff for the CABL001A2301 provides less than 24 months of follow-up data, (b) (4)

FDA requests a PMR for 24 months of follow-up data from the CABL001A2301 trial. (b) (4)

PMR#3 is to conduct a clinical trial to determine the appropriate dose of asciminib and to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of asciminib in pediatric patients with Ph+ CML-CP previously treated with one or more tyrosine kinase inhibitors, ages ≥1 to <18 years and provide the core study report with at least 12 months (52 weeks) data for all patients. They should include at least 15 patients ≥1 to <12 years old and 15 patients ≥12 to <18 years old. The rational is that the agreed iPSP for asciminib has a waiver for children <1 year and a deferral for children ≥1 year to <18 years. FDA requested a PREA PMR for their pediatric PK study in children aged ≥1 year to <18 years.

Refer to FDA action letter for final PMR/PMC wording.

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1. References

The Applicant's References:
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Biologics; 8:243-54.
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Soverini S, Colarossi S, Gnani A, et al (2006) Contributions of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients: by the GIMEMA Working Party on chronic myeloid leukemia. Clin Cancer Res; 12(24):7374-9.
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The FDA's References:
None

19.2. Financial Disclosure

The Applicant's Position:

The Applicant provided financial disclosure for all clinical investigators involved in the studies included in this submission in Form 3454 and Form 3455(s). No clinical investigators are full or part-time employees of Novartis Pharmaceuticals Corporation. Disclosable financial arrangements and interests are detailed in the disclosure forms that follow FDA Form 3455.
There were 10 investigators with disclosable financial arrangements (Table 44). Five of these investigators were designated as principal investigators.

Table 44: Summary of Disclosable Financial Arrangements and Interest

(b) (6)

Any bias resulting from these arrangements is minimized by independent data monitoring by Novartis, multiple investigators used in the studies and randomized trials.

CABL001A2301:

- (b) (6) The sub-investigator (b) (6) declared a payment for research funds for MDS registry in Dec2017 and this amount was not paid directly to the sub-investigator but to the institution. Therefore, an amended Financial Disclosure form was signed in Nov2020 without financial interests or arrangements.
- (b) (6): The sub-investigator (b) (6)) declared financial interest in Financial Disclosure (FD) form completed on 05May2017 (unknown amount). On 05Jan2018, the sub-investigator signed an amended FD form without any financial interest declared anymore. More information is not available as the sub-investigator left the site.
- (b) (6) The sub-investigator (b) (6) declared a financial interest in Mar2018. An amended FD was signed in Jun2020 by using a new form (TransCelerate v3.1) but the sub-investigator forgot to mention the financial interest. Therefore, an amended FD was signed again in Sep2020 mentioning the same amount than the original one.

The FDA's Assessment:
FDA agrees with the Applicant's presentation of financial disclosure information. CABL001A2301 and CABL001X2101 were covered studies.

Covered Clinical Study (Name and/or Number):* CABL001A2301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 600		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number):* CABL001X2101

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 253		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

Data:

The Applicant's Position:
Toxicology data is summarized in Section 5.5.

The FDA's Assessment:
FDA agrees with the Applicant.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Plasma, feces and urine concentrations or amount of asciminib were measured in clinical pharmacology trials (CABL001E2101, CABL001A2101, CABL001A2104, CABL001A2102, CABL001A2103, CABL001A2105, CABL001A1101, CABL001A2106, CABL001A2107) and clinical trials (CABL001X2101 and CABL001A2301). Based on results of human mass-balance Study CABL001A2102, asciminib is the predominant circulating moiety (93%) in plasma.

For all moieties measured, is free, bound, or total measured?

The total plasma concentrations of asciminib were measured in the clinical trials. The average binding of asciminib is about 97.3%.

Bioanalytical methods

A summary of the validation data supporting the bioanalytical methods used for determination of asciminib concentrations in human plasma and urine samples from clinical studies are provided in the following table.

Table 45: Summary method performance of a bioanalytical method to measure ABL001 in human plasma

Bioanalytical method validation report name, amendments, and hyperlinks (Bioanalytical Method A as outlined in the Summary of Biopharmaceutics)	Quantitative determination of ABL001 in human plasma by LC-MS/MS, Amendment no. 02 to Method Validation Report, [DMPK R1300134d-02]
Method description	200 µL acetonitrile was added to each well of a Sirocco protein precipitation plate located on top of a 2-mL 96-well collection plate. A 25 µL aliquot of D5-ABL001 internal standard working solution (500 ng/mL in 50/50 (v/v) acetonitrile/water) was added to each well except for the wells for blanks, where a 25 µL aliquot of 50/50 (v/v) acetonitrile/water was added. 25 µL plasma (blanks, zeros, standards, QCs or unknowns) was added to the designated well. The plate was covered and vortex-mixed for 1 minute on a pulse-vortex mixer. The plate was then centrifuged at 2500 rpm (approximately 1000 × g) for 5 minutes at room temperature. The filtrate was evaporated to dryness at approximately 45°C under a flow of nitrogen. 100 µL of reconstitution solution consisting of acetonitrile in water (20/80, v/v) with 0.1% formic acid was added to each well and mixed for 5 minutes. A 10 µL volume of the reconstituted extract was injected onto the LC-MS/MS system.
Materials used for calibration curve & concentration	**ABL001**: batch no. 1010000992 (purity 99.5%, re-test date Feb-2014) **D5-ABL001**: batch no. SSU6181-2013-8438-01 (chemical purity >96.9%, mass purity >99.9%)
Validated assay range	1.00 to 5000 ng/mL

Material used for QCs & concentration	**ABL001**: batch no. 1010000992 (purity 99.5%, re-test date Feb-2014) **D5-ABL001**: batch no. SSU6181-2013-8438-01 (chemical purity >96.9%, mass purity >99.9%)		
Minimum required dilutions (MRDs)	Not applicable		
Source & lot of reagents (LBA)	Not applicable		
Regression model & weighting	Quadratic regression, $1/x^2$		
Validation parameters	**Method validation summary**		**Source location**
Calibration curve performance during accuracy & precision (Runs 2 to 4)	Number of standard calibrators from LLOQ to ULOQ **Cs**: 1.00 (LLOQ), 2.00, 5.00, 10.0, 25.0, 50.0, 100, 500, 2000, 4500 and 5000 (ULOQ) ng/mL	11	[DMPK R1300134d-02-Table 5-15]
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.3 to 8.0%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 7.0%	
QCs performance during accuracy & precision (Runs 2 to 4)	**Cumulative accuracy (%bias) in 6 QCs** QCs: 1.00 (LLOQ), 2.00, 5.00, 400, 2000 and 4000 (HQC) ng/mL	-2.0 to 5.3%	[DMPK R1300134d-02-Table 5-16]
	Inter-batch %CV QCs: 1.00 (LLOQ), 3.00, 200, 2500 and 4000 (HQC) ng/mL	≤ 8.0%	
	Total error Not applicable	Not applicable	
Selectivity & matrix effect	**Selectivity** Six individual human plasma lots each evaluated in 3 replicates (n=3) **ABL001**: Responses measured in blank samples ranges from 1.9 to 13.0% of the mean response at the LLOQ **D_5-ABL001**: Responses measured in blank samples was 0% of the mean response at the working concentration level **Matrix effect** Six individual human plasma lots were evaluated each in 3 replicates for ABL001 at three concentration (Low, Mid and High) levels and for D_5-ABL001 at the working concentration level **ABL001**: Mean matrix factor at 3 concentration levels (2.00, 400, 4000 ng/mL): 0.798 (ranging from 0.761 to 0.818). Mean CV: 10.0% **D_5-ABL001**: Mean matrix factor at 500 ng/mL: 0.843 (ranging from 0.784 to 0.884). Mean CV: 9.6% **D_5-ABL001 normalized matrix effect for ABL001:** 0.948 (ranging from 0.921 to 0.973), Mean CV: 5.1%		[R1300134d-02-Table 5-1, Table 5-2] [DMPK R1300134d-02-Table 5-5, Table 5-6, Table 5-7]
Interference & specificity	**Interference from D_5-ABL001 to ABL001** Zero samples (blank with D_5-ABL001 at the working concentration level) were prepared in two lots of human plasma. Mean (n=3) interference observed for ABL001 was 5.2 and 15.3% of the mean response at the LLOQ.		[DMPK R1300134d-02-Table 5-3]

	Interference from ABL001 to D_5-ABL001 ULOQ samples without D_5-ABL001 were prepared in two lots of human plasma. Mean (n=3) interference observed for D_5-ABL001 was 0.0 and 0.1% of the mean response at the working concentration.	[DMPK R1300134d-02-Table 5-4]
Recovery	**Recovery** Six individual human plasma lots were evaluated each in 3 replicates for ABL001 at three concentration (Low, Mid and High) levels and for D_5-ABL001 at the working concentration level **ABL001**: Mean recovery at 3 concentration levels (3.00, 2500, 4000 ng/mL): 75.5% (ranging from 69.6 to 79.6%). Mean CV: 13.1% **D_5-ABL001**: Mean recovery at 500 ng/mL: 81.6% (ranging from 75.0 to 86.5%). Mean CV: 11.5% **D_5-ABL001 normalized recovery for ABL001:** 92.4% (ranging from 91.9 to 92.7%). Mean CV 4.1%	[DMPK R1300134d-02-Table 5-9, Table 5-10,Table 5-11]
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue: A single lot of hemolyzed (275 mg/dL) human plasma was evaluated in 3 replicates for ABL001 at one concentration (400 ng/mL) level and for D5-ABL001 at the working concentration level **ABL001**: Mean matrix factor: 0.889. Mean CV: 3.7% **D_5-ABL001**: Mean matrix factor at 500 ng/mL: 0.787. Mean CV: 3.9% **D_5-ABL001 normalized matrix effect for ABL001**: 0.915, Mean CV: 2.9%	[DMPK R1300134d-02-Table 5-8]
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue: A single lot of lipemic human plasma was evaluated in 3 replicates for ABL001 at one concentration (400 ng/mL) level and for D5-ABL001 at the working concentration level **ABL001**: Mean matrix factor: 0.767. Mean CV: 10.8% **D_5-ABL001**: Mean matrix factor at 500 ng/mL: 0.794. Mean CV: 8.5% **D_5-ABL001 normalized matrix effect for ABL001**: 0.966, Mean CV: 5.9%	[DMPK R1300134d-02-Table 5-9]
Dilution linearity & hook effect	Dilution QC at 25000 ng/mL was diluted 10-fold and 20-fold with blank plasma, followed by analysis. Mean (n=6) Bias% was -2.4 and 3.2%, respectively. CV% was 1.9 and 3.5%, respectively	[DMPK R1300134d-02-Table 5-19]
Bench-top/process stability	Stable in human plasma for at least 24 hours at room temperature Stable in post-preparative sample extract for at least 7 days at 5°C and 10°C	[DMPK R1300134d-02-Table 5-27] [DMPK R1300134d-02-Table 5-25]
Freeze-Thaw stability	Stable in human plasma after 3 freeze (at ≤-60°C) - thaw (room temperature) cycles	[DMPK R1300134d-02-Table 5-26]
Long-term storage	Stable in human plasma for at least 707 days when stored at ≤-60°C	[DMPK R1300134d-02-Table 5-28]
Parallelism	Not applicable	
Carry over	**ABL001**: Response observed in the blank sample injected immediately following injection of the ULOQ >20% (up to 145%) of the response	[DMPK R1300134d-02-

	observed for ABL001 at the LLOQ level. The observed carryover has no impact on study sample analysis. Refer to Special issue of method validation report amendment DMPK R1300134d-02. **D_5-ABL001**: Response after injection of one blank sample following injection of the D_5-ABL001 at the working concentration <5% of the D_5-ABL001 response observed at the working concentration	Table 5-12 and 5-13]
Method performance in study no. CABL001X2101 (the first part supported in house) Bioanalytical data report: Determination of ABL001 in human plasma, DMPK RCABL001X2101-02 (In addition to the report name, also provide hyperlink to the report)		
Assay passing rate	94.1% passed (48 out of 51 runs, including incurred sample reanalysis run)	[DMPK RCABL001X2101-02-Table 5-1]
Standard curve performance	• Cumulative bias range: -4.0 to 3.5% • Cumulative precision: ≤ 7.8% CV	[DMPK RCABL001X2101-02-Table 5-3]
QC performance	• Cumulative bias range: 0.0 to 5.0% • Cumulative precision: ≤ 4.6% CV • TE: Not applicable	[DMPK RCABL001X2101-02-Table 5-4]
Method reproducibility	Incurred sample reanalysis was performed in 0.4% of study samples (for 22 randomly selected study samples), and 100% of the sample results met the pre-specified criteria.	[DMPK RCABL001X2101-02-Table 9-3]
Study sample analysis/ stability	Describe storage stability coverage for standard/QC and samples: ABL001 is stable under the following conditions: (1) at least 7 days in post-preparative sample extracts stored at 5°C and 10°C; (2) at least 24 hours at room temperature in human plasma; (3) after at least 5 freeze/thaw cycles at ≤-60°C in human plasma; (4) at least 1191 days when stored at ≤-60°C in human plasma; and (5) at least 2 hours at room temperature in human whole blood. The established stability covers the period between sample collection and analysis for the study.	[DMPK R1300134d-02] [DMPK R1500058-02]
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ. **Cs**: 1.00 (LLOQ), 2.00, 10.0, 50.0, 100, 500, 2000, 4500 and 5000 (ULOQ) ng/mL	

Bioanalytical method validation report name, amendments, and hyperlinks (Bioanalytical Method C as outlined in the Summary of Biopharmaceutics)	Quantitative determination of ABL001 in human plasma (K_2EDTA) by LC-MS/MS, Amendment 01 to Method Validation Report, DMPK R1701209-02
Method description	50 µL plasma (blanks, zeros, standards, QCs or unknowns) was added to polypropylene tube. A 50 µL aliquot of D5-ABL001 internal standard working solution (500 ng/mL in 50/50 (v/v) acetonitrile/water) was added to each tube except for the tubes for blanks, where a 50 µL aliquot of 50/50 (v/v) acetonitrile/water was added. A 300 µL aliquot of acetonitrile was added to each tube. The tubes were vortex-mixed, followed by centrifugation at approximately 4000 rpm for 10 minutes at 10±2ºC. Supernatant was transferred to pre-labeled autosampler vials. A 5 µL aliquot of the reconstituted extract was injected onto the LC-MS/MS system.

Materials used for calibration curve & concentration	**ABL001**: batch no. 1010009610 (purity 100%, salt/base correction factor (b) (4), re-test date 31-Dec-2017 and 31-Dec-2019) **D_5-ABL001**: batch no. SSU6181-2013-8438-01 (chemical purity 98.4%, re-test date Jul-2020)		
Validated assay range	1.00 to 5000 ng/mL		
Material used for QCs & concentration	**ABL001**: batch no. 1010009610 (purity 100%, salt/base correction factor (b) (4), re-test date 31-Dec-2017 and 31-Dec-2019) **D_5-ABL001**: batch no. SSU6181-2013-8438-01 (chemical purity 98.4%, re-test date Jul-2020)		
Minimum required dilutions (MRDs)	Not applicable		
Source & lot of reagents (LBA)	Not applicable		
Regression model & weighting	Linear regression, $1/x^2$		
Validation parameters	**Method validation summary**		**Source location**
Calibration curve performance during accuracy & precision (Runs 17 to 22 and 24 to 32, 35 to 36)	Number of standard calibrators from LLOQ to ULOQ **Cs**: 1.00 (LLOQ), 2.00, 15.0, 40.0, 100, 250, 500, 1000, 2500 and 5000 (ULOQ) ng/mL	10	[DMPK R1701209-02-Table 6-16]
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.7 to 3.8%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 7.6%	
QCs performance during accuracy & precision (Runs 17 to 19)	**Cumulative accuracy (%bias) in 5 QCs** QCs: 1.00 (LLOQ), 3.00, 200, 2000 and 4000 (HQC) ng/mL	-5.0 to 8.0%	[DMPK R1701209-02-Table 6-17]
	Inter-batch %CV QCs: 1.00 (LLOQ), 3.00, 200, 2000 and 4000 (HQC) ng/mL	≤ 14.9%	
	Total error Not applicable	Not applicable	
Selectivity & matrix effect	**Selectivity** Six individual human plasma lots, one hemolyzed plasma lot and one lipemic plasma lot, each evaluated in 3 replicates (n=3) **ABL001**: Responses measured in blank samples ranges from 1.3 to 6.5% of the mean response at the LLOQ **D_5-ABL001**: Response measured in blank samples was 0% of the mean response at the working concentration **Selectivity in presence of imatinib, nilotinib and dasatinib** Four individual human plasma lots, one hemolyzed plasma lot and one lipemic plasma lot with singlet (n=1) spiked with imatinib (8000 ng/mL), nilotinib (5000 ng/mL) and dasatinib (400 ng/mL) were evaluated. Responses of ABL001 ranges from 0 to 2.06% of the mean response at the LLOQ; Responses of D_5-ABL001 ranged from 0 to 0.01% of the mean response at the working concentration.		[R1701209-02-Table 6-1 and Table 6-2] [DMPK R1701209-02-Table 6-36]

	Matrix effect Six individual human plasma lots, two hemolyzed plasma lots and two lipemic plasma lots were evaluated each in 3 replicates for ABL001 and D_5-ABL001. **ABL001**: Mean matrix factor at 3 concentration levels (3.00, 2000, 4000 ng/mL): 1.09 (ranging from 1.03 to 1.14). Mean CV: 6.0% **D_5-ABL001**: Mean matrix factor at 500 ng/mL: 1.10 (ranging from 1.05 to 1.13). Mean CV: 3.8% **D_5-ABL001 normalized matrix effect for ABL001:** 1.00 (ranging from 0.98 to 1.01), Mean CV: 3.8%	[DMPK R1701209-02-Table 6-6, Table 6-7 and Table 6-8]
Interference & specificity	**Interference from D_5-ABL001 to ABL001** Zero samples (blank with D_5-ABL001 at the working concentration) were prepared in a single lot of human plasma. Mean (n=3) interference observed for ABL001 was 2.3% of the mean response at the LLOQ. **Interference from ABL001 to D_5-ABL001** ULOQ samples without D_5-ABL001 were prepared in a single lot of human plasma. Mean (n=3) interference observed for D_5-ABL001 was 0% of the mean response at the working concentration. **Interference from concomitant medications** ABL001 QCs (3.00 and 4000 ng/mL) co-spiked with imatinib (8000 ng/mL), nilotinib (5000 ng/mL) and dasatinib (400 ng/mL) were evaluated in three replicates (n=3). Mean bias% was 4.7 and -1.5%, respectively. CV% was 3.4 and 1.9%, respectively.	[DMPK R1701209-02-Table 6-4] [DMPK R1701209-02-Table 6-5] [DMPK R1701209-02-Table 6-36]
Recovery	**Recovery** One human plasma lot was evaluated in 6 replicates for ABL001 and D_5-ABL001 **ABL001**: Mean recovery at 3 concentration levels (3.00, 2000, 4000 ng/mL): 76.0% (ranging from 68.6 to 83.1%). Mean CV: 9.6% **D_5-ABL001**: Mean recovery at 500 ng/mL: 80.6% (ranging from 77.6 to 86.1%). Mean CV: 6.0% **D_5-ABL001 normalized recovery for ABL001:** 94.0% (ranging from 89.1 to 97.3%), Mean CV: 4.6%	[DMPK R1701209-02-Table 6-10, Table 6-11 and Table 6-12]
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue: **Matrix effect** Two hemolyzed plasma lots were evaluated each in 3 replicates for ABL001 and D5-ABL001 **ABL001**: Mean matrix factor at 2000 ng/mL): 1.09 (ranging from 1.08 to 1.10). Mean CV: 1.0% **D_5-ABL001**: Mean matrix factor at 500 ng/mL: 1.10 (ranging from 1.09 to 1.10). Mean CV: 0.9% **D_5-ABL001 normalized matrix effect for ABL001**: 0.99 (ranging from 0.99 to 1.00), Mean CV: 0.9% One lot of hemolyzed plasma was evaluated for ABL001 at 3.00 and 4000 ng/mL levels. Mean (n=6) bias% was 8.7 and 7.5%, respectively. CV% was 4.8 and 6.3%, respectively.	[DMPK R1701209-02-Table 6-9] [DMPK R1701209-02-Table 6-35]
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue:	[DMPK R1701209-02-Table 6-35]

	One lot of lipemic plasma was evaluated for ABL001 at 3.00 and 4000 ng/mL levels. Mean (n=6) bias% was 8.7 and 8.8%, respectively. CV% was 4.8 and 4.9%, respectively.	
Dilution linearity & hook effect	Dilution QC at 24000 ng/mL was diluted 10-fold with blank plasma, followed by analysis. Mean (n=6) bias% was 6.7%. CV% was 1.5%	[DMPK R1701209-02-Table 6-20]
Bench-top/process stability	Stable in human plasma for at least 22 hours at room temperature Stable in post-preparative sample extract for at least 142 hours at 5±3ºC and 4 hours at room temperature	[DMPK R1701209-02- Table 6-27, Table 6-28, and Table 6-30]
Freeze-Thaw stability	Stable in human plasma after at least 5 freeze-thaw cycles when freezing at -20±5°C and thawing at room temperature Stable in human plasma after at least 5 freeze-thaw cycles when freezing at -78±8°C and thawing at room temperature	[DMPK R1701209-02-Table 6-29]
Long-term storage	Stable in human plasma for at least 179 days when stored at -20±5°C and -78±8°C	[DMPK R1701209-02-Table 6-31]
Parallelism	Not applicable	
Carry over	**ABL001:** Response after injection of one blank sample immediately following injection of the ULOQ <20% of the response observed for the LLOQ for all the runs (Runs 1 to 30, except Runs 23 and 34). **D_5-ABL001**: Response after injection of one blank sample following injection of the D5-ABL001 at the working concentration <5% of the D_5-ABL001 response observed at the working concentration for all the runs (Runs 1 to 36, except Runs 23 and 34)	[DMPK R1701209-02-Table 6-13 and Table 6-14]
Cross-lab check	30 samples assayed at Novartis were re-assayed at (b) (4) for cross check. 29 out of 30 sample results met the acceptance criteria (%difference within ±20% of mean values).	[DMPK R1701209-02-Table 6-19]
Method performance in study no. CABL001A2301 Bioanalytical data report: Determination of ABL001 in human plasma, DMPK RCABL001A2301-int-02 (In addition to the report name, also provide hyperlink to the report)		
Assay passing rate	100% passed (16 out of 16 runs, including incurred sample reanalysis run)	[DMPK RCABL001A2301-int-02-Table 5-1]
Standard curve performance	• Cumulative bias range: -2.5 to 1.4% • Cumulative precision: ≤ 7.1% CV	[DMPK RCABL001A2301-int-02-Table 5-3]
QC performance	• Cumulative bias range: -1.5 to 0.5% • Cumulative precision: ≤ 7.3% CV • TE: Not applicable	[DMPK RCABL001A2301-int-02-Table 5-7]
Drug-drug interference in presence of Bosutinib	ABL001 QCs (3.00 and 4000 ng/mL) co-spiked with Bosutinib (200 ng/mL) were evaluated in three replicates (n=3). Mean bias% was -3.7 and 5.0%, respectively. CV% was 3.5 and 0.7%, respectively.	[DMPK RCABL001A2301-int-02-Table 5-5]
Method reproducibility	Incurred sample reanalysis was performed in 3.8% of study samples (for 50 randomly selected study samples) and 96% of samples met the pre-specified criteria.	[DMPK RCABL001A2301-int-02-Table 9-3]
Study sample analysis/ stability	Describe storage stability coverage for standard/QC and samples: ABL001 is stable under the following conditions: (1) at least 7 days at 5°C and 10°C in post-preparative sample extracts; (2) for at least 24 hours at room temperature in human plasma; (3) after at least 5	[DMPK R1300134d-02] [DMPK R1500058-02]

	freeze/thaw cycles at ≤-60°C in human plasma; (4) at least 1191 days when stored at ≤-60°C in human plasma; and (5) at least 2 hours at room temperature in human whole blood. The established stability covers the period between sample collection and analysis for the study.	
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ. **Cs**: 1.00 (LLOQ), 2.00, 15.0, 40.0, 100, 250, 500, 1000, 2500 and 5000 (ULOQ) ng/mL	
Method performance in study no. CABL001X2101 Bioanalytical data report: Determination of ABL001 in human plasma, DMPK RCABL001X2101a-int-01 (In addition to the report name, also provide hyperlink to the report)		
Assay passing rate	80% passed (72 out of 90 runs, including incurred sample reanalysis run)	[DMPK RCABL001X2101a-int-01-Table 5-1]
Standard curve performance	• Cumulative bias range: -2.6 to 1.5% • Cumulative precision: ≤ 7.4% CV	[DMPK RCABL001X2101a-int-01-Table 5-3]
QC performance	• Cumulative bias range: -1.8 to -0.7% • Cumulative precision: ≤ 8.2% CV • TE: Not applicable	[DMPK RCABL001X2101a-int-01-Table 5-6]
Method reproducibility	Incurred sample reanalysis was performed in 19 randomly selected study samples and 94.74% of samples met the pre-specified criteria.	[DMPK RCABL001X2101a-int-01-Table 9-3]
Study sample analysis/ stability	Describe storage stability coverage for standard/QC and samples: ABL001 is stable under the following conditions: (1) at least 7 days at 5°C and 10°C in post-preparative sample extracts; (2) for at least 24 hours at room temperature in human plasma; (3) after at least 5 freeze/thaw cycles at ≤-60°C in human plasma; (4) at least 1191 days when stored at ≤-60°C in human plasma; and (5) at least 2 hours at room temperature in human whole blood. The established stability covers the period between sample collection and analysis for the study.	[DMPK R1300134d-02] [DMPK R1500058-02]
Standard calibration curve performance during accuracy and precision runs	Provide the number of standard calibrators from LLOQ to ULOQ. **Cs**: 1.00 (LLOQ), 2.00, 15.0, 40.0, 100, 250, 500, 1000, 2500 and 5000 (ULOQ) ng/mL	

FDA considers the bioanalytical methods used in the current submission are acceptable to support the clinical pharmacology program of asciminib.

19.4.2. Population PK Analysis

The Applicant's Position:

A population PK (PopPK) model was developed for asciminib in patients with CML-CP/-AP. PK data from CML-CP (chronic phase)/AP (acute phase) patients receiving asciminib (in studies

Study CABL001X2101 and Study CABL001A2301) in fasted condition were pooled. Patients who switched from bosutinib to asciminib in Study CABL001A2301were excluded from the pooled analysis. The influence of various covariates (including baseline aGFR, sex, body weight, baseline age, study effect, race (Asian vs. non-Asian), Japanese status (Japanese vs. non-Japanese), baseline disease characteristics (AP vs. CP), heavy smoking status, hepatic function, and T315I mutation) were evaluated on the PK of asciminib.

The model featured a two-compartmental structure with delayed first-order oral absorption and clearance dependent on dose. The model described well the PK data set that included 353 patients with diverse characteristics from two studies, Study CABL001X2101 and Study CABL001A2301.

The PopPK model included nominal total daily dose as a structural covariate on clearance, which was necessitated due to dose-dependent predictions from the initial base model. In addition, baseline weight, baseline aGFR were found to be significant covariates on clearance, whereas formulation was a significant covariate on the absorption rate constant. However, none of these covariates is expected to influence the PK of asciminib to any clinically relevant extent.

Goodness-of-fit plots and visual predictive check indicated that the PopPK model adequately described the observed data, and parameter estimates from bootstrap are within the 90% CI, demonstrating robustness of the model. Thus, the model was deemed appropriate for its intended purposes: the characterization of asciminib PK and the generation of exposure metrics for use in exposure response analyses.

The FDA's Assessment:

FDA noted that Applicant's final PopPK model was a 2-compartment model with a delayed first-order absorption, inter-individual variability (IIV) for absorption rate (Ka), clearance (CL), central volume of distribution (Vc) and peripheral volume of distribution (Vp), correlation between CL and Vc, and combined proportional and additive error model. The Applicant's final model also included nominal total daily dose, baseline body weight and baseline aGFR on CL, and formulation on Ka. FDA considers that the Applicant's final model may not be appropriate for the following reasons: 1) renal function (absolute glomerular filtrate rate, aGFR) may not significantly affect asciminib PK given that only 2.5% unchanged asciminib dose was recovered in the urine; and 2) it is not appropriate to estimate both aGFR and body weight as covariates on CL as aGFR is a function of body size and should have a strong correlation with body weight.

Therefore, FDA conducted independent PopPK analysis based on Applicant's PopPK dataset, which includes a total of 353 patients with CML-CP and CML-AP from Trials X2101 and A2301. The FDA's base PopPK model has the same structure as the Applicant's model, but includes IIV for absorption lag time (Tlag), Ka, CL, Vc, and Vp, and correlation between Tlag and Ka, as well as correlations among CL, Vc and Vp. FDA then further conducted covariate analysis using a forward inclusion and backward elimination approach. The forward inclusion step included the following covariates: formulation on Tlag, nominal total daily dose on CL, body weight on CL and Vc, sex on

CL and Vc, age on CL, Asian on Tlag, and formulation on Vc at p<0.05. Estimation of allometric scaling parameters for CL and Vc achieved significantly lower objective function value (OFV) as compared to fixing the parameters to 0.75 for CL and 1 for Vc. The backward elimination step indicated all these covariates were statistically significant at p<0.001. The FDA's final model yielded a significant lower OFV (94753.99) vs. the Applicant's final model (OFV = 96288.32).

The PK parameters of the FDA's final PopPK model are shown in Table 46. The goodness-of-fit (GOF) plots (Figure 9) and visual predictive check plot (Figure 10) show that the FDA's final PopPK model describes the observed asciminib PK well. Therefore, the derived average daily $AUC_{0\text{-}24h}$, Cmax and Cmin were used for the FDA's independent E-R analysis.

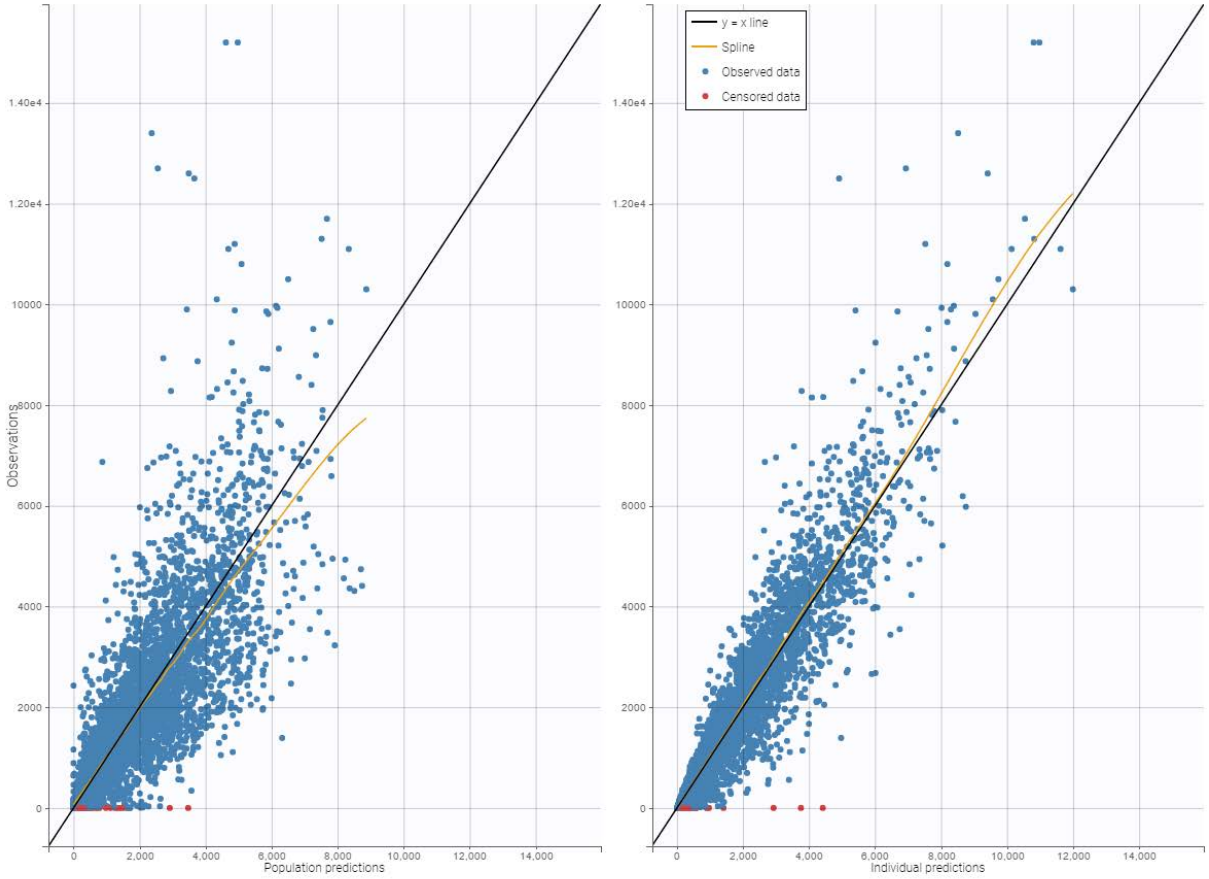
Table 46: PK Parameter Estimates from the FDA's Final Population PK Model

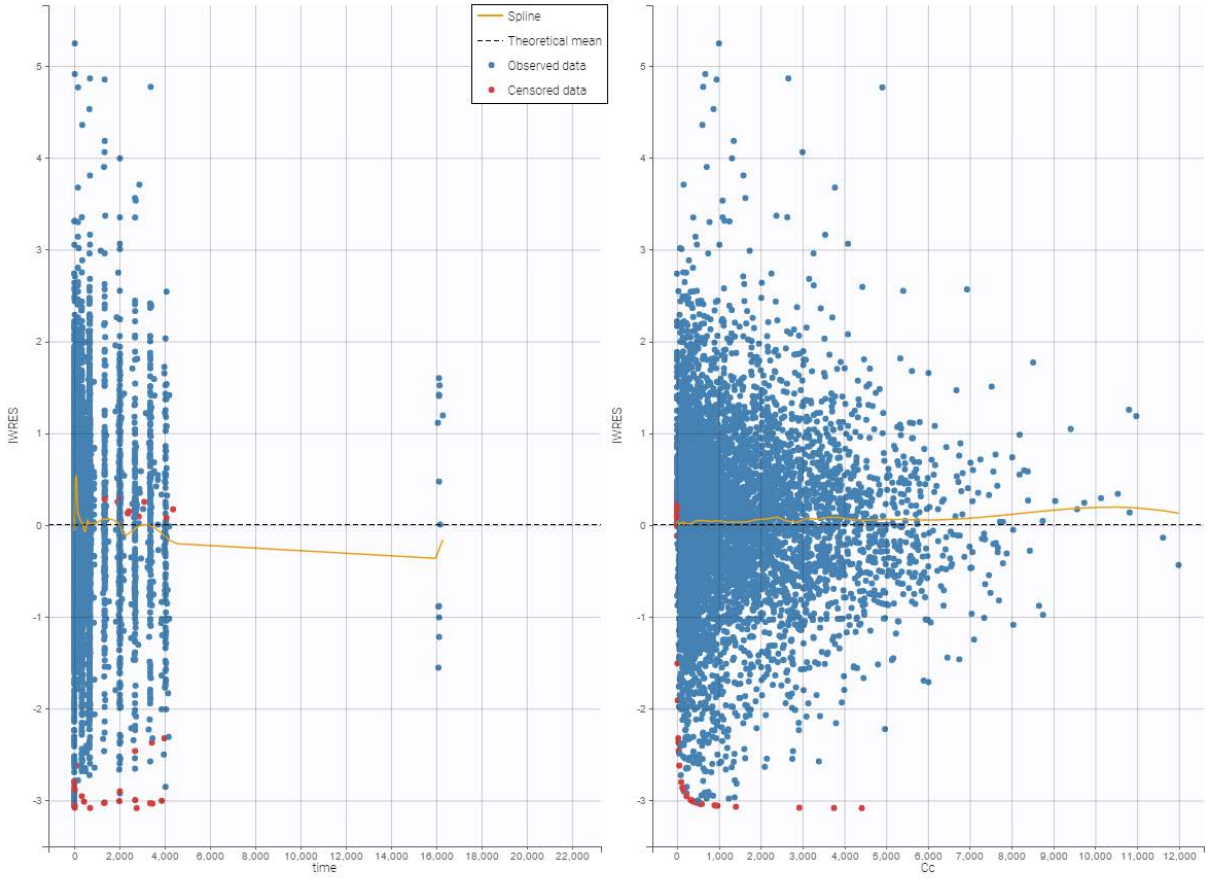
PK Parameter	Estimate	SE (%)	RSE (%)
Fixed effects			
Absorption lag time (Tlag), h	0.311	0.0164	5.29
θ‡ (Asian on Tlag)	0.371	0.0732	19.8
θ‡ (Formulation on Tlag)	0.615	0.0649	10.5
Absorption rate constant (Ka), h^{-1}	1.62	0.093	5.74
Central clearance (CL), L/h	9.48	0.751	7.93
θ‡ (age on CL)	-0.00614	0.00132	21.5
θ‡ (sex on CL)	-0.245	0.0469	19.2
θ‡ (total daily dose on CL)	-0.334	0.0282	8.44
θ‡ (weight on CL)	0.573	0.103	18.0
Central volume of distribution (Vc), L	55.8	2.42	4.33
θ‡ (formulation on Vc)	0.218	0.0443	20.3
θ‡ (sex on Vc)	-0.32	0.052	16.3
θ‡ (weight on Vc)	0.391	0.117	29.9
Peripheral clearance (Q), L	6.64	0.271	4.08
Peripheral volume of distribution (Vp), L	74.4	8.02	10.8
Standard Deviation of the Random Effects			
Tlag	0.431	0.0266	6.17
Ka	0.595	0.0545	9.17
CL	0.403	0.0173	4.29
Vc	0.375	0.0211	5.64
Vp	1.55	0.0867	5.60
Correlations between random effects			
Correlation Vc~ CL	0.449	0.0537	12.1
Correlation Vp~CL	-0.288	0.0693	24.1
Correlation Vc~Vp	0.404	0.0727	18.0
Correlation Ka~Tlag	-0.583	0.0811	13.9
Residual errors			

Additive	3.28	0.384	11.7
Proportional	0.324	0.00369	1.14

‡Covariate effect in linear scale is determined by taking exp(θ).
Source: FDA's independent analysis.

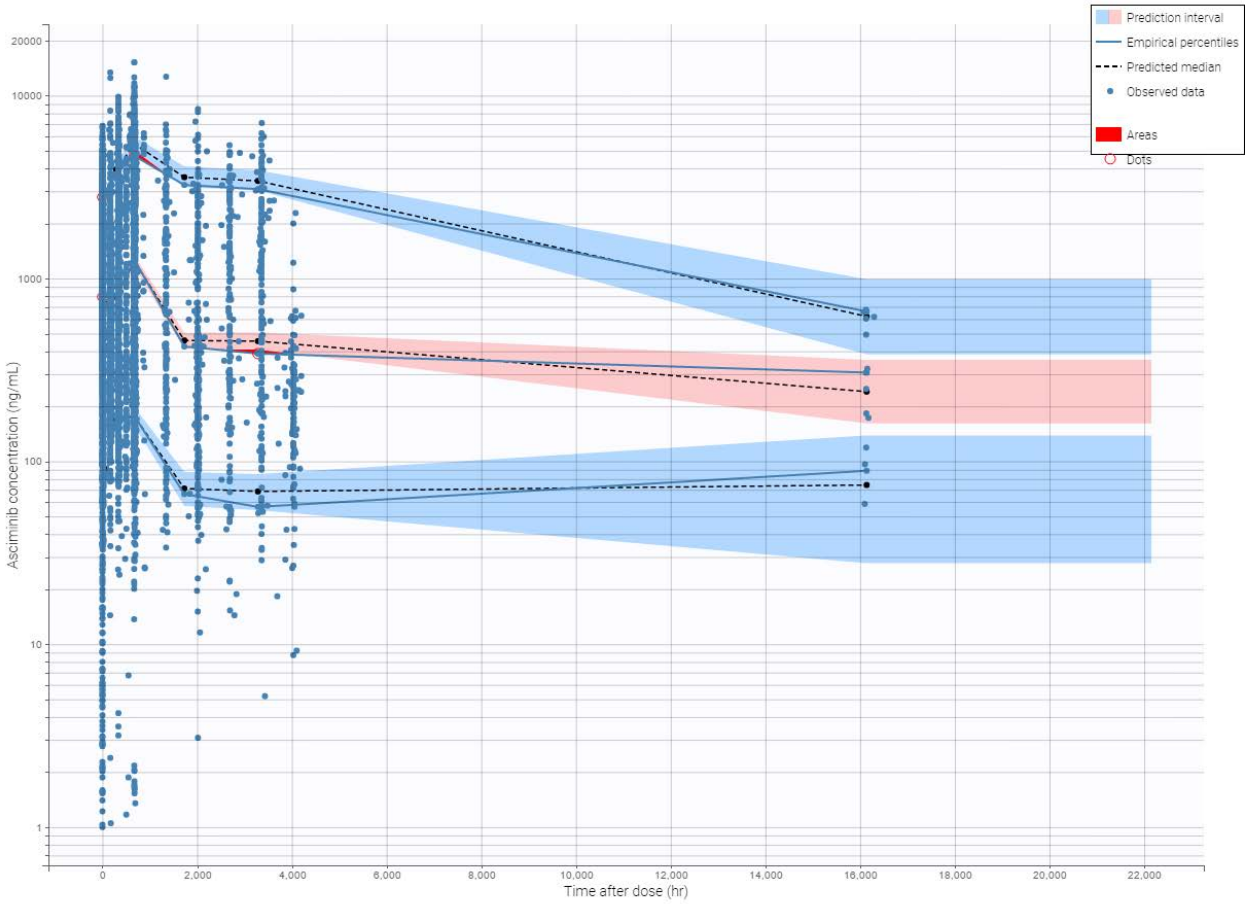
Figure 9: Goodness-of-fit Plots based on the FDA's Final Population PK Model





Upper left panel: observations vs. population predictions. Upper right panel: observations vs. individial predictions. Lower left panel: individual residual errors (IWRES) vs. time after dose (hour). Lower right panel: IWRES vs. log-transformed population predictions.
Blue dots: observations. Red dots: censored data. Yellow lines: spline regression lines.
Source: FDA's independent analysis.

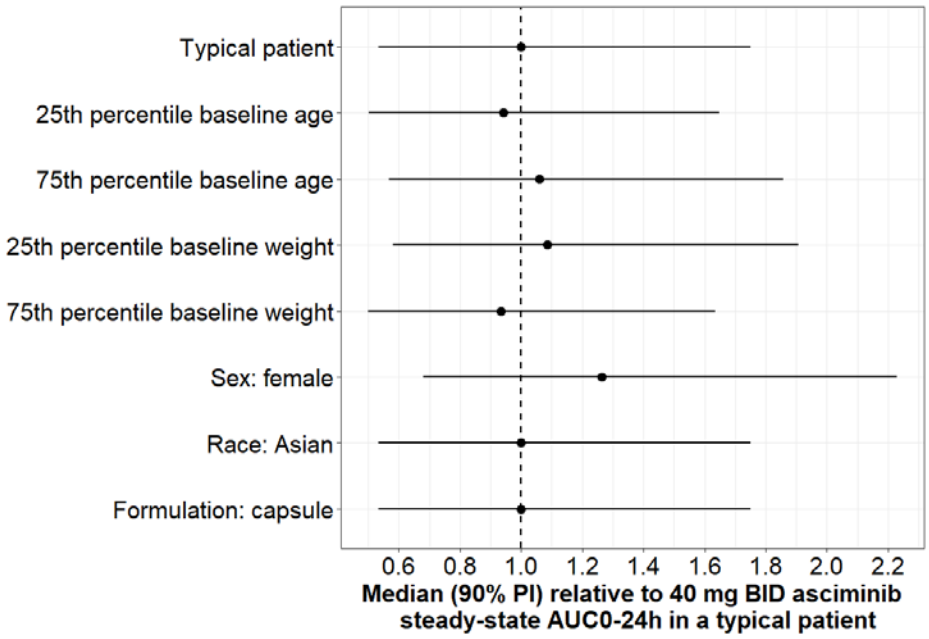
Figure 10: Visual Predictive Check Plot based on the FDA's Final Population PK Model



Blue dots: observations. Black dashed lines: 5th, 50th, and 95th percentiles of the observations. Blue solid lines: 5th, 50th, and 95th percentiles of the predictions. Blue shades: 95% confidence interval of 5th and 95th percentiles of the predictions. Red shade: 95% confidence interval of 50th percentile of the predictions.
Source: FDA's independent analysis.

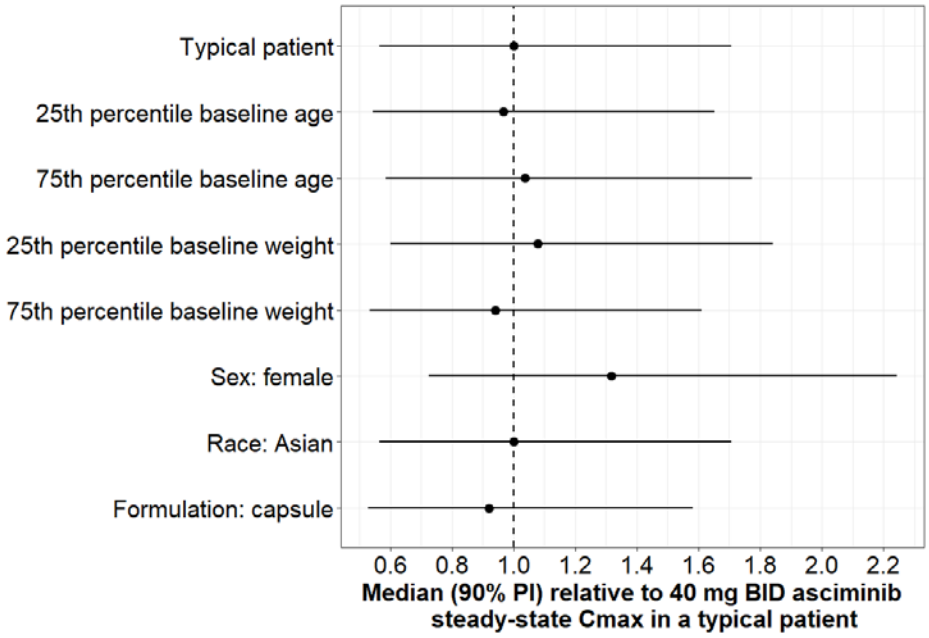
The univariate influence of each statistically significant covariate (body weight, age, sex, Asian race and capsule formulation) on the exposures of asciminb at steady state with 40 mg BID dosing was evaluated. The typical patient was defined as a non-Asian male patients with a body weight of 78 kg, age of 53 years, and treated with final market image tablet. The estimated effects for each significant covariate, independent of other covariate effects or correlated covariates on steady-state $AUC_{0\text{-}24h}$, Cmax, and Cmin are presented in Figure 11, Figure 12, and Figure 13, respectively. The differences of these three PK metrics between medians of the covariates to that of a typical patients was generally within 20%, while 90% prediction limits were generally similar to that of a typical patient, suggesting that the effects of these covariates are deemed clinically insignificant. Therefore, no dose adjustment is needed based on sex, race, age and body weight.

Figure 11: Univariate Impact of Statistically Significant Covariates on Steady-State AUC_{0-24h} after Asciminib 40 mg BID Administration



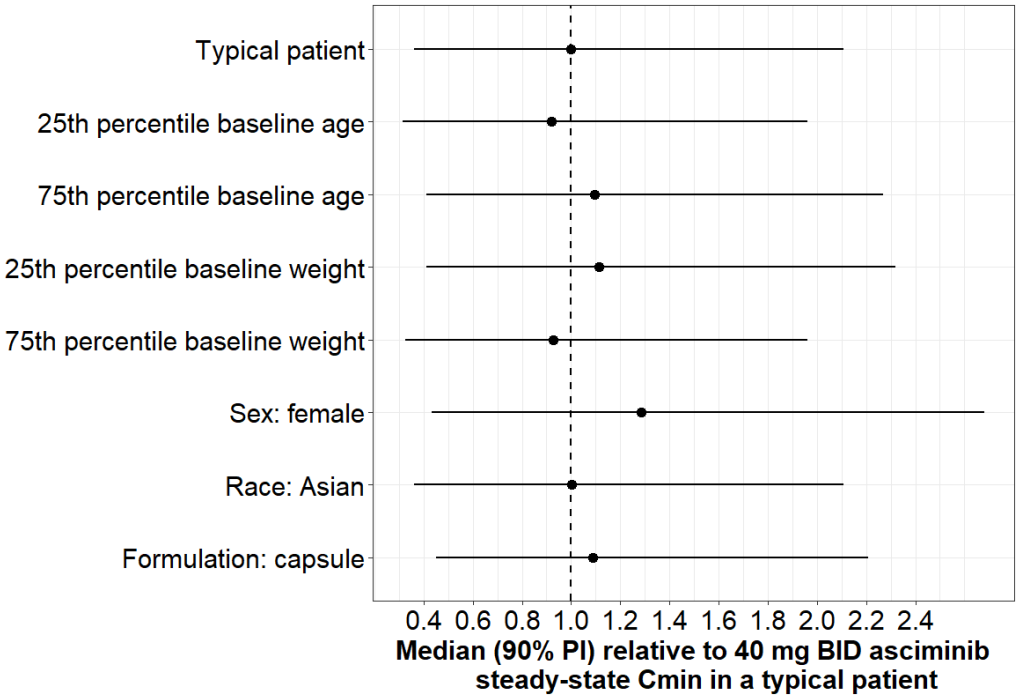
Source: FDA's independent analysis.

Figure 12: Univariate Impact of Statistically Significant Covariates on Steady-State Cmax after Asciminib 40 mg BID Administration



Source: FDA's independent analysis.

Figure 13: Univariate Impact of Statistically Significant Covariates on Steady-State Cmin after Asciminib 40 mg BID Administration



Source: FDA's independent analysis.

In addition, the FDA's final model was rerun using a pooled dataset with additional 43 patients with CML-BP and Ph+ ALL on asciminib monotherapy 40 – 280 mg BID from Trial X2101 Arm 5. No significant difference was found in the asciminib PK parameter estimates between these two models. The derived asciminib PK expsoures (average daily AUC, Cmax and Cmin) from this PopPK model were used for the FDA's exposure-safety analysis.

19.4.3. Exposure – Response Analysis

The Applicant's Position:

Exposure–response models have been established to characterize the exposure-efficacy and exposure–safety relationship of asciminib. The efficacy endpoint analyzed was the time-course of the BCR-ABL1 (%) (IS), transcript levels of the BCR-ABL1 fusion gene. The exposure-efficacy analysis included 303 patients with CML-CP from Study CABL001A2301 and Study CABL001X2101, up to the data cut-off date of 25-May-2020 and 02-Apr-2020 respectively. A total of 267 patients received twice-daily (BID) dosing, while 36 patients received once-daily (QD) dosing. At baseline, majority of the subjects had >10% BCR-ABL1 IS >1% levels. In total, 67 subjects harboring the T315I mutation were included. The time-course over 2 years in Study CABL001A2301 and over 5 years in Study CABL001X2101 showed decreases in $\log_{10}$-transformed

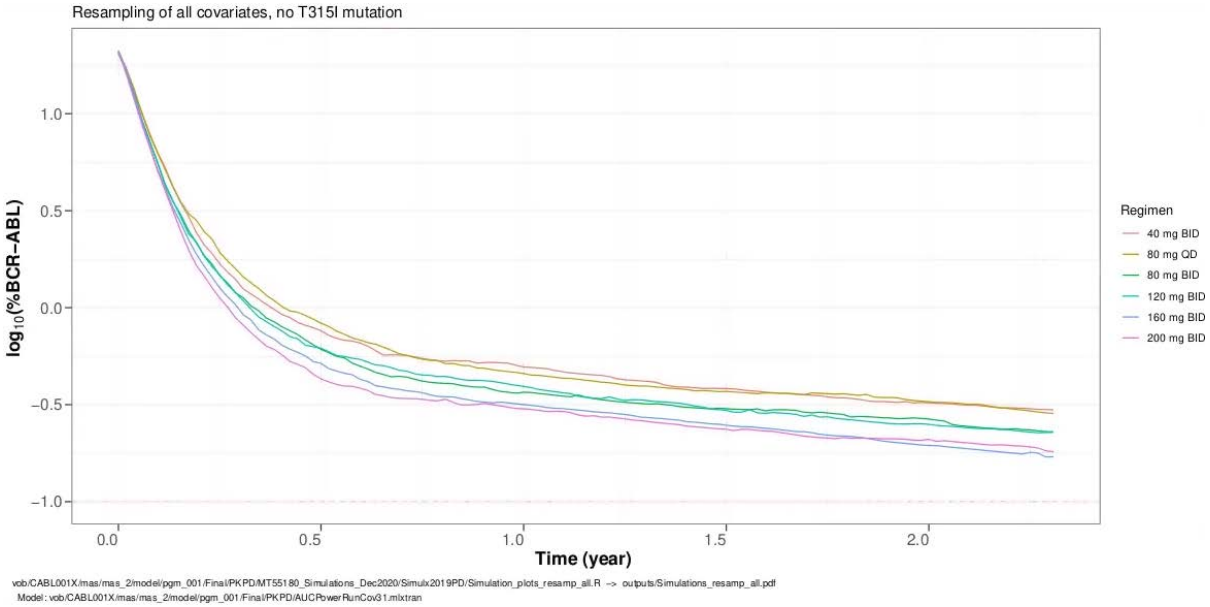
BCL-ABL1 for doses ranging from a total daily dose of 20 mg to 400 mg, taken as either BID or QD.

A semi-mechanistic model was developed to explore the effect of PK metrics (daily AUC, Cmax, Cmin) on BCR-ABL1. Separate models using the same semi-mechanistic model structure were evaluated in three datasets: (1) datasets including all patients with CML CP regardless of mutation status (N=303); (2) subset of patients without T315I mutation administered 40 mg BID or 80 mg QD as starting dose (N=194); and (3) subset of patients with T315I mutation (N=67).

Factors influencing BCR-ABL1 were baseline BCR-ABL1, number of prior TKIs and time since first CML diagnosis. These covariates indicated a biological explanation for drug resistance to therapy. Patients with lower baseline BCR-ABL1 levels were more likely to achieve treatment success. The longer the subjects were between first CML diagnosis and baseline, the higher the proportion of resistant cell population compared to the proliferating leukemic cells that respond to therapy. The drug killing effect on proliferating bone marrow cells decreased when subjects had more prior TKI treatments. The semi-mechanistic pharmacodynamic model used to fit the time course of BCR-ABL1 was found to be adequate and useful in describing patients' response to asciminib. The model was able to describe known biological processes affecting drug response, particularly, in its ability in distinguishing between different patterns of BCR-ABL1 due to resistance, effects of different number of prior TKIs, and different levels of baseline BCR-ABL1, in addition to the effect of drug holiday, especially for an extended period of time. The application of the semi-mechanistic model in evaluating exposure-efficacy relationship was suitable and supported by a similar approach that evaluated the effect of dose reduction of commercially available TKIs on their long-term treatment efficacy.

Figure 14 displays the median simulated BCR-ABL1 levels for various dosing regimens, highlighting the existence of a slightly positive exposure-efficacy relationship, that did not translate into meaningful difference in median predicted MMR rates (median predicted MMR) at Week 48 were 34%, 35%, and 39% for 40 mg BID, 80 mg QD and 200 mg BID).

Figure 14: Median simulated time-course of log_{10}-transformed BCR-ABL1 after various dose regimens with all covariates resampled from the original modeling data set, without T315I mutation

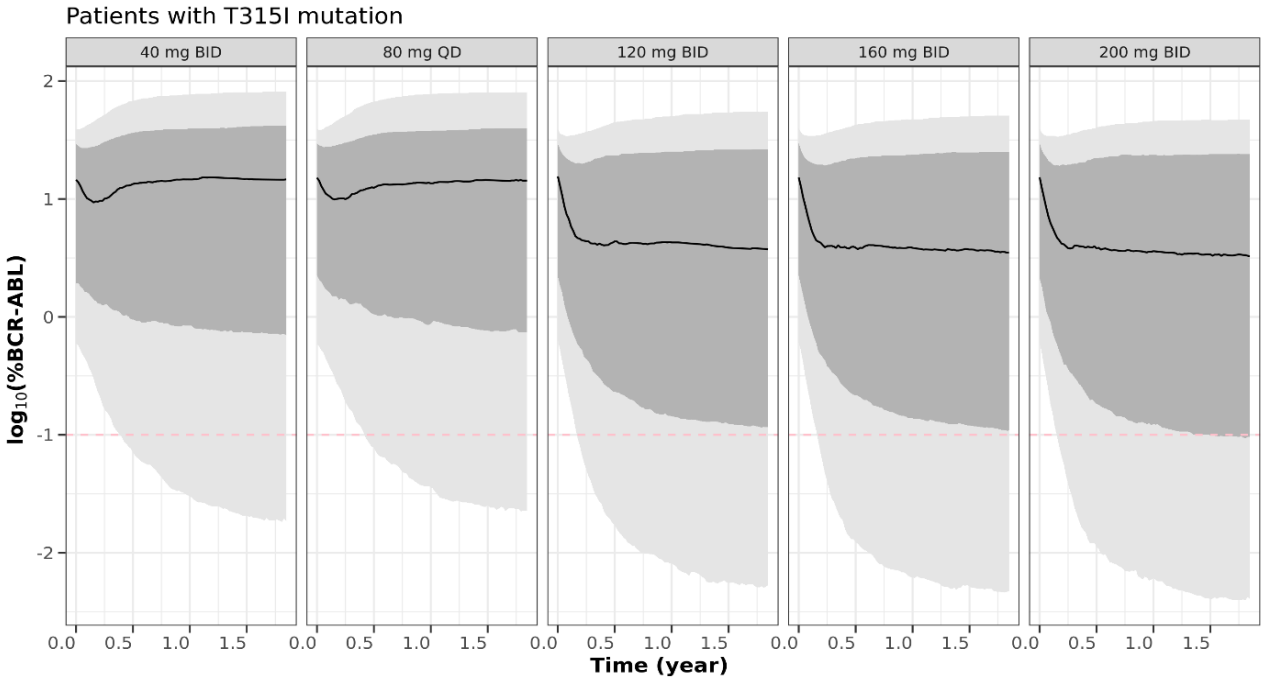


Source: Novartis ABL001A Summary of clinical pharmacology-Figure 3-7

The same structural model was applied to the second data set to investigate and compare the 40 mg BID and 80 mg QD regimens. The model predicted a similar BCR-ABL1 time course which resulted in similar predicted MMR rates between the two dosing regimens. The predicted MMR rate at Week 24 for asciminib 80 mg QD was 24.8 ± 4.2%, in agreement with the observed MMR rate. The predicted MMR rate at 40 mg BID for the same timepoint was 27.6 ± 4.5%.

For the third data set, an Emax function was used and successfully described the drug effect, which indicated that, compared to a dose of 200 mg BID, patients with T315I mutation treated with lower dose regimens were less likely to respond to treatment. The analysis showed that the 200 mg BID administration provided sufficient exposure to achieve maximal drug effect. Indeed, such exposure provided sufficient drug killing effect to bring BCR-ABL down to <0.1% over time in a portion of the patient population, as shown in Figure 15, which displayed the predicted time-course of BCR-ABL1 levels, assuming an uninterrupted oral administration of either 40 mg BID, 80 mg QD, 120 mg BID, 160 mg BID or 200 mg BID over the course of 2 years.

Figure 15: Simulated time-course of log_{10}-transformed BCR-ABL1 in patients with T315I mutation who were administered 40 mg BID, 80 mg QD, 120 mg BID, 160 mg BID, and 200 mg BID asciminib



The black line represents the median over the 100 replicates of the 50th percentile of log_{10} (BCR-ABL1). The darker gray area represents the median of 25th and 75th percentiles of log_{10} (BCR-ABL1) and the lighter gray area is the median of 10th and 90th percentiles of log_{10} (BCR-ABL1)

Source: Novartis ABL001A Summary of clinical pharmacology-Figure 3-12.The exposure-safety analyses were conducted using a pooled data set of CML-CP/-AP subjects from single agent cohorts (Arm 1) in Study X2101 and subjects in the asciminib treatment arm from Study A2301. The exposure-safety analyses included 199 subjects from Study X2101 and 154 subjects from Study A2301 which were the patients from the Safety set providing at least one predicted daily AUC/Cmax/Cmin from the popPK model.

The exposure-safety analyses used repeated logistic regression model to assess the association between asciminib exposure and the probability of safety event based on laboratory parameters (amylase, lipase, platelets count, neutrophils, hemoglobin, AST, ALT, total bilirubin and triglycerides), vital signs (SBP and DBP) for hypertension, AEs for fatigue and asthenia, and Grade ≥ 3 TEAEs.

The analyses indicated a lack of association between exposure and chance of safety events.

In addition, the relationship between exposure and TEAE leading to dose adjustment (reduction only) and/or interruption was also explored based on the pooled data from the two studies X2101 and A2301 (N=353). Time to onset of TEAE leading to dose adjustment was analysed using an

extended Cox regression model. Although the results of the extended Cox model showed a small positive estimate across three PK metrics used (AUC, Cmin and Cmax), the effects were not statistically significant, suggesting that hazard for dose reduction or dose interruption due to TEAE is not associated with exposure.

The assessment of the potential effect of asciminib on renal transporters was also explored with a linear mixed effects model using change from baseline in serum creatinine as the dependent variable based on the pooled data. The changes in serum creatinine at the 40 mg BID geometric mean Cmin is 2.84 µmol/L in Study X2101 and 1.20 µmol/L in Study A2301 and were predicted to increase to 2.92 (95% CI 1.63-4.21) and 1.28 (95% CI -0.30-2.86) at 5-times this exposure, which is not considered clinically relevant. For AUC and Cmax, the predicted change in serum creatinine is in the same range as for Cmin. However, for these exposure metrics the increase in exposure is associated with a decrease in serum creatinine and the effect of exposure is therefore not considered clinically relevant.

Finally, concentrations-QT analyses demonstrated that at therapeutic doses, asciminib does not have a clinically relevant effect on cardiac repolarization. Based on data available from 239 patients in Study X2101, the concentration-QTcF analysis identified a slightly positive relationship with asciminib exposure. However, the estimated mean and upper bound of the 90% CI QTcF increase did not exceed 10 ms (the threshold that is considered clinically significant according to the regulatory guidance) at all the therapeutic doses as well as at the highest clinical relevant exposure (HCRE) (determined based on the geometric mean Cmax at 200 mg BID, dose, and accounting for a 1.59-fold increase in Cmax observed in a drug-drug interaction study).

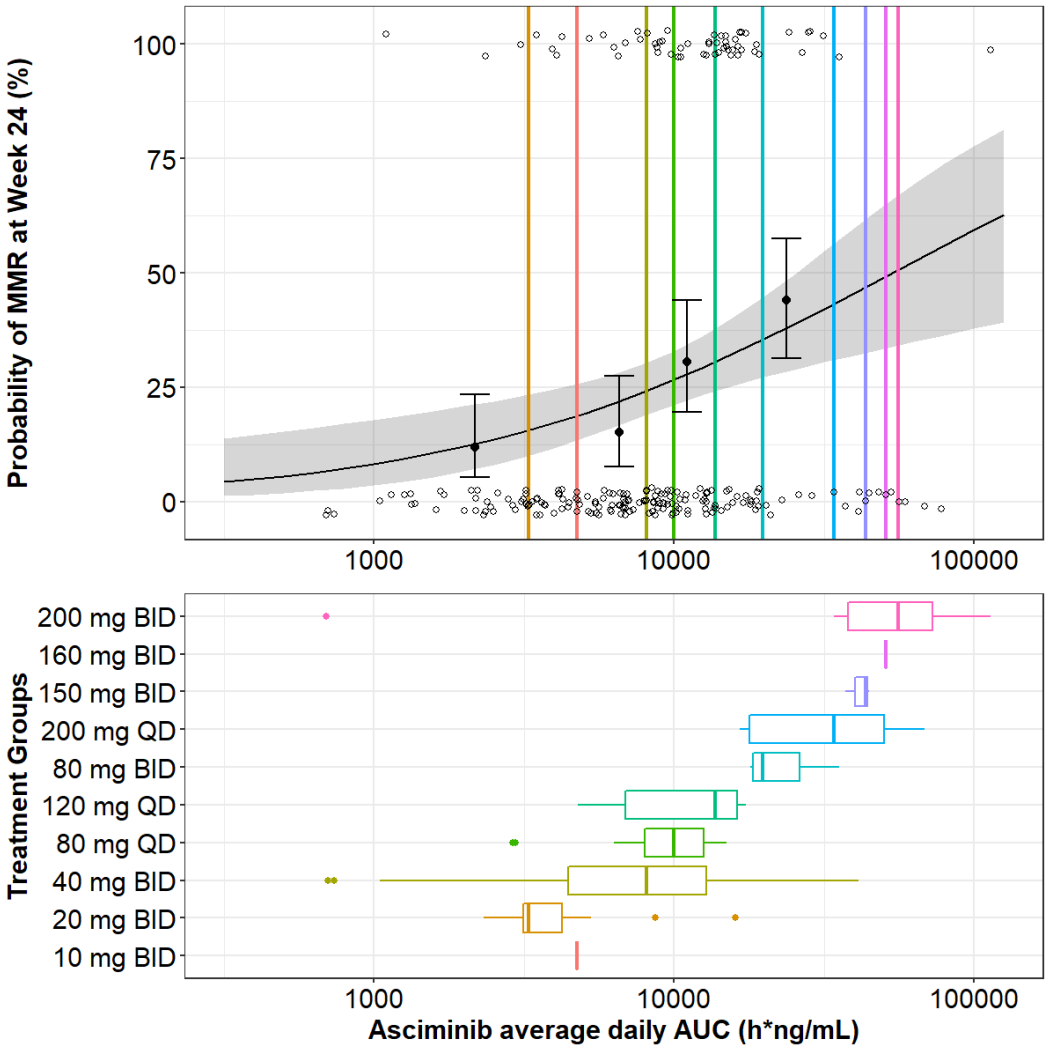
In summary, based on the available clinical data as well as the extensive exposure-efficacy and efficacy-safety analyses, the risk/benefit ratio of asciminib administered at 80 mg QD in patients with CML not harboring the T315I mutation is not different than that of asciminib 40 mg BID. Overall, the dose of asciminib 80 mg QD is considered favorable and can be used as an alternative, more convenient, patient-centric dose regimen for this patient population. In addition, the 200 mg BID regimen is considered favorable and the appropriate dose in patients with CML harboring the T315I mutation.

The FDA's Assessment:

Exposure-Response Analysis for Efficacy

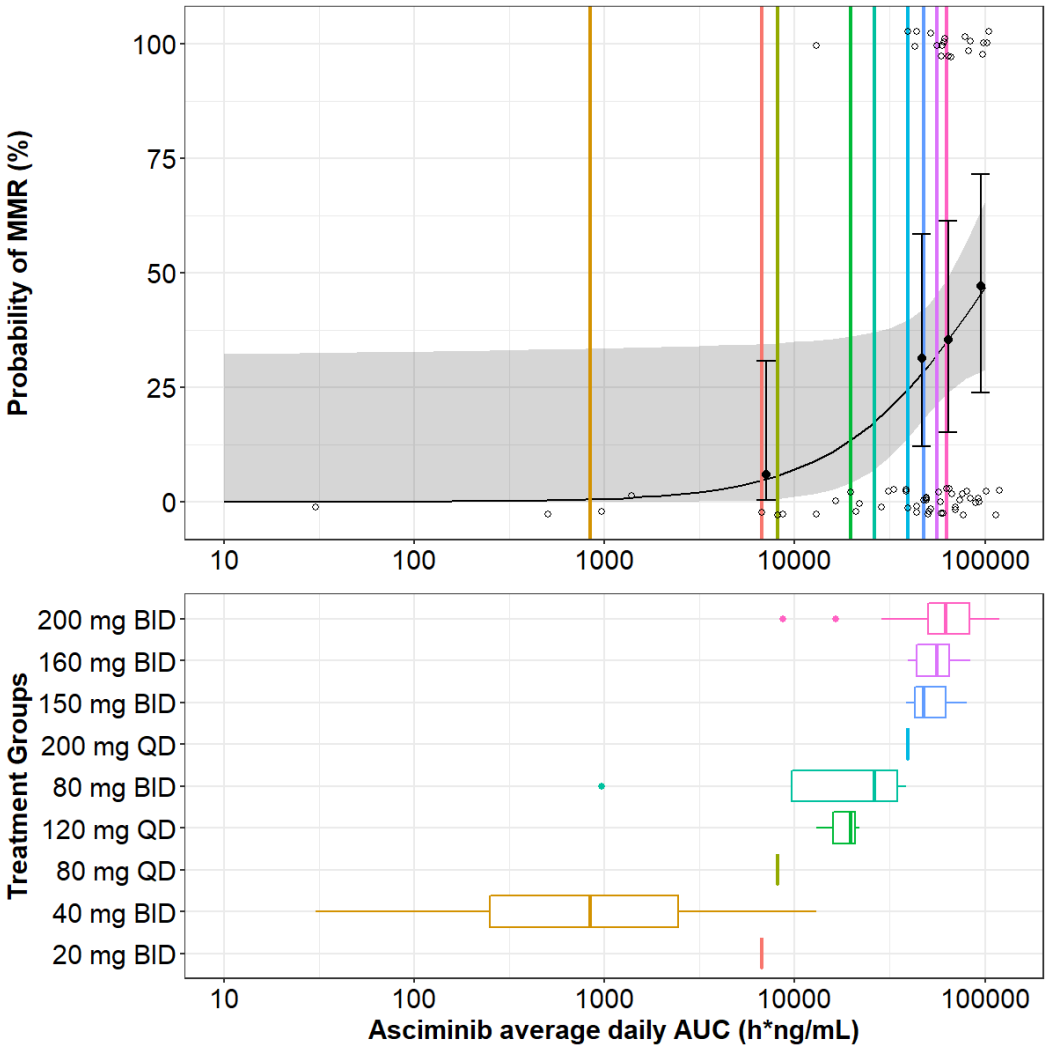
The Reviewer conducted independent E-R analyses for the primary efficacy endpoint, MMR at Week 24, using asciminib average daily AUC, Cmax and Cmin derived from the FDA's final PopPK model. The E-R analyses were conducted in 236 patients not harboring T315I mutation (85 from Study X2101 and 151 from Study A2301) and 67 patients harboring T315I mutation (64 from Study X2101 and 3 from Study A2301), respectively. Univariate logistic regression analyses showed that increase in MMR at Week 24 was most associated with increasing asciminib average daily AUC (vs. Cmax and Cmin) in patients without T315I mutation at a dose range of 10 mg BID to 200 mg BID (Figure 16), and in patients with T315I mutation at a dose range of 20 mg BID to 200 mg BID (Figure 17).

Figure 16: FDA's Univariate Exposure-Response Analysis for Probability of MMR at Week 24 Vs. Asciminib Average Daily AUC in Patients without T315I Mutation



Upper panel: open black dots represent observed MMR events; closed black dots and bars represent observed mean and 95%CI probability of MMR at week 24 for each quartile of asciminib average daily AUC; black line and gray area represent predicted mean and 95% CI probability of MMR at week 24; color lines represent the median asciminib average daily AUC at each dosage level.
Lower panel: boxes and lines represents distribution of asciminib average daily AUC at each dosage level.
Source: FDA's independent analysis.

Figure 17: FDA's Univariate Exposure-Response Analysis for Probability of MMR at Week 24 Vs. Asciminib Average Daily AUC in Patients with T315I Mutation



Upper panel: open black dots represent observed MMR events; closed black dots and bars represent observed mean and 95%CI probability of MMR at week 24 for each quartile of asciminib average daily AUC; black line and gray area represent predicted mean and 95% CI probability of MMR at week 24; color lines represent the median asciminib average daily AUC at each dosage level.
Lower panel: boxes and lines represents distribution of asciminib average daily AUC at each dosage level.
Source: FDA's independent analysis.

Multivariate logistic regression E-R analysis (Table 47) retained asciminib average daily AUC as a significant predictor of MMR at Week 24, which suggests that patients without T315I mutation may benefit from a higher dose than the Applicant's proposed 40 mg BID and 80 mg QD. In addition, multivariate analysis identified two statisitically significant covariates on MMR at Week 24 in patients without T315I mutation. Lower MMR at Week 24 was associated with higher baseline BCR-ABL and prior TKI treatment ≥3.

Table 47: FDA's Multivariate Exposure-Response Analysis for Probability of MMR at Week 24 Vs. Asciminib Average Daily AUC in Patients without T315I Mutation

Parameter	Estimate	Standard error	95% CI	P value
Intercept (β_0)	-4.78	1.87	-8.44, -1.12	1.06×10^{-2}
$\log_{10}$AUC	1.24	0.466	0.324, 2.15	7.92×10^{-3}
$\log_{10}$BCR-ABL	-0.942	0.206	-1.35, -0.539	4.70×10^{-6}
TKI3A	-0.859	0.338	-1.52, -0.196	1.11×10^{-2}
Logistic Regression $Ln(p/(1-p)) = \beta 0 + \beta_{AUC} \bullet \log_{10}AUC + \beta_{BCR-ABL} \bullet \log_{10}BCR\text{-}ABL + \beta_{TKI3A} \bullet TKI3A$				

$\log_{10}$AUC represents $\log_{10}$-transformed asciminib average daily AUC; $\log_{10}$BCR-ABL represents $\log_{10}$-transformed baseline BCR-ABL; TKI3A represents prior TKI treatment ≥3.
Source: FDA's independent analysis.

In patients with T315I mutation, multivariate logistic regression E-R analysis (Table 48) identified two statisitically significant covariates on MMR at Week 24. Lower MMR at Week 24 was associated with higher baseline BCR-ABL and longer time since first CML diagnosis. After including these two covariates, asciminib average daily AUC was not a statistically significant predictor of MMR at Week 24. However, this should be interpreted with caution because most (45/67) of patients with T315I mutation received 200 mg BID and so there is limited data to inform the E-R at other dose levels.

Table 48: FDA's Multivariate Exposure-Response Analysis for Probability of MMR at Week 24 Vs. Asciminib Average Daily AUC in Patients with T315I Mutation

Parameter	Estimate	Standard error	95% CI	P value
Intercept (β_0)	-7.99	6.66	-21.0, 5.06	0.230
$\log_{10}$AUC	2.10	1.41	-0.657, 4.86	0.135
$\log_{10}$BCR-ABL	-2.10	0.587	-3.25, -0.952	3.41×10^{-6}
FDIAG	-0.220	0.102	-0.420, -0.0196	3.15×10^{-2}
Logistic Regression $Ln(p/(1-p)) = \beta 0 + \beta_{AUC} \bullet \log_{10}AUC + \beta_{BCR-ABL} \bullet \log_{10}BCR\text{-}ABL + \beta_{FDIAG} \bullet FDIAG$				

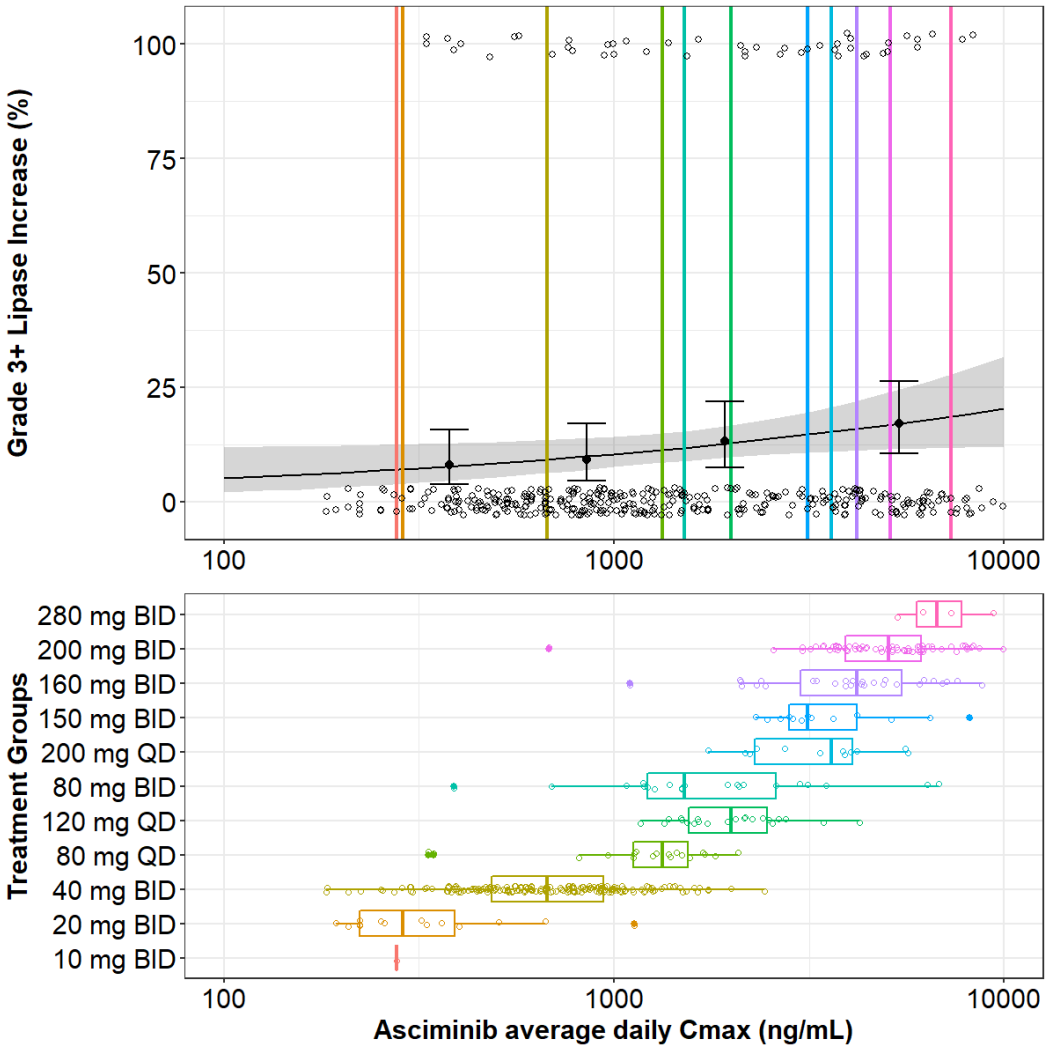
$\log_{10}$AUC represents $\log_{10}$-transformed asciminib average daily AUC; $\log_{10}$BCR-ABL represents $\log_{10}$-transformed baseline BCR-ABL; FDIAG represents time since first CML diagnosis.
Source: FDA's independent analysis.

Exposure-Response Analysis for Safety

The Reviewer also conducted independent E-R logistic regression analyses for the following safety measures: overall TEAE, platelets decrease, neutrophils decrease, hemoglobin decrease, amylase increase lipase increase and hemoglobin decrease at grade ≥3, ALT increase, AST increase and bilirubin increase at grade ≥2, and lipase increase, amylase increase, triglycerides , hypertension, fatigue and asthenia, TEAE leading to dose modification at any grade. The PK metrics for the E-R analyses included asciminib average daily AUC, Cmax and Cmin up to the occurrence of the first adverse event derived from the FDA's final PopPK model. The E-R safety

analyses were conducted in 394 patients with CML-BP, CML-CP and Ph+ ALL on asciminib monotherapy ranging 10 mg BID to 280 mg BID in Studies X2101 and A2301. Univariate logistic regression analyses showed that increasing asciminib Cmax was associated with slightly higher incidence of grade 3+ lipase increase (Figure 18), grade 3+ hemoglobin decrease (Figure 19), grade 2+ ALT increase (Figure 20), grade 2+ AST increase (Figure 21), grade 2+ bilirubin increase (Figure 22), and any grade lipase increase (Figure 23). Mutivariate analyses showed the baseline levels of these laboratory measures were significant predictors of the TEAEs.

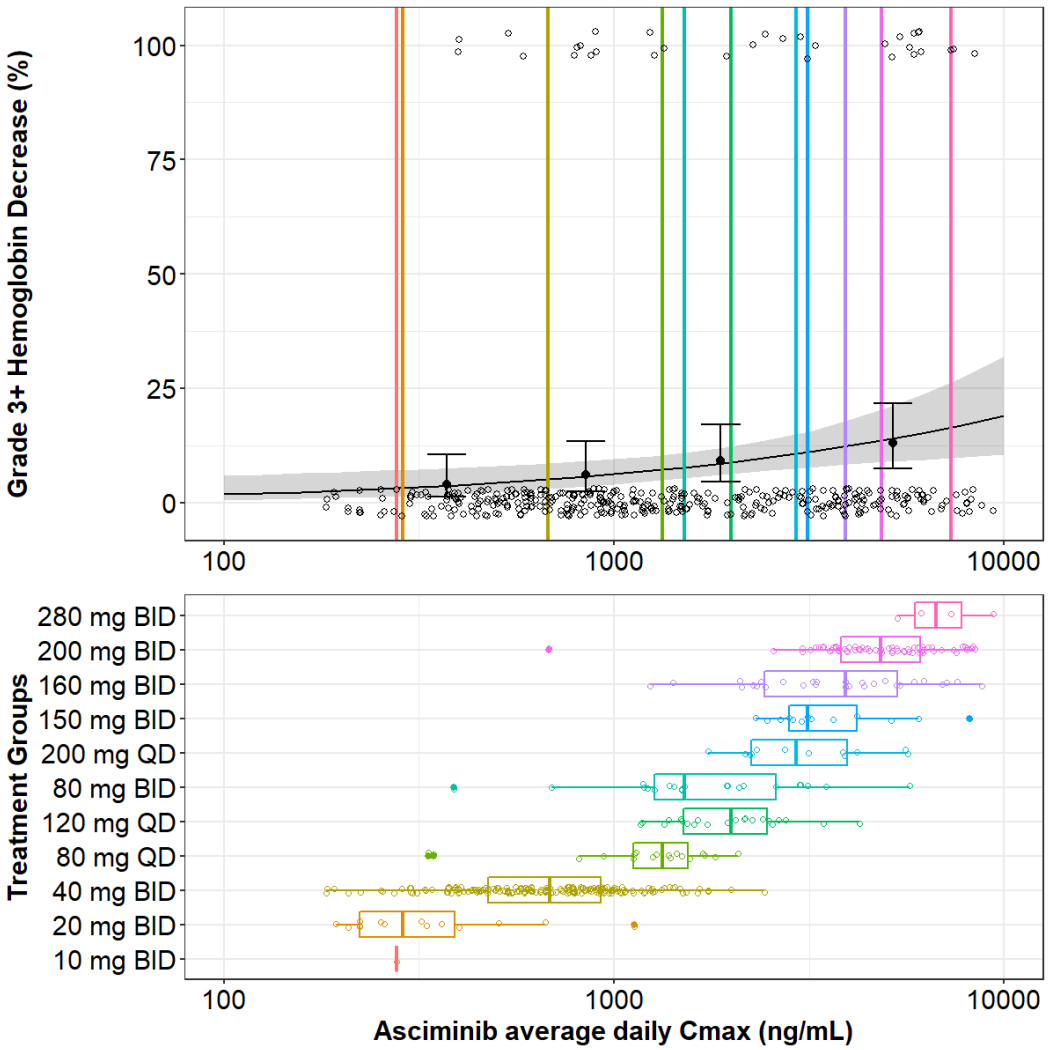
Figure 18: FDA's Univariate Exposure-Response Analysis for Probability of Grade 3+ Lipase Increase Vs. Asciminib Daily Cmax



Upper panel: open black dots represent observed grade 3+ lipase increase events; closed black dots and bars represent observed mean and 95%CI probability of grade 3+ lipase increase for each quartile of asciminib average daily Cmax; black line and gray area represent predicted mean and 95% CI probability of grade 3+ lipase increase; color lines represent the median asciminib average daily Cmax at each dosage level.

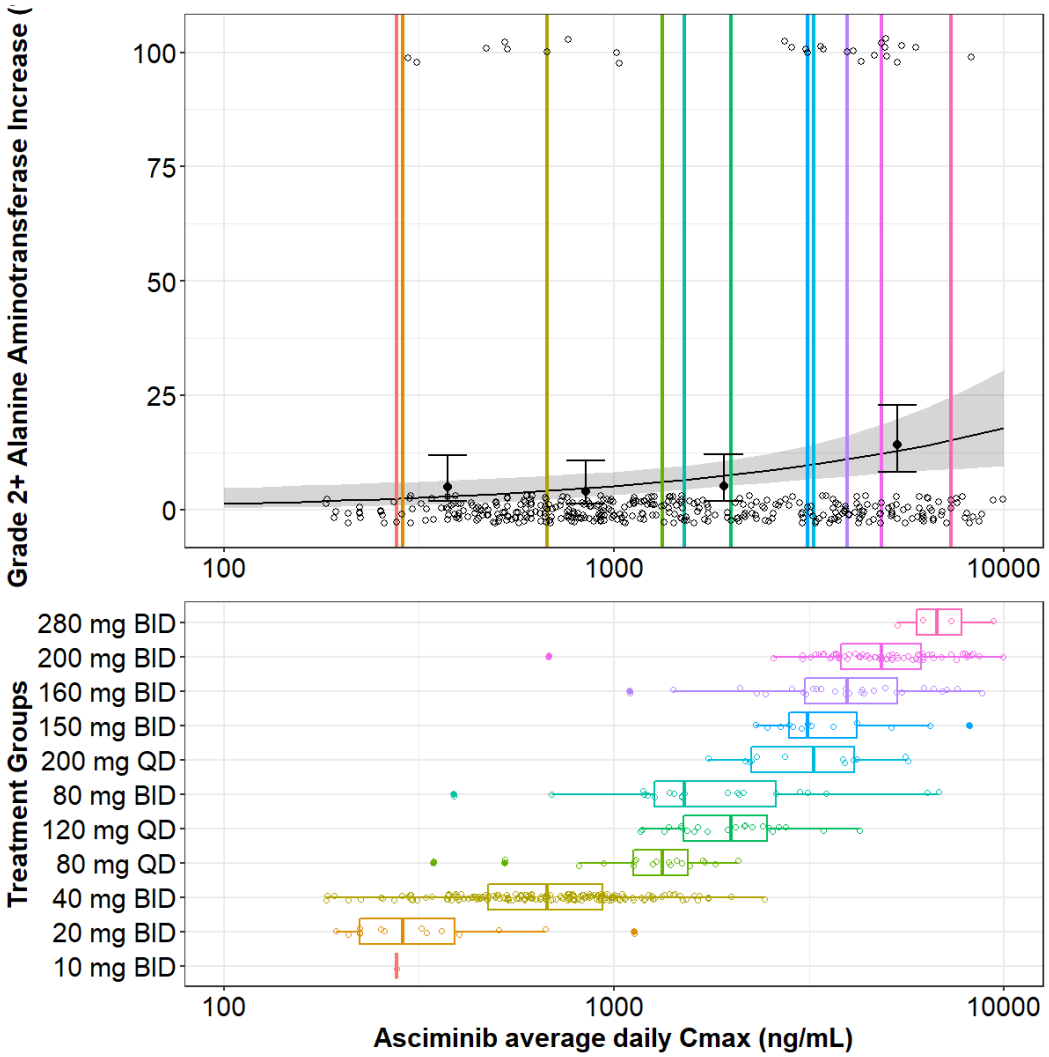
Lower panel: color dots, boxes and lines represents distribution of asciminib average daily Cmax at each dosage level.
Source: FDA's independent analysis.

Figure 19: FDA's Univariate Exposure-Response Analysis for Probability of Grade 3+ Hemoglobin Decrease Vs. Asciminib Daily Cmax



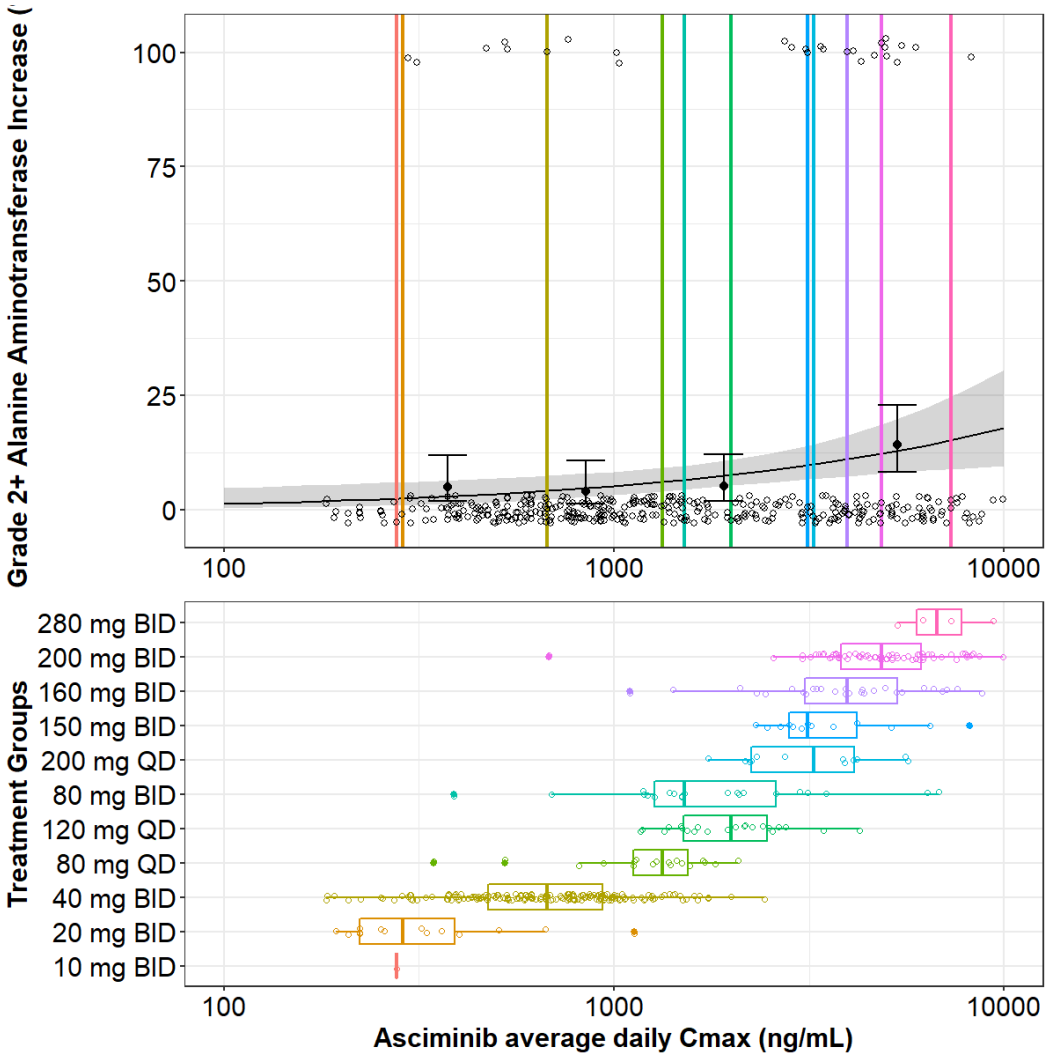
Upper panel: open black dots represent observed grade 3+ hemoglobin decrease events; closed black dots and bars represent observed mean and 95%CI probability of grade 3+ hemoglobin decrease for each quartile of asciminib average daily Cmax; black line and gray area represent predicted mean and 95% CI probability of grade 3+ hemoglobin decrease; color lines represent the median asciminib average daily Cmax at each dosage level.
Lower panel: color dots, boxes and lines represents distribution of asciminib average daily Cmax at each dosage level.
Source: FDA's independent analysis.

Figure 20: FDA's Univariate Exposure-Response Analysis for Probability of Grade 2+ ALT Increase Vs. Asciminib Daily Cmax



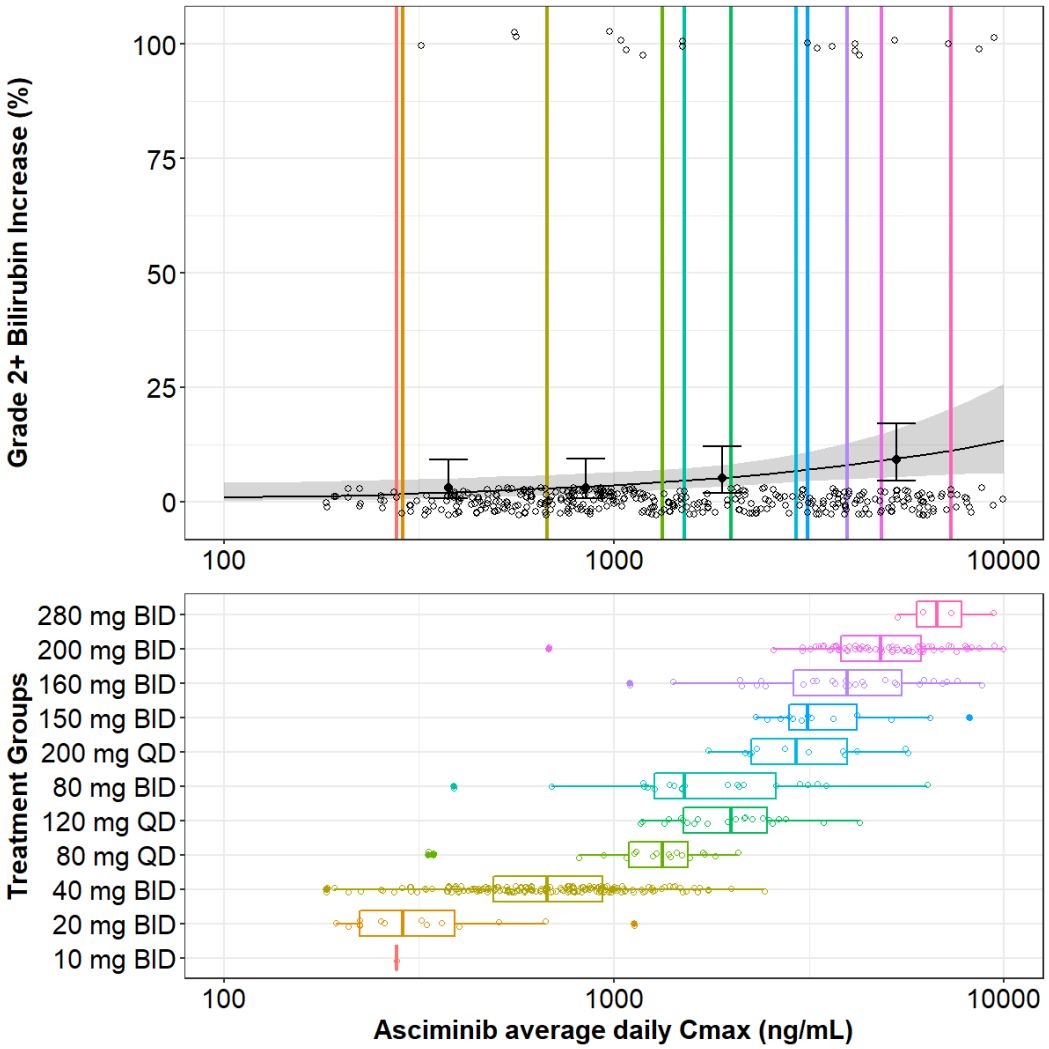
Upper panel: open black dots represent observed grade 2+ ALT increase events; closed black dots and bars represent observed mean and 95%CI probability of grade 2+ ALT increase for each quartile of asciminib average daily Cmax; black line and gray area represent predicted mean and 95% CI probability of grade 2+ ALT increase; color lines represent the median asciminib average daily Cmax at each dosage level.
Lower panel: color dots, boxes and lines represents distribution of asciminib average daily Cmax at each dosage level.
Source: FDA's independent analysis.

Figure 21: FDA's Univariate Exposure-Response Analysis for Probability of Grade 2+ AST Increase Vs. Asciminib Daily Cmax



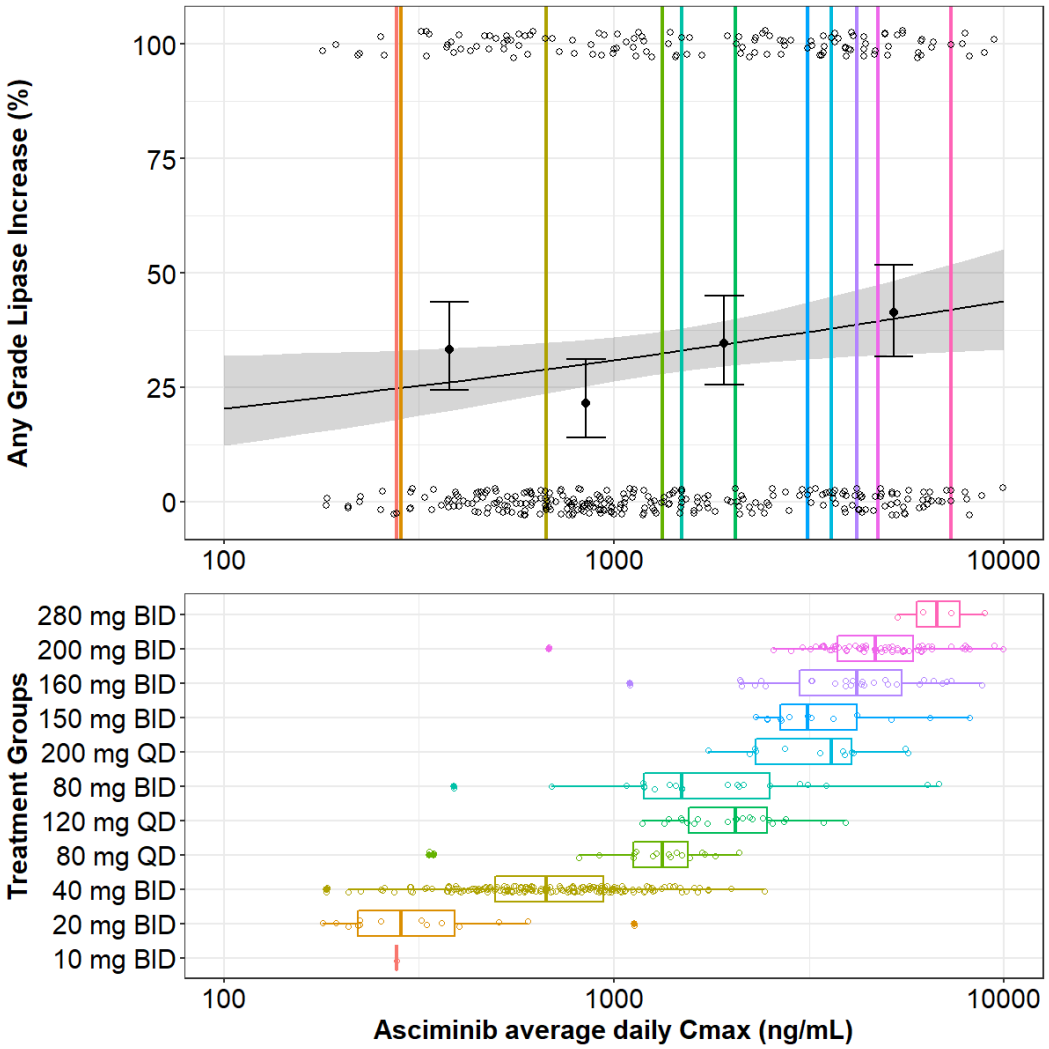
Upper panel: open black dots represent observed grade 2+ AST increase events; closed black dots and bars represent observed mean and 95%CI probability of grade 2+ AST increase for each quartile of asciminib average daily Cmax; black line and gray area represent predicted mean and 95% CI probability of grade 2+ AST increase; color lines represent the median asciminib average daily Cmax at each dosage level.
Lower panel: color dots, boxes and lines represents distribution of asciminib average daily Cmax at each dosage level.
Source: FDA's independent analysis.

Figure 22: FDA's Univariate Exposure-Response Analysis for Probability of Grade 2+ Bilirubin Increase Vs. Asciminib Daily Cmax



Upper panel: open black dots represent observed grade 2+ bilirubin increase events; closed black dots and bars represent observed mean and 95%CI probability of grade 2+ bilirubin increase for each quartile of asciminib average daily Cmax; black line and gray area represent predicted mean and 95% CI probability of grade 2+ bilirubin increase; color lines represent the median asciminib average daily Cmax at each dosage level.
Lower panel: color dots, boxes and lines represents distribution of asciminib average daily Cmax at each dosage level.
Source: FDA's independent analysis.

Figure 23: FDA's Univariate Exposure-Response Analysis for Probability of Any Grade Lipase Increase Vs. Asciminib Daily Cmax



Upper panel: open black dots represent observed any grade lipase increase events; closed black dots and bars represent observed mean and 95%CI probability of any grade lipase increase for each quartile of asciminib average daily Cmax; black line and gray area represent predicted mean and 95% CI probability of any grade lipase increase; color lines represent the median asciminib average daily Cmax at each dosage level.
Lower panel: color dots, boxes and lines represents distribution of asciminib average daily Cmax at each dosage level.
Source: FDA's independent analysis.

19.4.4. Physiologically based Pharmacokinetic Modeling Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to predict the following:

- DDI effect of strong CYP3A inhibitor or inducer on the exposure of asciminib at 40 mg BID, 80 mg QD and 200 mg BID
- Effect of food (low-fat and high-fat meal) on the exposure of asciminib at 40 mg BID, 80 mg QD and 200 mg BID
- Effect of hepatic or renal impairment on the exposure of asciminib at 40 mg BID, 80 mg QD and 200 mg BID
- DDI potential of asciminib on the exposure of substrates of CYP2C8 (repaglinide), CYP2C9 (warfarin), and CYP2C19 (omeprazole)
- DDI potential of asciminib on the exposure of a CYP3A substrate (midazolam)
- DDI potential of asciminib on the exposure of a CYP1A2 substrate (caffeine)
- DDI potential of asciminib on the exposure of a UGT1A1 substrate (raltegravir)
- DDI potential of asciminib on the exposure of substrates of the transporters P-gp and BCRP/ OATP1B
- DDI potential of elevated gastric pH caused by an acid reducing agent (ARA) on the exposure of asciminib following 200 mg dose

The Division of Pharmacometrics has reviewed the PBPK submission (reports DMPK R2000208 and R2001088, modeling files) and responses to FDA's request for information to conclude the following:

- The PBPK analysis was inadequate to predict the effect of strong CYP3A modulators on the exposure of asciminib
- The PBPK analysis was inadequate to predict the changes in exposure of asciminib, at higher dose levels, in the presence of food
- The PBPK analysis was inadequate to predict the changes in exposure of asciminib due to hepatic impairment or renal impairment
- The PBPK analysis was inadequate to confirm a negative DDI potential of asciminib with a BCRP/OATP1B substrate
- The PBPK analysis indicated a DDI potential of asciminib with a P-gp substrate cannot be excluded
- The PBPK analysis indicated a DDI potential of asciminib with a CYP1A2 substrate (via induction) cannot be excluded
- The PBPK analysis indicated a DDI potential of asciminib with a UGT1A1 substrate cannot be excluded
- For asciminib 80 mg total daily dose, a weak interaction effect (1.25≥AUC ratio <2) was predicted with CYP2C9 substrates, whereas no or marginal interaction effect was predicted with CYP3A, CYP2C8, and CYP2C19 substrates. For asciminib 200 mg BID, a moderate

interaction with CYP2C9 (2≥AUC ratio <5) and weak interaction (1.25≥AUC ratio <2) with CYP3A, CYP2C8, and CYP2C19 substrates were predicted.

- The ADAM (Advance Dissolution, Absorption and Metabolism) PBPK model of asciminib, along with the in vitro dissolution data and clinical DDI data with an ARA, was adequate to evaluate the effect of elevated gastric pH on the exposure of asciminib following 200 mg dose. The predicted effect of elevated gastric pH due to co-administration of an ARA on asciminib exposure is unlikely to be clinically meaningful.

Background

The proposed asciminib dosing regimen is a total daily dose of 80 mg taken either as 40 mg BID (twice daily) or 80 mg QD (once daily) on fasted state (no food to be consumed for at least 2 hours before and 1 hour after the dosing). For patients with CML harboring the T315I mutation, asciminib dosing regimen of 200 mg BID is proposed.

Asciminib exhibited a slight dose over-proportional increase in systemic exposure (AUC and Cmax) for the BID dosing regimens [Analysis of Study X2101]. The average accumulation ratio is approximately 2-fold for the BID dosing regimen (1.65 at 40 mg BID and 1.92 at 200 mg BID) and 1.30 for the QD dosing regimen (at 80 mg QD). Steady-state levels were reached within 3 days at 40 mg BID. The median Tmax was around 2 to 3 hours, independent of dose. The absorption of asciminib was affected by food. Following a low-fat or high-fat meal, the AUCinf of asciminib 40 mg single dose was decreased by 30% or 62%, respectively [Study E2101]. The apparent terminal elimination half-life (t1/2) of asciminib was between 7 and 15 hours, and the apparent clearance (CL/F) was 4.34 L/h in healthy subjects (80 mg single dose, ADME study A2102]. The population PK estimate of the apparent clearance for a typical individual (i.e., 70 kg male, with normal renal function) was 6.31 L/h for a total daily dose of 80 mg. No time-dependent PK was observed. There was no apparent difference in the PK of asciminib in patients compared to healthy subjects. Age and gender were not significant covariates based on population PK analysis. No major plasma metabolite of asciminib was observed (<10% of total drug related AUC).

Asciminib was metabolized by CYP3A4 and the UGT isoforms 2B7, 2B17 and 1A3/4 in vitro. A clinical DDI study evaluated the effect of co-administration of the strong CYP3A inhibitors clarithromycin and itraconazole, and the strong CYP3A inducer rifampicin on the PK of asciminib 40 mg single dose in healthy volunteers [Study A2107].

In vitro, asciminib was determined to be a reversible inhibitor of the CYP isoforms 1A2, 2B6, 2C8, 2C9, 2C19 and 3A, without apparent time-dependent inhibition towards these enzymes [DMPK R1300242]. Asciminib was determined to be an inducer of CYP3A and CYP1A2 mRNA in vitro with potential for in vivo induction based on basic models (R3<0.8), while no in vitro potential for induction of CYP2C9, CYP2C19, and CYP2B6 [DMPK R1809192, DMPK R1701235]. A clinical DDI study in healthy volunteers evaluated the effect of asciminib 40 mg BID on the PK of the index CYP substrates midazolam (CYP3A), warfarin (CYP2C9) and repaglinide (CYP2C8)

[Study A2106]. Asciminib was also determined to be an in vitro inhibitor of the UGT isoforms 1A1 and 2B7 [DMPK R1600146].

Asciminib showed pH-dependent solubility in vitro with a pKa of around 4. A clinical DDI study evaluated the effect of the ARA rabeprazole on the PK of asciminib 40 mg single dose in Japanese healthy volunteers [Study A1101]. The result indicated that elevated gastric pH due to co-administration of rabeprazole did not affect the bioavailability of asciminib following 40 mg oral administration.

Methods

Model Development

The PBPK analyses were performed using the PBPK software Simcyp® (V19r1 for enzyme- and transporter-mediated DDI assessment, and V20r1 for gastric pH-mediated DDI assessment, Simcyp Ltd., Sheffield, UK).

The PBPK model of asciminib was developed based on physicochemical properties, preclinical, and clinical PK data. The absorption of asciminib, for the final market image (FMI) tablet formulation (asciminib-HCl salt form film-coated tablet) under fasted condition, was described using a first-order absorption model. The model used the in vitro permeability data of asciminib in MDCK-KO cells (Papp=22.1 $x10^{-6}$ cm/s) calibrated against the permeability of the control propranolol [RD-2020-00101]. The fraction absorbed (fa) was assumed to be 1 (see additional comments below). The first order absorption rate constant (Ka=1.3 1/h) with lag time (0.374 h) was optimized to recover the observed PK data and population PK estimates. The values of Qgut (nominal flow through gut model) and unbound fraction in enterocytes (fugut) were optimized based on parameter sensitivity analysis (PSA) using the clinical DDI data with the CYP3A4 substrate midazolam.

Additional comments: In vitro, asciminib is a substrate of BCRP and P-gp [DMPK R1300249]; however, these transporters were not accounted for in the absorption model of asciminib. The Applicant claimed that transporter-mediated intestinal efflux by either P-gp or BCRP would unlikely limit the absorption of asciminib at the clinically relevant doses. This assumption was due to (1) the lack of effect of the P-gp inhibitor quinidine on both the rate (GMR Cmax = 0.887) and extent (GMR AUCinf = 0.871) of absorption of asciminib (40 mg single dose, Study A2107] and (2) BCRP mediated efflux in the intestine is expected to be saturated even at lowest therapeutic dose of 40 mg: asciminib's expected GI luminal concentration (356 µM) is about 200-fold higher than the apparent Km of BCRP (= 1.83 µM, DMPK R1300249).

In vitro, the unbound fraction of asciminib in plasma (fup) was 0.027 and the blood-plasma partitioning ratio was 0.8, independent of the dose [DMPK R1300135]. The volume of distribution at steady state (Vss= 0.43 L/kg) was predicted using the Rodgers-Rowland method, and the Kp scalar was user defined by optimization to recover the clinical PK of a single 40 mg dose (Study A2107, cohort 5, control arm). The apparent volume of distribution (Vz/F) was 89.0

L based on the ADME study [A2102] and the population PK estimate for the combined volumes of central and peripheral compartments were approximately 111 L, for a typical individual.

In vitro studies suggested no evidence for a major active uptake mechanism (by OCT1, OCT2, or OATP) for asciminib into human hepatocytes [DMPK R1300252, DMPK R1300355]. The permeability limited model for liver was used to account for the inclusion of biliary clearance mediated by BCRP to the overall elimination of asciminib. The kinetic parameters of BCRP-mediated hepatic efflux, Jmax (maximum rate of transporter mediated efflux) and Km (intracellular=0.14 µM) were initially calculated from Caco-2 cells data [DMPK R1300249] and the equations according to Kalvass and Pollack (2007). The Jmax and Km values, together with the passive diffusion clearance value (CL_{PD}), were then optimized to recover the training PK datasets (asciminib 20, 40 and 160 mg BID from Trial X2101). The Applicant assumed that the biliary clearance contributed 31% to the total clearance of asciminib. This value was indirectly calculated by comparing the predicted clearances at 20 mg BID (lowest tested dose) with (CL/F= 7.19 L/h) and without (CL/F=4.96 L/h) the inclusion of BCRP, assuming no degree of saturation of BCRP at this dose level.

In vitro studies suggested that the major metabolic route of asciminib was direct glucuronidation (~65%) followed by oxidative metabolism (~35%) [DMPK R1200921, DMPK R1300172-01]. The in vitro phenotyping study [DMPK R1400553] indicated the relative contribution of CYP isoforms 3A4, 2J2, 2C8 and 2D6 to the oxidative metabolism was 96.0%, 2.08%, 1.36% and 0.574%, respectively. The relative contribution of UGT isoforms 1A3/4, 2B7 and 2B17 to the total UGT contribution was 24.2%, 47.9% and 27.9%, respectively [DMPK R1709012]. The Applicant assumed the relative contributions of CYPs and UGTs to the total clearance to be around 36% and 58%, respectively, in the model, based on analysis of human ADME data, in vitro metabolic studies and enzyme reaction phenotyping [DMPK R1709012]. The contributions of each CYP isoform (fmCYP) to total clearance of asciminib were then calculated to be about 35%, 0.5%, 0.2% and 0.76% for CYP3A4, 2C8, 2D6 and 2J2, respectively. The contribution of biliary clearance, mediated by BCRP efflux (fCL,bile), was deducted from the total contribution of UGTs, which gave a final total contribution of UGTs to total clearance of about 27% (≃58% - 31%)). Based on in vitro estimates of fm values for each UGT isoform, the final contribution for UGT1A3/4, 2B7 and 2B17 were calculated to be about 6.8%, 13.3% and 7.8%, respectively, to the total clearance of asciminib.

Additional comments: The estimation of the relative contributions of the various clearance pathways of asciminib depended on interpretation and assumptions of the human ADME data. In the absence of intravenous administration of asciminib, there is uncertainty on its absorbed fraction. In the ADME study [A2102], the minimum extent of oral absorption of asciminib 80 mg (oral suspension) was 33% of the dose based on total recovery of metabolites in feces (22%), and parent and metabolites in urine (11%). Unchanged asciminib in feces accounted for 56.7% of the dose, while the major metabolite (M30.5), product of direct O-glucuronidation of asciminib, was not detected in feces. A maximum extent of absorption of asciminib was estimated to be 57% (22% as metabolites in feces + 24% of parent in feces as result of

glucuronide metabolite back-conversion to parent +11% as parent and metabolites in urine). Based on the assumptions of either 33% or 57% absorption of asciminib, different relative contributions of clearance pathways could be estimated from the human ADME data [DMPK-R1709012]. Considering the scenario of 33% absorption (assumed unchanged drug in feces was unabsorbed), the relative contributions of CYPs and UGTs to total clearance were estimated to be around 64% and 28%, respectively. While for the scenario of 57% absorption, the relative contributions of CYPs and UGTs to total clearance were around 37% and 58%, respectively. The Applicant implemented in the model complete absorption of asciminib (fa=1, as model input), assuming all parent drug in feces represented direct biliary excretion of asciminib and/or glucuronide metabolite conversion back to parent and no enterohepatic recycling. However, the relative contributions of CYPs and UGTs to total clearance were not recalculated for fa=1 from the scenario of fa=0.57, including estimate of the relative contribution of biliary excretion. The assignment of biliary secretion (or the fraction transported by BCRP) in the model was arbitrary (not derived from mass balance calculations, transporter-mediated parameters [CL_{PD}, Jmax, Km] were optimized for "visual PK fit") with assumption of lower contributions of UGT pathways, but not CYP pathways.

The retrograde method was used to calculate the unbound intrinsic clearance values (CLint,u CYP/UGT). The respective CYP/UGT isoforms kinetic parameters, Km and Vmax values, were used in the model. The Km values were determined in vitro [DMPK R1400553], and Vmax were derived from the apparent clearance optimized for the established fm values for each CYP and UGT isoform. Additional intrinsic clearance in liver microsomes (HLM CLint,u) was attributed to hydrolysis (contribution of 0.71% to the overall metabolic clearance). Renal clearance of asciminib was minimal (CLr=0.18 L/h), based on urinary recovery of unchanged asciminib (average of 2.5%) in the ADME study [A2102].

The values of the unbound reversible inhibition constant (Ki,u=in vitro IC50/2, corrected for the unbound fraction) for the CYP isoforms 2C8, 2C19 and 3A4/5 were 0.466, 1.5 and 0.348 µM, respectively [DMPK R1300242]. The fumic values for asciminib were determined in vitro [DMPK R1300242]. The in vitro determined CYP2C9 Ki of 0.407 µM was optimized to 0.03 µM based on the clinical DDI data with warfarin. The in vitro determined Ki values (corrected for the unbound fraction) for the UGT isoforms 1A1 (Ki,u= 0.35 µM) and 2B7 (Ki,u=7.28 µM) were used as input [DMPK R1600146].

The CYP3A4 induction parameters IndC50 and Indmax, used in the model, were 2.057 µM and 1.53-fold, respectively [DMPK R1809192]. These in vitro values were calibrated against rifampin data as positive control. The in vitro CYP1A2 induction parameters IndC50 and Indmax (=Emax +1) were 0.59 µM and 4.5-fold, respectively [DMPK R1809192]. Calibration of CYP1A2 induction parameters were not performed due to lack of reference data. The Ki values for the transporters OATP1B1, OATP1B3, P-gp, and BCRP were 2.46, 1.92, 21.7 and 24.3 µM, respectively, with unbound fraction (fu,inc) arbitrarily assigned as 1 [DMPK R1300051, R1300052, R2000050].

The virtual population models North European Caucasian (NEC) and Cancer (Sim-Cancer) were used to represent healthy and oncology populations, respectively. Briefly, the Sim-Cancer model has different levels of hematocrit, albumin, alpha acid glycoprotein, and OATP1B1/3 abundance, compared to the NEC model. The default compound models (software's library, V19) for dabigatran etexilate, clarithromycin, midazolam, omeprazole, repaglinide, raltegravir, rifampin, rosiglitazone and S-warfarin were used in the simulations for the respective DDIs. A literature model [Chen et al 2019] for itraconazole and its hydroxyl metabolite, capsule formulation, was used for DDI simulations.

In response to the FDA's information request to address the effect of elevated gastric pH on the PK of asciminib following administration of 200 mg dose, the Applicant developed a mechanistic absorption model (ADAM, Advance Dissolution, Absorption and Metabolism) coupled with a full PBPK model to describe the absorption and PK of asciminib.

The Applicant analyzed the in vitro dissolution and solubility data using the Simcyp In Vitro Data Analysis Toolkit (SIVA, v3.0) to obtain the key input parameters for the ADAM model, including pKa, and micelle-water partition coefficients (logKm:w) for the natural and ionized forms of asciminib. The input parameters for the asciminib ADAM-PBPK model are summarized in Table 49. Briefly, the pKa value was calibrated based on the measured solubility for asciminib HCL salt in aqueous buffer with various pH conditions. Of note, the calibrated pKa of 4.45 was comparable to the measured pKa of 3.93 ± 0.02 [Summary of Biopharmaceutic Studies]. The partition coefficients between water and bile salt micelles for the neutral species (Km:w,neutral) and ionised species (Km:w, ion) of asciminib were estimated from its solubility in biorelevant media (i.e., FaSSIF). The micelle: water partition coefficient (Km:w) is a key parameter determining asciminib solubility in bile salts. Of note, the surfactant concentrations in the FaSSIF V1 Level II and FaSSIF V2 Level II (3.75 and 3.2 mM, respectively) in the in vitro test were comparable to the bile salt concentration in the duodenum compartment (3.31 mM) in the model.

The in vitro dissolution test suggested that asciminib HCL salt can form supersaturation solution in both aqueous buffer and biorelevant medium, i.e., the maximum amounts of asciminib HCL salt dissolved are higher than the equilibrium solubility measured in the corresponding media. The Applicant incorporated supersaturation and precipitation in the ADAM model. (b) (4)

Table 49. Input parameters for the asciminib ADAM-PBPK model

Parameter	Value		Reference/Comments
Absorption model	ADAM		
fu,gut	0.25		DMPK R2000208
pKa	4.45		pKa and logKm:w (neutral and ion) values were estimated by simultaneous fitting to the in vitro aqueous and biorelevant solubility values, respectively, using SIVA
$LogK_{m:w,\ neutral}$	5.46		
$LogK_{m:w\ ion}$	1.10		
Human effective permeability Peff ($x10^{-4}$ cm/s)	3.729		Converted from $P_{app,MDCK\ LE\ V2}$=22.1 x 10^{-6} cm/s [RD-2020-00101]
Formulation	Immediate release (IR)		
Segregated transit times model	Activated ("Use only ascending colon transit time" Activated)		Gastric MRT for fine particles and fluid/dissolved drug was set to 0.4 h in all population models
Particle dissolution model	Diffusion Layer Model		
Particle handling model	Particle population balance		
Particle heff model	Hintz-Johnson		
Fluid volumes model	Advanced fluid dynamics(aFVD)		
Particle size distribution	(b) (4)		
Particle radius (um)			
Model two solid states (SS)	Activated		
	SS1	**SS2**	
Form	Salt	(b) (4)	
Fraction in Dose (%)	100		Refers to the % of SS1 in the dosage form prior to dosing
Solubility at pHmax (mg/mL)	1.91		Aqueous solubility for asciminib HCL salt at pH 1.1
Ksp (mM2)	14.9		Back calculated from solubility at pH_{max}
Intrinsic solubility (mg/mL)	0.032		SS1: Calculated based on the maximum percent dissolved of asciminib 40 mg tablets (at 120 min) in 900 mL of USP phosphate buffer (b) (4)
Precipitation to SS	Deselected		
Precipitation model			
Critical supersaturation ratio Fasted / Hypochlorhydric state			
Precipitation rate constant (h^{-1}) Fasted / Hypochlorhydric state			
Elimination			
Percentage available for re-absorption (%)	0		Use of ADAM activates EHC (not available in first order absorption) – Asciminib is excreted as glucuronide which back-converts to the parent drug in colon. Negligible re-absorption is assumed

(Source: Applicant's Response to Clinical Pharmacology IR submitted on September 16, 2021).

Model Verification

PK performance

- single dose of asciminib 40 mg in healthy subjects, fasted state [Study A2107, cohorts 3 and 6, control groups, and Studies A2103 and A2105, healthy subject groups]
- multiple doses of asciminib 20, 40, 80, 160, 200 mg BID and 40, 80, 200 mg QD in patients [Studies X2101 and A2301]

Victim DDI potential of asciminib as a CYP3A substrate

- asciminib 40 mg single dose (on day 5), administered with clarithromycin (500 mg BID for 8 days) in healthy volunteers, fasted state [Study A2107, cohort 5]
- asciminib 40 mg single dose (on day 5), administered with itraconazole (200 mg QD, capsule, for 8 days) in healthy volunteers, fasted state [Study A2107, cohort 6]
- asciminib 40 mg single dose (on day 5), administered with rifampin (600 mg QD for 6 days) in healthy volunteers, fasted state [Study A2107, cohort 3]

Perpetrator DDI potential of asciminib as a CYP inhibitor

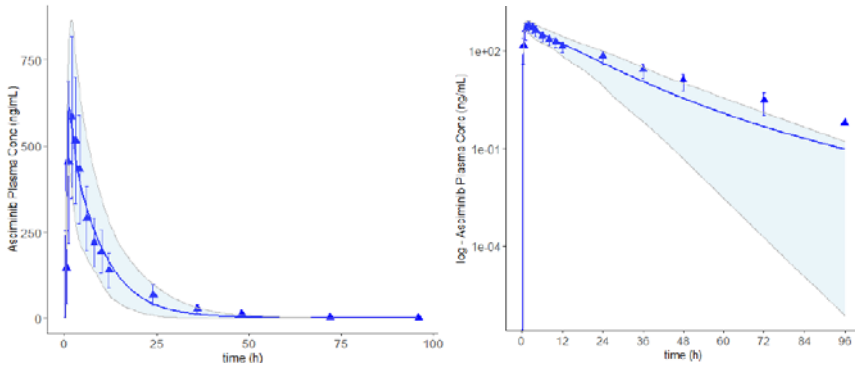
- midazolam 4 mg single oral dose (on day 3), administered with asciminib 40 mg BID (for 5 days) in healthy volunteers [Study A2106]
- S-warfarin 2.5 mg single oral dose (on day 3), administered with asciminib 40 mg BID (for 8 days) in healthy volunteers [Study A2106]
- repaglinide 0.5 mg single oral dose (on day 3), administered with asciminib 40 mg BID (for 3 days) in healthy volunteers [Study A2106]

Results

Q1. Can the PBPK model adequately describe the PK profiles of asciminib?

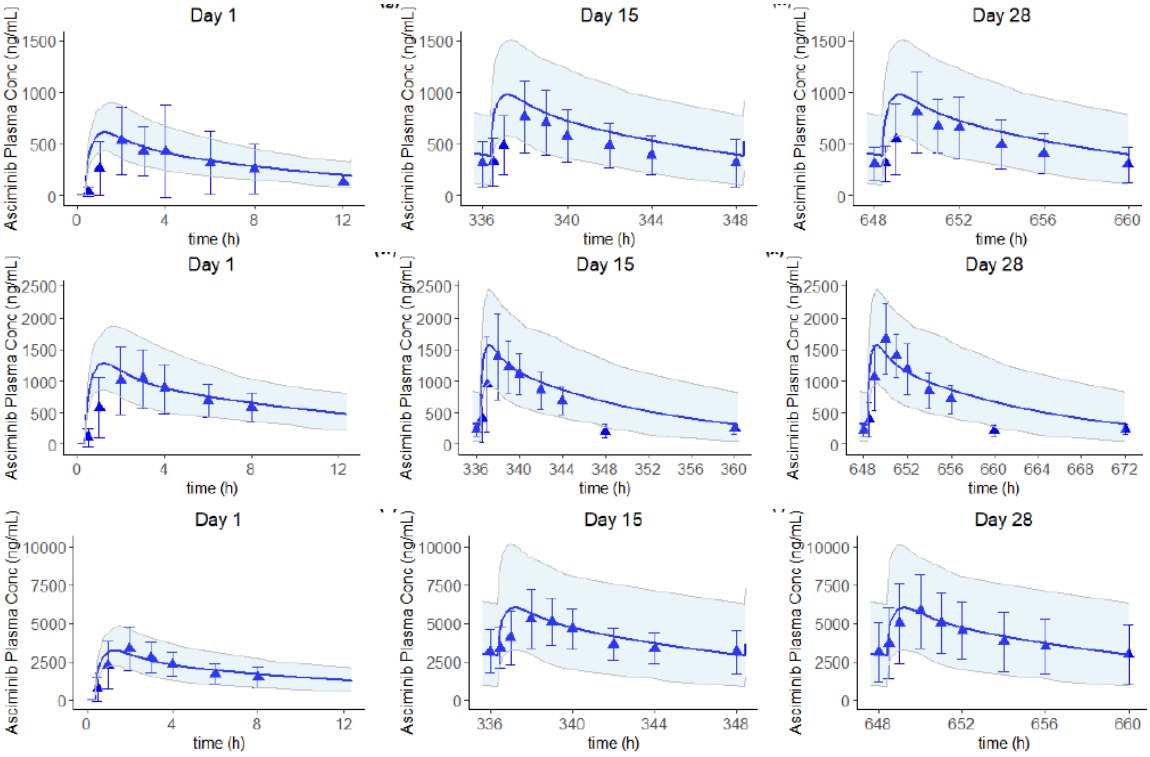
Yes, the PBPK model of asciminib adequately described asciminib PK following administration of single dose in healthy subjects (Figure 24) and multiple dosing in cancer patients (Figure 25 and Table 50).

Figure 24: Predicted and observed plasma PK profiles of asciminib after a single 40 mg dose in healthy subjects



Blue solid lines: arithmetic mean for the predicted population PK profile (N=100, n=10 subjects x 10 trials). Triangles: mean observed PK data (study A2107 Cohort 6-control arm) with error bars. Shaded areas: 5th-95th percentile of the total simulated population PK. Simulations using the NEC population model. PK profiles in linear (left) and in semi-logarithmic scale (right) (Source: DMPK R2000208, Figure 7-3).

Figure 25: Predicted and observed plasma concentration-time profiles of asciminib after multiple dosing in cancer patients



Blue solid lines: arithmetic mean for the predicted population PK profile (N=100, n=10 subjects x 10 trials). Triangles: mean observed PK data (Study X2101 40 mg BID (top), 80 mg QD (middle) and 200 mg BID (bottom)), with error bars. Shaded areas: 5th-95th percentile of the total simulated population PK. Simulations using the Sim-Cancer population model. PK profiles in linear (left) and in semi- logarithmic scale (right) (Source: DMPK R2000208, Figure 7-4).

Table 50: Predicted and observed PK parameters of asciminib following single dose in healthy subjects and multiple dosing in cancer patients

Asciminib dosage	Population [Study]	Cmax (ng/ml)		$AUC_{0\text{-}24h}$ (ng/ml.h)		Ctrough (ng/ml)	
		Obs	Pred	Obs	Pred	Obs	Pred
20 mg BID Day 1	Cancer [X2101]	249	305 (%PE=23)	1053	1529 (%PE=45)	NA	NA
20 mg BID Day 28	Cancer [X2101]	537	445 (%PE=-17)	2977	3216 (%PE=8.0)	128	149 (%PE=16)
40 mg SD	Healthy [A2107,control]	594	623 (%PE=4.9)	6000	5436 (%PE=-9.4)	NA	NA
	Healthy [E2101,fasted]	589	619 (%PE=5.1)	6040	5299 (%PE=-12)	NA	NA
	Healthy [A2103,HV]	584	659 (%PE=13)	5000	6306 (%PE=26)	NA	NA
	Healthy [A2105, HV]	584	696 (%PE=19)	5720	6904 (%PE=21)	NA	NA

40 mg BID Day 1	Cancer [X2101]	653	618 (%PE=-5.4)	2695	3187 (%PE=18)	NA	NA
40 mg BID Day 15	Cancer [A2301]	1010	1030 (%PE=2)	6070	8062 (%PE=33)	324	422 (%PE=30)
40 mg BID Day 28	Cancer [X2101]	873	980 (%PE=12)	5777	7544 (%PE=31)	NA	NA
80 mg QD Day 1	Cancer [X2101]	1253	1301 (%PE=3.8)	5780	6874 (%PE=19)	NA	NA
80 mg QD Day 28	Cancer [X2101]	1826	1587 (%PE=-13)	15663	17544 (%PE=12)	208	303 (%PE=46)
200 mg BID Day 1	Cancer [X2101]	3646	3275 (%PE=-10)	16788	17646 (%PE=5.1)	NA	NA
200 mg BID Day 28	Cancer [X2101]	6069	6050 (%PE=-0.3)	40639	50622 (%PE=25)	3137	2906 (%PE=-7.4)

PK parameters are mean values. AUC values represent: AUCinf for single 40 mg dose, $AUC_{0\text{-}8h}$ for Day 1 and AUCtau for Day 15 and Day 28. Simulated trials: 10 trials of 10 subjects (N=100) with age range and proportion of females matching the demographics of each study and dosing cohort of trial X2101. Simulations using the Sim-Cancer population model for cancer patients and NEC model for healthy subjects. %PE: = [(predicted value – observed value)/observed value] x 100. NA: not available (Source: DMPK R2000208, Tables 6-2 and 6-3).

The PK predictions showed that the model could reasonably estimate asciminib plasma exposure in cancer patients following multiple doses (20, 40, 80, 160, 200 mg BID and 40, 80, 200 mg QD). The prediction errors (PE%) for AUC and Cmax were equal or less than 45%. Following single dose in healthy volunteers, the predicted median Tmax was around 1.2 h [range 0.9-2 h] while the observed median Tmax was around 2 h [range 1-4 h] across studies. The model had a bias for over-predicting AUC at steady state (Day 15 or 28) and accumulation ratio for all doses above 80 mg total daily dose.

To evaluate the impact of the virtual population model on the PK predictions, simulation of the patient trial X2101 for asciminib 80 mg total daily dose and 20-200 mg BID was performed using both the NEC and the Sim-Cancer population models. The PK predictions were comparable between the two population models, with about 10% difference or less in the predicted AUC and Cmax.

Additional comments: While the intended purpose of the PBPK analysis is to predict CYP-mediated DDIs in cancer patients, DDI simulations were performed using the healthy volunteer population model because the clinical DDI studies were performed in healthy volunteers. In this context, there were two assumptions:

(1) The PK of asciminib in healthy subjects is similar to that in cancer patients. This assumption may be supported by the Cmax of 601 ng/mL (GM, CV% 42.5), following a single 40 mg dose of asciminib across all healthy subject studies in the fasted state (N=227), comparable to the Cmax of 537 ng/mL (GM, CV% 74) in cancer patients from trial X2101 (Cycle 1 Day 1, N=32. Similarly, the AUCinf (= 6520 ng/mL.h) following a single 40 mg dose in healthy subjects was comparable to the AUCtau at steady-state observed in cancer patients (≈5800-6100 ng/mL.h) [Clinical Pharmacology Report].

(2) There are no differences in CYP enzyme abundance/activity between healthy subjects and cancer patients. While there is evidence that activity or expression of CYP enzymes may be altered in cancer patients [Schwenger et al 2018], these changes are not incorporated in the cancer population model. Consequently, the DDI simulations should be interpreted with caution.

Q2. Can PBPK analyses predict the effect of a CYP3A modulator on the PK of asciminib at steady state?

No. PBPK analysis was considered inadequate to estimate the effects of CYP3A inhibitors and inducers on the PK of asciminib at steady state and a higher dose level, such as 200 mg BID, due to the following reasons:

(b) (4)

(b) (4)

It should be highlighted the overall model risk is high because the predictions would be the regulatory basis for dose modification/avoidance with CYP3A modulators in labeling, and the decision consequences. Therefore, a low model confidence due to the above limitations is not acceptable.

Additional comments: The asciminib model was considered inadequate for use as a substrate. However, the model was considered reasonable for use as a perpetrator because the exposure for the therapeutic levels were reasonably estimated (see Q1).

Q3. Can PBPK analyses predict the effect of imatinib on the PK of asciminib at steady state?
No. (b) (4) In general, in-vitro-in-vivo extrapolations of UGT inhibition and BCRP inhibition have not been established. Further, the deficiencies in the asciminib model as a substrate of CYP/UGT/BCRP (see Q2) precluded its application for simulating DDI effect with imatinib on the exposure of asciminib at steady-state and a higher dose level (such as 200 mg BID).

Q4. Can PBPK analyses predict the interaction effects of asciminib on the PK of CYP substrates?
Yes, the PBPK analyses were adequate to predict the interaction effects of asciminib on the PK of the substrates of CYP3A (midazolam), CYP2C8 (repaglinide and rosiglitazone), CYP2C9 (S-warfarin) and CYP2C19 (omeprazole). The model of asciminib was considered adequate for DDI risk assessment of asciminib as a CYP perpetrator in untested dosing regimens of asciminib, based on the following:

CYP3A substrate: DDI simulations were conducted with the CYP3A substrate midazolam and compared to observed data from study A2106. The initial asciminib model overpredicted the observed interaction effect of asciminib (40 mg BID for 5 days) on the PK of midazolam (single 4 mg dose on day 3): predicted GMR AUCinf=1.39 and Cmax =1.33 *vs* observed GMR AUCinf=1.28 and Cmax= 1.11. These results led to optimization of fugut and Qgut values on the final asciminib model by the Applicant to better recover the interaction effect. In vivo optimization of in vitro CYP3A interaction parameters were not needed. Predictions at 40 mg BID agreed with the clinical DDI effect on midazolam (PE<7.5%) (Table 4).

Asciminib was both a reversible inhibitor and inducer of CYP3A in vitro. DDI simulations conducted with and without the CYP3A induction parameters showed minimal contribution of induction in the predicted CYP3A interaction for both midazolam and repaglinide. This

observation is supported by the calculated relative induction score (RIS=0.070), which predicted a low CYP3A4 induction potential by asciminib (corresponding to ≈14% decrease in midazolam AUC [DMPK R1809192]). Asciminib is predicted to be a weak inhibitor (i.e., 1.25≥AUC ratio <2) of CYP3A4 at 40 mg BID, 80 mg QD, and 200 mg BID (Table 52).

CYP2C9 substrate: DDI simulations were conducted with S-warfarin and compared to observed data from study A2106. The initial DDI simulations using the in vitro determined CYP2C9 (Ki of 0.407 µM) underpredicted the observed interaction effect of asciminib (40 mg BID for 8 days) on the PK of S-warfarin (single 2.5 mg dose on day 3) (predicted GMR AUCinf=1.04 and Cmax= 1.01 vs observed GMR of AUCinf=1.41 and Cmax=1.08). PSA analysis was performed to identify the in vivo CYP2C9 Ki value predictive of the S-warfarin clinical DDI. A CYP2C9 Ki value of 0.03 µM was selected. Following the in vivo optimization of CYP2C9 Ki, predictions at 40 mg BID agreed with the clinical DDI effect on S-warfarin (PE<5%). Asciminib is predicted to be a weak inhibitor of CYP2C9 at 40 mg BID and at 80 mg QD, but a moderate (2≥AUC ratio <5) inhibitor of CYP2C9 at 200 mg BID (Table 52).

CYP2C8 substrate: Repaglinide is a substrate of CYP2C8 (fm≈0.7)and CYP3A (fm≈0.3), and subject to OATP1B1-mediated hepatic uptake. The repaglinide model has been validated, by the model developer, for the contributions of CYP2C8 pathway using the clinical DDI studies with trimethoprim (CYP2C8 inhibitor) and gemfibrozil (CYP2C8 and OATP1B1/3 inhibitor).

Asciminib was an inhibitor of CYP2C8, CYP3A and OATP1B1 in vitro. The interaction effect of asciminib on the PK of repaglinide may be caused by the net inhibition effects on CYP2C8, CYP3A and OATP1B1. DDI simulations were conducted considering the interaction effect of asciminib in all these pathways and compared to observed data from study A2106. Predictions at 40 mg BID agreed with the clinical observation (PE<6.5%) (Table 52). A weak interaction effect (1.25≥AUC ratio <2) is predicted for asciminib 200 mg BID, but no inhibition potential (AUC ratio <1.25) at asciminib 80 mg total daily dose (Table 52). Exploratory predictions of the effect of asciminib on the individual pathways of repaglinide were also conducted.

CYP2C8 and CYP2C9 substrate: Rosiglitazone is a substrate of CYP2C8 (fm≈0.6) and CYP2C9 (fm≈0.3) rosiglitazone. A weak interaction effect (1.25≥AUC ratio <2) is predicted for asciminib 200 mg BID, but no inhibition potential (AUC ratio <1.25) at 80 mg total daily dose (Table 52). Exploratory prediction of the effect of asciminib only on the CYP2C8 pathway of rosiglitazone was also conducted.

CYP2C19 substrate: Omeprazole is a substrate of CYP2C19 (fm≈0.9) and CYP3A (fm≈0.1, CYP2C19 normal metabolizers). No clinical DDI study has been conducted with asciminib and a CYP2C19 substrate. A lower value for the inhibition constant than in vitro (≈14-fold lower) was needed to recover the clinical DDI effect with the CYP2C9 substrate S-warfarin. Therefore, a PSA for the in vitro CYP2C19 inhibition parameter as part of risk analysis was recommended. In response to FDA's request for information, the Applicant provided a PSA of CYP2C19 Ki,u on the predicted DDI effect with omeprazole. Based upon the experimental mean and standard

deviation (SD) values of IC50 for the CYP enzymes, where the coefficient of variation (CV) did not exceed 42%, the Applicant selected a 50% variability as a worst-case scenario. The CYP2C19 Ki,u (=IC50,u/2) value and the PSA range were 1.5 µM and 0.75-2.25 µM, respectively. A Ki,u value 10-fold lower than the in vitro CYP2C19 was also tested by the Reviewer. Asciminib is predicted to be a weak inhibitor of CYP2C19 at 200 mg BID (1.25≥AUC ratio <2), but no inhibition potential at 80 mg total daily dose. In the context of PSA using a 10-fold lower value for CYP2C19 Ki,u, asciminib is predicted to be a weak inhibitor of CYP2C19 at 80 mg total daily dose and a moderate inhibitor at 200 mg BID (Table 52).

Table 52: Predicted exposure changes of CYP substrates by co-administration of asciminib

Substrate (pathway) *Asciminib Ki,u*	**Asciminib dosage** / **Substrate dosage**	**GMR Cmax**				**GMR AUC[&]**			
		40 mg BID		**80 mg QD**	**200mg BID**	**40 mg BID**		**80 mg QD**	**200mg BID**
		[#]Obs	**Pred**	**Pred**	**Pred**	**[#]Obs**	**Pred**	**Pred**	**Pred**
Midazolam (CYP3A) *Ki,u=0.348 µM*	4 mg SD	1.11	1.18 (%PE=6.3)	1.17	1.58	1.28	1.23 (%PE=-3.9)	1.24	1.88
	4 mg QD	NA	1.20	1.18	1.65	NA	1.25	1.26	1.98
S-Warfarin (CYP2C9) *Ki,u=0.03 µM*	2.5 mg SD	1.08	1.03 (%PE=-4.6)	1.04	1.07	1.41	1.40 (%PE=-0.7)	1.52	4.14
	2.5 mg QD	NA	1.39	1.37	3.38	NA	1.57	1.57	4.41
Repaglinide (CYP2C8, 3A, OATP1B1)	0.5 mg SD	1.14	1.07 (%PE=-6.1)	1.08	1.25	1.08	1.10 (%PE=1.9)	1.12	1.42
	0.5 mg QD	NA	1.07	1.08	1.25	NA	1.10	1.12	1.42
Repaglinide (CYP2C8) *Ki,u=0.466 µM (CYP3A) Ki,u=0.348 µM*	0.5 mg QD	NA	1.06*	1.06*	1.19*	NA	1.08*	1.09*	1.31*
Repaglinide (CYP2C8) *Ki,u*=0.466 *µM*	0.5 mg QD	NA	1.01	1.00	1.05	NA	1.02	1.02	1.11
Rosiglitazone (CYP2C8) *Ki,u=0.466 µM (CYP2C9) Ki,u=0.03 µM*	4 mg SD	NA	1.03	1.02	1.08	NA	1.20	1.24	1.66
	4 mg QD	NA	1.04	1.03	1.14	NA	1.20	1.24	1.67
Rosiglitazone (CYP2C8) *Ki,u=0.466 µM*	4 mg QD	NA	1.01	1.00	1.03	NA	1.03	1.04	1.16
Omeprazole (CYP2C19) *Ki,u=1.5 µM*	20 mg SD	NA	1.03	1.04	1.12	NA	1.04	1.06	1.22
	20 mg BID	NA	1.04	1.04	1.23	NA	1.07	1.06	1.41
Omeprazole (CYP2C19) *Ki,u/2*	20 mg SD	NA	1.04[§]	1.08[§,*]	1.18[§]	NA	1.06[§]	1.05[§,*]	1.30[§]
	20 mg BID	NA	1.10[§,*]	1.08[§,*]	1.31[§,*]	NA	1.06[§,*]	1.05[§,*]	1.67[§,*]
Omeprazole	20 mg SD	NA	1.13[§,*]	1.17[§,*]	1.60[§,*]	NA	1.20[§,*]	1.29[§,*]	2.26[§,*]

(CYP2C19) *Ki,u/10*	20 mg BID	NA	1.17[§,*]	1.15[§,*]	1.84[§,*]	NA	1.32[§,*]	1.27[§,*]	3.15[§,*]

[&]AUCinf (single dose) or AUCtau ratio (multiple dose). Simulations were conducted using the NEC population model. In single dose DDI, the substrate was administered on day 3. Midazolam, omeprazole, repaglinide and rosiglitazone were administered for 14 days (d1-d15) and asciminib was also administered for 14 days (d1-d15) as 40 mg BID, 80 mg QD, and 200 mg BID. S-Warfarin and asciminib were administered for 35 days (d1-d36) at 40 mg BID and 80 mg QD, whereas for 63 days (d1-d64) at 200 mg BID. [#]Observed values are reported as the adjusted geometric mean values from study A2106. [§]Simulations were performed using a population representative of the NEC model. NA: Not available/Not applicable (Source: DMPK 2001088, Tables 6-1 and 6-2, Response to Clinical Pharmacology IR, and *Reviewer's Analysis).

In summary, the DDI simulations for asciminib 40 mg BID or 80 mg QD, and regardless of single or multiple dosing of substrate, predicted a weak interaction (1.25≥AUC ratio<2) with CYP2C9 substrates; while no or marginal interaction effect was predicted with CYP3A, CYP2C8 or CYP2C19 substrates. For asciminib 200 mg BID, a moderate interaction with CYP2C9 substrates (2≥AUC ratio<5) and weak interaction (1.25≥AUC ratio<2) with CYP3A, CYP2C8 or CYP2C19 substrates were predicted.

Q5. Can PBPK analyses predict the interaction effects of asciminib on the PK of CYP1A2 substrate?

Yes, the PBPK analysis was considered adequate to estimate the interaction potential of asciminib with a sensitive CYP1A2 substrate, such as caffeine.

The caffeine model has been validated, by the model developer, for the use of DDI predictions caused by reversible inhibition of CYP1A2, but not by induction. Asciminib is both a reversible inhibitor and inducer of CYP1A2. DDI simulations were conducted considering the combined (inhibition and induction) effect of asciminib (40 mg BID, 80 mg QD, 200 mg BID) on the PK of caffeine (single 150 mg oral dose at day 3 or multiple dosing for 14 days). Simulations, conducted to differentiate between asciminib induction and inhibition effects, showed that interaction would be a result of CYP1A2 induction with dose-dependency, but minimal CYP1A2 inhibition effect (regardless of asciminib or caffeine dosing regimen).

The IVIVE of CYP1A2 induction has not been established, and limited positive correlation was reported so far [Wong et al 2020]. In response to FDA's information request, the Applicant provided a PSA of CYP1A2 induction parameters of asciminib on the predicted DDI effect with caffeine, as part of a DDI risk assessment. The PSA range was defined as the mean experimental value ±1 x SD of the respective parameter. The in vitro determined values were IndC50= 0.59 µM (SE=0.13 µM) and Emax 3.5-fold (SD=0.47), and the PSA range for IndC50 and Indmax was 0.36-0.82 µM and 3.9-5.1-fold, respectively. The PSA range was considered limited, by the Reviewer, because it did not consider the uncertainties related to IVIVE of CYP1A2 induction. A 10-fold reduction of IndC50 was also tested by the Reviewer (Table 53). The DDI risk assessment indicated that the potential for interaction (assumed as AUCR<0.8) of asciminib with a sensitive CYP1A2 substrate cannot be excluded.

Table 53: Predicted induction effects of asciminib the exposure of a sensitive CYP1A2 substrate

Substrate	Asciminib CYP1A2 nduction parameters	AUC_{inf} Ratio		Cmax Ratio	
	Asciminib dose	40mg BID	200mg BID	40mg BID	200mg BID
Caffeine	Indmax=4.5-fold IndC50= 0.59 µM	0.90	0.64	0.96	0.86
Caffeine	Indmax=5.1-fold IndC50=0.36 µM	0.90§	0.63§	0.98§	0.90§
Caffeine	Indmax= 4.5-fold IndC50= 0.059 µM	0.68§,*	0.43§,*	0.92§,*	0.80§,*

Indmax=Emax +1 ; SD (Indmax) calculated based on the %CV of Emax which was reported as 3.5 ± 0.47-fold. Standard error (SE) of the triplicates (n=3) was reported as 0.13; The SD (IndC50) was calculated as $SD = SE \cdot \sqrt{n}$. Values are expressed as geometric means. Simulations consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and proportion of female 0.5, using the NEC population model. §Simulations were performed using a population representative of the NEC model. (Source: DMPK R2001088, Table 6-2, Response to Clinical Pharmacology IR, and *Reviewer's Analysis).

Q6. Can PBPK analyses predict the inhibitory effects of asciminib on the PK of UGT1A1 substrates?

Yes, the PBPK analysis was considered adequate to assess the interaction potential of asciminib with an UGT1A1 substrate, such as raltegravir.

The relative contribution of UGT1A1 (fmUGT1A1) to raltegravir overall clearance was partially verified, by the model developer, against clinical DDI with rifampin as an UGT1A1 inducer and atazanavir as an UGT1A1 inhibitor. The raltegravir model assumed the drug is only metabolized by UGT1A1 and 9% eliminated by renal clearance. The raltegravir model reasonably captured the observed PK profile of raltegravir 400 mg SD and 400 mg BID. DDI simulations also adequately predicted the increase in raltegravir exposure in the presence of atazanavir, reported in four different clinical DDI studies. Overall, the predicted/observed ratios for AUC and Cmax ratios were within 0.88-1.28 of the reported values. The UGT1A1 inhibition constant of atazanavir was determined in vitro (Ki=1.9 µM) [Zhang et al 2005].

Additional comments: The Reviewer acknowledged the partial validation of fmUGT1A1 for raltegravir as it was not verified with available clinical phenotype study in UGT1A1 PM population. Additionally, as mentioned above, all non-renal clearance of raltegravir was assumed to be mediated by UGT1A1. The involvement of UGT1A9 in the metabolism of raltegravir has not been incorporated into the model. However, in case of lower contribution of UGT1A1 (lower fmUGT1A1), a lower DDI effect with a UGT1A1 inhibitor would be expected, i.e., the current model of raltegravir is conservative to evaluate the effect of a UGT1A1 inhibitor. Lasty, the Reviewer noted that currently there is a limited validation of the DDI predictive performance of raltegravir model as it was conducted using clinical DDI data of a single inhibitor, atazanavir.

After oral co-administration of raltegravir 400 mg BID with asciminib 40 mg BID, 80 mg QD or 200 mg BID (both starting at day 1 and for a total duration of 14 days), the predicted geometric mean AUC and Cmax ratios were 1.16, 1.09, 1.62 and 1.16, 1.09, 1.54, respectively (Table 54).

The IVIVE of UGT1A1 inhibition effect has not been established. In response to FDA's request for information, the Applicant provided a PSA of UGT1A1 inhibition constant on the predicted DDI effect with raltegravir. Based upon the experimental mean and SD values of IC50 for the CYP enzymes, where CV did not exceed 42% , the Applicant selected a 50% variability of UGT1A1 Ki value as worst-case scenario. The UGT1A1 Ki,u value and the sensitivity analysis range were 0.35 µM and 0.175-0.525 µM, respectively. This PSA range may be limited because it was an arbitrary assumption of UGT Ki variability based on intra-lab variability of in vitro IC50 values for CYPs. Nonetheless, this initial analysis indicated that asciminib has the potential for a positive interaction with a UGT1A1 substrate (AUC ratio>1.25) (Table 54). The DDI risk assessment indicated that the potential for interaction of asciminib with a UGT1A1 substrate cannot be excluded.

Table 54: Predicted inhibitory effects of asciminib the exposure of a UGT1A1 substrate

Substrate	UGT1A1 Ki	AUC_{inf} Ratio		Cmax Ratio	
	Asciminib dose	40mg BID	200mg BID	40mg BID	200mg BID
Raltegravir	Ki,u=0.35 µM	1.16	1.62	1.16	1.54
Raltegravir	Ki,u/2	1.28§	2.14§	1.28§	1.91§

Simulations consisted of 10 trials of 10 subjects (n=100) with an age range of 20-55 years, and proportion of female 0.5, using the NEC population model. Asciminib was administered on day 3 one hour prior to the administration of the probe substrate to maximize the interaction effect. §Simulations were performed using a population representative of the NEC model. (Source: DMPK R2001088, Table 6-2, Response to Clinical Pharmacology IR,).

Q7. Can PBPK analysis predict the inhibitory effects of asciminib on the PK of P-gp substrates?
Yes, the PBPK analysis was considered adequate to assess the interaction potential of asciminib with substrates of the transporter P-gp, such as digoxin and dabigatran etexilate.

The digoxin model has been developed as a probe substrate of intestinal and hepatic P-gp. The renal elimination mediated by P-gp is not included in the model, thus inhibition of renal P-gp cannot currently be simulated. The ability of the digoxin model to predict P-gp interaction was assessed using a limited number of clinical DDIs (with verapamil and ritonavir, observed Cmax and AUC increase < 50%) by the model developer. The PBPK team has expanded the validation of the digoxin model, concluding that digoxin model can capture >25% increase in Cmax and AUC in the presence of a P-gp perpetrator. While acknowledging the model underpredicted clarithromycin and quinidine DDI effects possibility be due to the lack of interaction mechanism incorporated at the systemic level, such as kidney.

DDI simulations were also conducted using the P-gp substrate dabigatran etexilate. Dabigatran etexilate is a prodrug converted by esterase-catalyzed hydrolysis to dabigatran, which is not a P-gp substrate. The effect of a P-gp inhibitor on dabigatran etexilate is assessed by changes in

dabigatran plasma exposure. The ability of the dabigatran etexilate and dabigatran model to predict P-gp interaction was assessed using clinical DDIs with verapamil, clarithromycin, quinidine and ketoconazole, by the model developer.

It has been reported that the in vitro values generally underestimate the observed transporter-mediated DDIs. Additionally, the values of the P-gp inhibition parameter (IC50 or Ki) vary largely depending on the experimental conditions and analysis. In response to FDA's information request, the Applicant acknowledged the uncertainties of IVIVE for P-gp DDI potential. The Applicant provide IVIVE analysis with other know P-gp perpetrators and suggested that a scaling factor of 0.003 would be needed to correlate the in vitro P-gp inhibition constant to the in vivo effect with digoxin as a P-gp substrate.

Regarding the perpetrator concentration at the site of P-gp interaction, when using the first order absorption model, the unbound portal vein concentration (fugut*Cpv) was considered the relevant perpetrator concentration. The maximal unbound portal vein concentration (fugut*Cpv,max) with the estimated GI luminal concentration (=dose/250 mL) and the solubility for asciminib was compared by the Reviewer. The maximal unbound portal vein concentration of asciminib was much lower than its solubility or the estimated GI luminal concentrations (For the dosing regimens of 40 mg BID, 80 mg QD and 200 mg BID, estimated GI luminal concentrations were 0.16, 0.32 and 0.8 mg/mL and the model prediction of maximal unbound portal vein concentration was approximately 3×10^{-4}, 6×10^{-4}, and 2×10^{-3} mg/mL, respectively). Thus, a first order absorption model for asciminib may underestimate its gut concentration at the site of P-gp interaction.

To account for the forementioned uncertainties of predicting the P-gp DDI potential of asciminib, DDI simulations with digoxin and dabigatran were conducted considering the experimentally determined P-gp Ki,u value of 21.7 µM (assumed fu,inc=1) and a PSA range for P-gp Ki,u value of 15-100 fold lower values (Table 55).

Table 55: ***Predicted inhibitory effects of asciminib the exposure of P-gp substrates***

Substrate	P-gp K_i	AUC_{inf} Ratio			Cmax Ratio		
	Asciminib dose	40mg BID	80mg QD	200mg BID	40mg BID	80mg QD	200mg BID
Digoxin	Ki,u=21.7 µM	1.00	1.01	1.02	1.00	1.01	1.03
Digoxin	Ki,u/15	1.06§*	1.07§*	1.21§*	1.09§*	1.13§*	1.30§*
Digoxin	Ki,u/100	1.23§*	1.25§*	1.44§*	1.33§*	1.41§*	1.67§*
Dabigatran	Ki,u=21.7 µM	1.01	1.02	1.06	1.01	1.02	1.06
Dabigatran	Ki,u/15	1.14§*	1.21§*	1.60§*	1.15§*	1.23§*	1.61§*
Dabigatran	Ki,u/100	1.68§*	1.93§*	2.74§*	1.69§*	1.93§*	2.56§*

§Simulations were performed using a population representative of the NEC model. (Source: DMPK R2001088, Table 6-2, Response to Clinical Pharmacology IR and *Reviewer's analysis).

In addition, the Applicant explored the potential for systemic inhibition of P-gp by asciminib based on its total and unbound systemic and local tissue levels, in response to FDA's information request. Using the P-gp Ki,u value of 21.7 µM, no systemic inhibition of P-gp was suggested based on the [I]/Ki ratios being lower than 0.1 when using total and unbound plasma concentrations, extracellular water in the liver and total kidney concentrations after asciminib 40 mg BID dosage. At asciminib 200 mg BID, a systemic P-gp inhibition risk was indicated when using total plasma concentrations. Additionally, DDI simulations using digoxin and the scaled P-gp Ki,u value (=0.0651 µM) indicated a minor potential for inhibition of canalicular efflux by asciminib 40 mg BID (13% reduction of canalicular efflux clearance). While for asciminib 200 mg BID, a higher potential for inhibition of canalicular efflux was predicted (56% reduction). In summary, the potential for systemic P-gp inhibition by asciminib 200 mg BID cannot be excluded, while it may be minor after asciminib 40 mg BID dosage.

In conclusion, the DDI risk assessment indicated that the potential for interaction of asciminib with a substrate of P-gp cannot be excluded. The interaction potential would be dependent on asciminib dosage and substrate drug.

Additional comments: The Reviewer emphasized the DDI simulations was not considered adequate to accurately predict the effect of asciminib on the PK of a P-gp substrate due to the uncertainties regarding the perpetrator concentration and IVIVE. The modeling efforts showed a potential for a positive inhibitory effect of asciminib on the PK of digoxin (a NTI drug) and dabigatran.

Q8. Can PBPK analysis predict the interaction effect of asciminib on the PK of a BCRP/OATP1B substrate?

No, the PBPK analysis was considered inadequate to evaluate the interaction potential of asciminib with a substrate of the transporters BCRP and OATP1B, such as rosuvastatin.

The rosuvastatin model has been developed as a probe substrate of BCRP and OATP1B1/3. The model can describe rosuvastatin plasma PK data following a single or multiple dosing of rosuvastatin at various dosing levels. However, the validation of this model was considered insufficient because it was conducted with limited clinical DDI datasets regarding the BCRP/OATP1B1/3 pathways, and phenotype studies regarding the BCRP or OATP1B1 pathway. The model captured the DDI effect of rifampicin (single dose of 600 mg) with the caveat of rifampin being an inhibitor for multiple transporters, and the model underpredicted the magnitude of interaction with cyclosporine, a prototypical inhibitor of BCRP/OATP1B1 [Simonson et al 2004]. The rosuvastatin model was considered inadequate for use as an BCRP/OATP1B substrate model in the intended context of use (i.e., demonstrate negative DDI potential). In addition, IVIVE of in vitro inhibition parameters had not been established for BCRP- and OATP1B-mediated DDIs.

Q9. Can PBPK analyses predict the effects of food on the PK of asciminib?

No, the absorption model of asciminib was not mechanistic to allow evaluation of the effect of food on the exposure of asciminib at higher dose levels. The Applicant optimized the absorption parameters (fa and ka) with the observed food effect at asciminib 40 mg single dose and assumed the same negative food effect would be extrapolated to 80 mg QD and 200 mg BID. The Applicant concluded the food effect was independent of the dose. However, this was an assumption incorporated in the model; not a simulation outcome. Detail assessment is as follows:

(b) (4)

Q10. Can PBPK analyses predict the effects of renal impairment on the PK of asciminib?
No. Using the default population model for severe renal impairment (RI, Sim-Renal GFR_less_30), the PBPK analysis underpredicted (%PE= (b) (4)) the observed effect of severe RI on asciminib exposure (AUCinf ratio predicted (b) (4) vs observed (b) (4)), following asciminib 40 mg single dose [Study A2105].

(b) (4)

(b) (4). Further, deficiencies in the asciminib model as a substrate of CYP/UGT/BCRP (see Q2) precluded its application for evaluation of effects of organ impairment on the drug exposure.

Q11. Can PBPK analyses predict the effects of hepatic impairment on the PK of asciminib?
No. Using the default population models for mild, moderate and severe hepatic impairment (HI, Sim-Cirrhosis CP-A, CP-B and CP-C, respectively), the PBPK analysis underpredicted (%PE= (b) (4)) the effect of HI on asciminib exposure observed following asciminib 40 mg single dose [Study A2103].

(b) (4)

Further, deficiencies in the asciminib model as a substrate of CYP/UGT/BCRP (see Q2) precluded its application for evaluation of the effects of organ impairment on the drug exposure.

Q12. Can the ADAM-PBPK model evaluate the effect of elevated gastric pH on the PK of asciminib following a 200 mg oral administration?
Yes, the asciminib ADAM-PBPK model, along with the in vitro dissolution data and clinical DDI study with the ARA rabeprazole [Study A1101], was adequate to evaluate the effect of elevated gastric pH on the exposure of asciminib following 200 mg dose.

The ADAM-PBPK model of asciminib was validated against the observed PK in healthy subjects and in patients in the dose range of 40 mg to 200 mg (Table 56), and the clinical DDI study (A1101) with rabeprazole (Table 57).

Table 56: ***ADAM-PBPK model predicted and observed PK parameters of asciminib following single-dose in healthy subjects and multiple dosing in patients***

Asciminib Dosage	Cmax ± SD (ng/mL)			AUC ± SD (ng·h/mL)		
	Observed	Predicted	%PE	Observed	Predicted	%PE
40 mg SD	567 ± 187	710 ± 167	25.2	6040 ± 2020	6575 ± 2422	8.86

(Cohort 5 control)						
40 mg SD (Cohort 3 control)	595 ± 207	712 ± 166	19.7	5870 ± 1720	6636 ± 2432	13.1
40 mg SD (Cohort 6 control)	594 ± 225	709 ± 165	19.4	6000 ± 2210	6536 ± 2379	8.93
40 mg BID Day 1	653 ± 468	729 ± 197	11.6	2695 ± 1679	3948 ± 1317	46.5
40 mg BID Day 15	806 ± 365	1220 ± 472	51.4	5519 ± 2782	9893 ± 4849	79.3
40 mg BID Day 28	873 ± 369	1220 ± 472	39.7	5777 ± 2439	9892 ± 4848	71.2
80 mg QD Day 1	1253 ± 448	1448 ± 396	15.6	5780 ± 2043	8015 ± 2648	38.7
80 mg QD Day 15	1595 ± 551	1778 ± 588	11.5	14702 ± 4219	20406 ± 9883	38.8
80 mg QD Day 28	1826 ± 422	1778 ± 588	-2.63	15633 ± 4070	20404 ± 9883	30.5
200 mg BID Day 1	3646 ± 1161	3130 ± 1047	-14.1	16788 ± 4964	18301± 6552	9.01
200 mg BID Day 15	5700 ± 1782	5927 ± 2683	3.98	45641 ± 13252	52416 ± 27642	14.8
200 mg BID Day 28	6069 ± 2447	5925 ± 2682	-2.37	40639 ± 18474	52387 ± 27637	28.9

PK parameters are mean values. SD: single dose, BID: twice daily, QD: once daily. Observed PK from studies A2107 (healthy subjects) and CABL001X2101 (patients). For single-dose administration, AUC is reported as mean AUCinf. For multiple-dose administration (CABL001X2101), AUC is reported as mean $AUC_{0\text{-}8\ h}$ for Day 1 and as mean AUC_{tau} (AUC_{ss}) for Day 15 and Day 28. Simulated trials: 10 trials of 10 subjects (n=100) with age range and proportion of females matching the actual demographics of the respective clinical studies. The virtual population model was the Cancer model with the advanced fluid volume dynamic model selected and gastric mean residence time of 0.4 h. %PE, (%) calculated prediction error = [(predicted value – observed value)/observed value] x 100. (Source: Applicant's response to Clinical Pharmacology IR submitted on September 16, 2021).

Table 57: ADAM-PBPK model Predicted and observed PK parameters following oral administration of 40 mg asciminib with and without co-administration of rabeprazole

Scenario	Geometric Mean Cmax (ng/mL)			Geometric Mean AUCinf (ng·h/mL)		
	Observed	Predicted	Pred/Obs	Observed	Predicted	Pred/Obs
Asciminib alone (40 mg)	943	849	0.90	9850	7949	0.81
Asciminib with rabeprazole	856	844	0.99	9710	7949	0.82
Ratio (with/without rabeprazole)	0.908 (0.849, 0.972)	0.994	1.09	0.986 (0.959, 1.01)	1.00	1.01

Observed values are reported as the adjusted geometric mean values from Study A1101. Simulated trials:10 trials of 10 subjects (n=100) with age range and proportion of females matching the actual demographics of the respective clinical studies. The virtual population model was the Japanese model (same population as study A1101) with the advanced fluid volume dynamic model selected and gastric mean residence time of 0.4 h. The DDI ratios were comparisons of asciminib PK simulated with a normal gastric pH, i.e. default value of 1.5 (asciminib alone simulations) with asciminib PK simulated with a gastric pH of 5.0 (asciminib with rabeprazole simulations). (Source: Applicant's response to Clinical Pharmacology IR submitted on September 16, 2021).

Overall, the ADAM-PBPK model was able to capture the observed PK of asciminib with prediction error within 50%, except for the PK following oral administration of 40 mg BID asciminib on days 15 and 28. Of note, the first-order absorption PBPK model also had the trend of over-predicting AUC at steady state (see Q1).

In addition, a reasonable in vitro to in vivo extrapolation of dissolution and solubility data for asciminib could be inferred based on adequate prediction of observed PK. The model predicted in vivo solubility values are consistent with the in vitro values, i.e., ~0.032 mg/mL and ~0.4

mg/mL in aqueous and bile salts solutions, respectively. These are the highest values based on dissolution studies in aqueous buffer and FaSSIF medium (pH≈6.5), respectively.

A default value of 10 µm for particle radius was used. In the response to FDA's IR submitted on September 22,2021, the Applicant indicated that the mean particle radius of the registration batch (no. 1010019997) was 21.5 µm. The 10^{th} and 90^{th} percentiles of the particle radius were 2.75 µm and 49 µm, respectively. The Applicant conducted PSA on particle radius (1-60 µm) and particle density (0.6-2.4 g/L) to conclude that neither factor had significant impact (less than 5% decrease in fraction absorbed) on asciminib absorption at both 40 mg and 200 mg dose levels. The reviewer conducted simulations using particle radius of 25 µm, 50 µm, and 100 µm. The simulation suggested that the AUC decreased by 8%, 25%, and 48%, respectively, compared to the simulated AUC using particle radius of 10 µm at the 200 mg dose level under the fasting condition. Nevertheless, the using a particle radius of 25 µm, which is close to the experimentally measured mean value, appears to be able to describe to the PK of asciminib in the dose range of 40 to 200 mg.

Besides particle size, the other key input parameters for mechanistic absorption modeling include the partition coefficients of the drug between water and bile salts (logKm:w) for the neutral form, and the critical supersaturation ratio (CSR). The predicted Cmax and AUC decrease to a larger extent with the decreasing CSR and logKm:w at 200 mg compared to 40 mg. Using a set of values for CSR of 4.6, logKm:w for neutral form of 5, and particle radius of 25 µm, the predicted Cmax and AUC were approximately 55%, and 61%, respectively, of the predicted values using the default set of parameters (CSR of 46, logKm:w for neutral form of 5.46, and particle radius of 10 µm) following a single dose of 200 mg administration under the fasting condition. Therefore, this set of parameter values is considered as a 'conservative' condition to evaluate the effect of an ARA on asciminib absorption. Under this condition, the predicted decrease in Cmax and AUC were 12% and 5%, and 28% and 25%, respectively, when 40 mg and 200 mg of asciminib was co-administered with an ARA.

Conclusions

- The PBPK analysis was inadequate to predict the effect of strong CYP3A4 inhibitors and inducers on the exposure of asciminib at steady state because of uncertainties of estimation of the contribution of CYP3A to asciminib clearance and overall model risk.
- The PBPK analysis was inadequate to predict the changes in exposure of asciminib, at higher dose levels, in the presence of food
- The PBPK analysis was inadequate to predict the changes in exposure of asciminib due to hepatic impairment and renal impairment.
- The PBPK analysis was inadequate to evaluate the effect of asciminib on the PK of a OATP1B/BCRP substrate because of the limited validation of the rosuvastatin model and the IVIVE has not been established for the BCRP- and OATP1B-mediated DDIs.
- The PBPK DDI-risk assessment indicated that the DDI potential of asciminib with substrates of P-gp, CYP1A2 or UGT1A1 cannot be excluded.

- For asciminib 80 mg total daily dose, a weak interaction effect (1.25≥AUC ratio <2) was predicted with CYP2C9 substrates, whereas no or marginal interaction effect was predicted with CYP3A, CYP2C8, and CYP2C19 substrates. For asciminib 200 mg BID, a moderate interaction with CYP2C9 (2≥AUC ratio <5) and weak interaction (1.25≥AUC ratio <2) with CYP3A, CYP2C8, and CYP2C19 substrates were predicted.
- The ADAM-PBPK model simulations suggested that changes on gastric pH does not have much effect on asciminib exposure due to its high solubility in bile salts attributed to supersaturation, which override the pH effect. The predicted effect of elevated gastric pH on asciminib PK following 200 mg administration is unlikely to be clinically meaningful.

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19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
Grouped preferred terms are displayed in the Table below.

Grouped term	Preferred terms
Abdominal Pain	Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort, Gastrointestinal pain, Hepatic pain
Acute Kidney Injury	Acute kidney injury, Anuria, Azotaemia, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Nephropathy toxic, Oliguria, Renal disorder, Renal failure, Renal impairment, Renal injury, Renal tubular acidosis, Renal tubular atrophy, Renal tubular disorder, Renal tubular dysfunction, Renal tubular injury, Renal tubular necrosis
Arrhythmia	Accelerated idioventricular rhythm, Accessory cardiac pathway, Adams-Stokes syndrome, Agonal rhythm, Arrhythmia, Arrhythmia supraventricular, Atrial conduction time prolongation, Atrial fibrillation, Atrial flutter, Atrial parasystole, Atrial tachycardia, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Atrioventricular node dysfunction, Bifascicular block, Bradyarrhythmia, BRASH syndrome, Brugada syndrome, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Cardiac fibrillation, Conduction disorder, Congenital supraventricular tachycardia, Defect conduction intraventricular, Electrocardiogram delta waves abnormal, Electrocardiogram PR prolongation, Electrocardiogram PR shortened, Electrocardiogram QRS complex prolonged, Electrocardiogram QT prolonged, Electrocardiogram repolarisation abnormality, Frederick's syndrome, Heart alternation, Heart rate irregular, Holiday heart syndrome Junctional ectopic tachycardia, Lenegre's disease, Long QT syndrome, Nodal arrhythmia, Nodal rhythm, Pacemaker generated arrhythmia, Pacemaker syndrome, Parasystole, Paroxysmal arrhythmia, Paroxysmal atrioventricular block, Pulseless electrical activity, Reperfusion arrhythmia, Rhythm idioventricular, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus bradycardia, Sinus node dysfunction, Sinus

	tachycardia, Supraventricular extrasystoles, Supraventricular tachyarrhythmia, Supraventricular tachycardia, Torsade de pointes, Trifascicular block, Ventricular arrhythmia; Ventricular asystole, Ventricular dyssynchrony, Ventricular extrasystoles, Ventricular fibrillation, Ventricular flutter Ventricular parasystole, Ventricular pre-excitation, Ventricular tachyarrhythmia, Ventricular tachycardia, Wandering pacemaker, Withdrawal arrhythmia, Wolff-Parkinson-White syndrome
Cardiovascular Toxicity	Acute coronary syndrome, Acute myocardial infarction, Angina pectoris, Angina unstable, Aortic dilatation, Aortic wall hypertrophy, Aphasia, Arterial thrombosis, Arteriosclerosis, Arteriosclerosis coronary artery, Arteriospasm coronary, Blood creatine phosphokinase MB increased, Cardiac aneurysm, Cardiac arrest, Cardiac discomfort, Cardiac disorder, Cardio-respiratory arrest, Carotid arteriosclerosis, Carotid artery occlusion, Carotid artery stenosis, Cerebellar infarction, Cerebral arteriosclerosis, Cerebral artery stenosis, Cerebral infarction, Cerebral ischaemia, Cerebrovascular accident, Cerebrovascular disorder, Cerebrovascular insufficiency, Chest discomfort, Chest pain, Clumsiness, Coeliac artery occlusion, Coeliac artery stenosis, Coronary artery disease, Coronary artery occlusion, Coronary artery stenosis, Coronary vascular graft occlusion, Dry gangrene, Electrocardiogram ST segment depression, Electrocardiogram T wave abnormal, Embolism arterial, Extremity necrosis, Haemorrhagic vasculitis, Hemiparesis, Intermittent claudication, Ischaemic cardiomyopathy, Ischaemic stroke, Lacunar infarction, Mesenteric arterial occlusion, Monoparesis, Myocardial infarction, Myocardial ischaemia, Myocardial necrosis, Peripheral arterial occlusive disease, Peripheral artery occlusion, Peripheral artery restenosis, Peripheral artery stenosis, Peripheral coldness, Peripheral ischaemia, Peripheral vascular disorder, Poor peripheral circulation, Raynaud's phenomenon, Renal artery stenosis, Retinal artery occlusion, Retinal vascular disorder, Splenic infarction, Subclavian artery stenosis, Sudden death, Transient ischaemic attack, Troponin I increased, Troponin increased, Vasculitis, Ventricular remodelling, Vertebral artery stenosis

	Also, MedDRA version 23.1 narrow SMQs of Ischemic Central Nervous System Vascular Conditions, Ischemic Heart Disease (narrow), and Embolic and thrombotic events, arterial are included.
Cardiac Failure Congestive	Cardiac failure, Ejection fraction decreased, Left ventricular hypertrophy, Pericardial effusion
Cough	Allergic cough, Atopic cough, Cough, Productive cough, Upper-airway cough syndrome
Diarrhea	Autoimmune colitis, Colitis, Colitis microscopic, Diarrhoea, Diarrhoea haemorrhagic, Enteritis, Enterocolitis, Frequent bowel movements
Dizziness	Cervicogenic vertigo, Dizziness, Dizziness exertional, Dizziness postural, Vertigo, Vertigo CNS origin, Vertigo labyrinthine, Vertigo positional
Dysgeusia	Ageusia, Anosmia, Dysgeusia, Hypergeusia, Hypogeusia, Product taste abnormal
Dyspnea	Dyspnoea, Dyspnoea at rest, Dyspnoea exertional
Edema	Eye oedema, Eyelid oedema, Face oedema, Generalised oedema, Gravitational oedema, Lip oedema, Localised oedema, Oedema, Oedema genital, Oedema peripheral, Penile oedema, Periorbital oedema, Scrotal oedema, Skin oedema, Swelling, Testicular oedema, Vulval oedema
Fatigue	Asthenia, Fatigue
Headache	Basilar migraine, Cervicogenic headache, Chronic paroxysmal hemicrania, Cluster headache, Cold-stimulus headache, Craniocervical syndrome, Drug withdrawal headache, Exertional headache, External compression headache Headache, Hemiplegic migraine, Medication overuse headache, Migraine, Migraine postdrome, Migraine with aura, Migraine without aura, New daily persistent headache, Occipital neuralgia, Ophthalmoplegic migraine, Post-traumatic headache, Postictal headache, Primary cough headache, Primary headache associated with sexual activity, Retinal migraine, Sinus headache, Status migrainosus, SUNCT syndrome, Tension headache, Thunderclap headache, Typical aura without headache, Vascular headache, Vestibular migraine
Hemorrhage	Abdominal wall haemorrhage, Acute haemorrhagic conjunctivitis, Adenoviral haemorrhagic cystitis, Administration site haemorrhage, Adrenal haemorrhage

	Anal fissure haemorrhage, Anal haemorrhage, Anal ulcer haemorrhage, Anastomotic haemorrhage, Anastomotic ulcer haemorrhage, Anorectal varices haemorrhage, Application site haemorrhage, Arterial haemorrhage, Arteriovenous fistula site haemorrhage, Arteriovenous graft site haemorrhage, Basal ganglia haemorrhage, Brain stem haemorrhage, Brain stem microhaemorrhage, Breast haemorrhage, Bronchial haemorrhage, Bronchial varices haemorrhage, Catheter site haemorrhage, Central nervous system haemorrhage, Cerebellar haemorrhage, Cerebellar microhaemorrhage, Cerebral arteriovenous malformation haemorrhagic, Cerebral cyst haemorrhage, Cerebral haemorrhage, Cerebral microhaemorrhage, Cervix haemorrhage uterine, Choroidal haemorrhage, Chronic gastrointestinal bleeding, Ciliary body haemorrhage, Coital bleeding, Conjunctival haemorrhage, Corneal bleeding, Cystitis haemorrhagic, Diverticulitis intestinal haemorrhagic Diverticulum intestinal haemorrhagic, Duodenal ulcer haemorrhage, Duodenitis haemorrhagic, Dysfunctional uterine bleeding, Ear haemorrhage, Encephalitis haemorrhagic, Enterocolitis haemorrhagic, Epidural haemorrhage, Epistaxis, Extra-axial haemorrhage, Eye haemorrhage, Eyelid bleeding, Gastric haemorrhage, Gastric ulcer haemorrhage, Gastric ulcer haemorrhage, obstructive, Gastric varices haemorrhage, Gastritis alcoholic haemorrhagic, Gastritis haemorrhagic, Gastroduodenal haemorrhage, Gastrointestinal haemorrhage, Gastrointestinal polyp haemorrhage, Gastrointestinal ulcer haemorrhage, Gastrointestinal vascular malformation haemorrhagic, Genital haemorrhage, Gingival bleeding, Graft haemorrhage, Haematuria, Haemoptysis, Haemorrhage, Haemorrhage coronary artery, Haemorrhage intracranial, Haemorrhage subcutaneous, Haemorrhage subepidermal, Haemorrhage urinary tract, Haemorrhagic adrenal infarction, Haemorrhagic arteriovenous malformation, Haemorrhagic ascites, Haemorrhagic breast cyst, Haemorrhagic cerebral infarction, Haemorrhagic cholecystitis, Haemorrhagic cyst, Haemorrhagic diathesis, Haemorrhagic disorder, Haemorrhagic erosive gastritis, Haemorrhagic hepatic cyst, Haemorrhagic infarction, Haemorrhagic necrotic pancreatitis, Haemorrhagic ovarian cyst, Haemorrhagic stroke, Haemorrhagic thyroid cyst, Haemorrhagic transformation stroke, Haemorrhagic tumour

	necrosis, Haemorrhagic urticaria, Haemorrhagic vasculitis, Haemorrhoidal haemorrhage, Hepatic haemorrhage, Implant site haemorrhage, Incision site haemorrhage, Infusion site haemorrhage, Injection site haemorrhage, Instillation site haemorrhage, Internal haemorrhage, Intestinal varices haemorrhage, Intra-abdominal haemorrhage, Intracranial tumour haemorrhage, Intraventricular haemorrhage, Iris haemorrhage, Joint microhaemorrhage, Lacrimal haemorrhage, Large intestinal haemorrhage, Large intestinal ulcer haemorrhage, Laryngeal haemorrhage, Lip haemorrhage, Lower gastrointestinal haemorrhage, Lymph node haemorrhage, Mediastinal haemorrhage, Medical device site haemorrhage, Mesenteric haemorrhage, Mouth haemorrhage, Mucocutaneous haemorrhage, Mucosal haemorrhage, Muscle haemorrhage, Myocardial haemorrhage, Naevus haemorrhage, Nail bed bleeding, Nephritis haemorrhagic, Ocular retrobulbar haemorrhage, Oesophageal haemorrhage, Oesophageal ulcer haemorrhage, Oesophageal varices haemorrhage, Oesophagitis haemorrhagic, Optic disc haemorrhage, Optic nerve sheath haemorrhage, Ovarian haemorrhage, Pancreatic haemorrhage, Pancreatitis haemorrhagic, Papillary muscle haemorrhage, Paranasal sinus haemorrhage, Parathyroid haemorrhage, Parotid gland haemorrhage, Pelvic haemorrhage, Penile haemorrhage, Peptic ulcer haemorrhage, Pericardial haemorrhage, Periorbital haemorrhage, Pharyngeal haemorrhage, Pituitary haemorrhage, Post procedural haemorrhage, Post-traumatic punctate intraepidermal haemorrhage, Postmenopausal haemorrhage, Procedural haemorrhage, Proctitis haemorrhagic, Pulmonary alveolar haemorrhage, Pulmonary haemorrhage, Puncture site haemorrhage, Putamen haemorrhage, Radiation associated haemorrhage, Rectal haemorrhage, Rectal ulcer haemorrhage, Renal cyst haemorrhage, Renal haemorrhage, Respiratory tract haemorrhage, Retinal haemorrhage, Retinopathy haemorrhagic, Retroperitoneal haemorrhage, Scleral haemorrhage, Shock haemorrhagic, Skin haemorrhage, Skin neoplasm bleeding, Skin ulcer haemorrhage, Small intestinal haemorrhage, Small intestinal ulcer haemorrhage, Soft tissue haemorrhage, Spermatic cord haemorrhage, Spinal cord

	haemorrhage, Spinal epidural haemorrhage, Spinal subarachnoid haemorrhage, Spinal subdural haemorrhage, Splenic haemorrhage, Splenic varices haemorrhage, Splinter haemorrhages, Spontaneous haemorrhage, Stoma site haemorrhage, Stomatitis haemorrhagic, Subarachnoid haemorrhage, Subchorionic haemorrhage, Subdural haemorrhage, Subendocardial haemorrhage, Subgaleal haemorrhage, Testicular haemorrhage, Thalamus haemorrhage, Thoracic haemorrhage, Thyroid haemorrhage, Tongue haemorrhage, Tonsillar haemorrhage, Tooth pulp haemorrhage, Tooth socket haemorrhage, Tracheal haemorrhage, Traumatic haemorrhage, Traumatic intracranial haemorrhage, Tumour haemorrhage, Ulcer haemorrhage, Umbilical haemorrhage, Upper gastrointestinal haemorrhage, Ureteric haemorrhage, Urethral haemorrhage, Urinary bladder haemorrhage, Urogenital haemorrhage, Uterine haemorrhage, Vaccination site haemorrhage, Vaginal haemorrhage, Vascular access site haemorrhage, Vascular graft haemorrhage, Venous haemorrhage, Vessel puncture site haemorrhage, Vitreous haemorrhage, Vulval haemorrhage, Wound haemorrhage
Hepatotoxicity	Alanine aminotransferase increased, Ascites, Aspartate aminotransferase increased, Bilirubin conjugated increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Blood bilirubin unconjugated increased, Gamma-glutamyltransferase increased, Glutamate dehydrogenase increased, Hepatic lesion, Hepatic pain, Hepatocellular injury, Hepatomegaly, Hyperbilirubinaemia, Hypoalbuminaemia, Liver disorder, Transaminases increased
Hypersensitivity	Allergic transfusion reaction, Bronchospasm, Circulatory collapse, Conjunctivitis allergic, Dermatitis, Dermatitis acneiform, Dermatitis allergic, Dermatitis bullous, Dermatitis contact, Dermatitis exfoliative, Dermatitis exfoliative generalized, Documented hypersensitivity to administered product, Drug eruption, Drug hypersensitivity, Eczema, Eczema nummular, Eczema vesicular, Eczema weeping Erythema, Erythema multiforme, Eyelid oedema, Face oedema, Hypersensitivity, Lip swelling, Periorbital oedema, Rash, Rash erythematous, Rash follicular, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash morbilliform, Rash popular, Rash papulosquamous, Rash pruritic, Rash pustular, Rash vesicular, Rhinitis allergic,

	Swelling face, Swollen tongue, Urticaria, Wheezing
Hypertension	Blood pressure ambulatory increased, Blood pressure diastolic increased, Blood pressure increased, Blood pressure orthostatic increased, Blood pressure systolic increased, Diastolic hypertension, Hypertension, Hypertensive crisis, Labile hypertension, Malignant hypertension, Orthostatic hypertension, Secondary hypertension, Supine hypertension, Systolic hypertension, Withdrawal hypertension
Hypotension	Blood pressure decreased, Diastolic hypotension, Hypotension, Orthostatic hypotension
Hypothyroidism	Autoimmune hypothyroidism, Blood thyroid stimulating hormone increased, Hypothyroidic goitre, Hypothyroidism, Primary hypothyroidism, Secondary hypothyroidism, Tertiary hypothyroidism
Lower Respiratory Tract Infection	Bronchitis, Latent tuberculosis, Metapneumovirus infection Mycobacterium avium complex infection, Tracheobronchitis
Musculoskeletal Pain	Arthritis, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Neck pain, Non-cardiac chest pain, Pain in extremity, Spinal pain
Neuropathy Peripheral	Autoimmune neuropathy, Dysaesthesia, Hyperaesthesia Hypoaesthesia, Immune-mediated neuropathy, Neuralgia, Neuropathy peripheral, Paraesthesia, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Polyneuropathy
Pancreatic Toxicity	Amylase increased, Hyperlipasaemia, Lipase increased, Pancreatitis, Pancreatitis acute
Pancreatitis	Pancreatitis, Pancreatitis acute
Pneumonia	Atypical mycobacterial lower respiratory tract infection, Atypical mycobacterial pneumonia, Atypical pneumonia, Candida pneumonia, Embolic pneumonia, Enterobacter pneumonia, Eosinophilic pneumonia, Eosinophilic pneumonia acute, Eosinophilic pneumonia chronic, Haemorrhagic pneumonia, Herpes simplex pneumonia, Idiopathic interstitial pneumonia, Idiopathic pneumonia syndrome, Lower respiratory tract herpes infection, Lower respiratory tract infection, Lower respiratory tract infection bacterial, Lower respiratory tract infection fungal, Lower respiratory tract infection viral, Lung abscess, Miliary pneumonia, Neonatal pneumonia, Paracancerous pneumonia, Parasitic pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia

	Acinetobacter, Pneumonia adenoviral, Pneumonia anthrax, Pneumonia aspiration, Pneumonia bacterial, Pneumonia Blastomyces, Pneumonia Bordetella, Pneumonia chlamydial, Pneumonia cryptococcal, Pneumonia cytomegaloviral, Pneumonia Escherichia, Pneumonia fungal, Pneumonia haemophilus, Pneumonia helminthic, Pneumonia herpes viral, Pneumonia influenzal, Pneumonia klebsiella, Pneumonia legionella, Pneumonia lipoid, Pneumonia measles, Pneumonia Moraxella, Pneumonia mycoplasmal, Pneumonia necrotizing, Pneumonia parainfluenzae viral, Pneumonia pneumococcal, Pneumonia proteus, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia salmonella, Pneumonia serratia, Pneumonia staphylococcal, Pneumonia streptococcal,, Pneumonia toxoplasmal, Pneumonia tularaemia, Pneumonia viral, Post procedural pneumonia, Varicella zoster pneumonia
Pneumonitis	Acute interstitial pneumonitis, Immune-mediated pneumonitis, Interstitial lung disease, Organising pneumonia, Pneumonitis
Pyrexia	Body temperature increased, Hyperpyrexia, Hyperthermia Pyrexia
Rash	Autoimmune dermatitis, Dermatitis, Dermatitis acneiform, Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalized, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Dyshidrotic eczema, Eczema, Eczema asteatotic, Erythema multiforme, Exfoliative rash, Eyelid rash, Genital rash, Immune-mediated dermatitis, Lichen planus, Mucocutaneous rash, Nodular rash, Palmar-plantar erythrodysaesthesia syndrome, Pemphigoid, Penile rash, Perineal rash, Perivascular dermatitis, Rash, Rash erythematous, Rash follicular, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash morbilliform, Rash popular, Rash papulosquamous, Rash pruritic, Rash pustular, Rash vesicular, Scrotal dermatitis, Skin exfoliation, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, Urticarial dermatitis, Vasculitic rash, Vulvovaginal rash
Stomatitis	Aphthous ulcer, Cheilitis, Gingival erosion, Gingival ulceration, Glossitis, Mouth ulceration, Mucosal hyperaemia, Mucosal inflammation, Oral mucosal blistering, Oral mucosal erythema, Pharyngeal inflammation Stomatitis, Tongue ulceration

Upper Respiratory Tract Infection	Nasopharyngitis, Pharyngitis, Pharyngotonsillitis , Respiratory tract infection, Rhinitis, Upper Respiratory Tract Infection
Urinary Tract Infection	Bacterial pyelonephritis, Cystitis, Cytomegalovirus urinary tract infection, Emphysematous pyelonephritis, Escherichia pyelonephritis, Escherichia urinary tract infection, Pyelonephritis acute, Pyelonephritis chronic, Pyelonephritis fungal, Pyelonephritis mycoplasmal, Pyelonephritis viral, Streptococcal urinary tract infection, Urinary tract infection, Urinary tract infection bacterial, Urinary tract infection enterococcal, Urinary tract infection fungal, Urinary tract infection pseudomonal, Urinary tract infection staphylococcal, Urinary tract infection viral
Vomiting	Discoloured vomit, Faecal vomiting, Haematemesis, Retching Vomiting

NDA 215358
SCEMBLIX (asciminib)
Multidisciplinary Review and Evaluation DHM1

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	**Select one:** _X_ Authored ___Approved
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Signatures

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Clinical Reviewer	Gulsum Pamuk, MD	Office of Oncologic Diseases (OOD)/ Division of Hematologic Malignancies I (DHM1)	Sections: 2, 3, 4, 7, 8, 9, 10, 12, 13, 19.1, 19.2, 19.5	**Select one:** X Authored ___ Approved
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Clinical Team Leader	Lori Ehrlich, MD, PhD	OOD/DHM1	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 19.1, 19.2, 19.5	**Select one:** ___ Authored X Approved
	Signature: Lori Ehrlich -S Digitally signed by Lori Ehrlich -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lori Ehrlich -S, 0.9.2342.19200300.100.1.1=2001528093 Date: 2021.10.25 17:00:18 -04'00'			
Clinical Pharmacology Reviewer	Yibo Wang, PhD	Office of Clinical Pharmacology/ Division of Cancer Pharmacology I	Sections: 6 and 18.4	**Select one:** X Authored ___ Approved
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Clinical Pharmacology Team Leader	Edwin Chiu Yuen Chow, PhD	Office of Clinical Pharmacology/ Division of Cancer Pharmacology II	Sections: 6 and 18.4	**Select one:** ___ Authored X Approved
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Clinical Pharmacology Division Director	Brian Booth, PhD	Office of Clinical Pharmacology/ Division of Cancer Pharmacology I	Sections: 6, 18.4	**Select one:** ___ Authored X Approved
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DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Pharmacometrics Reviewer	Liang Li, PhD	Division of Pharmacometrics/ OCP/OTS	Sections: 6, 18.4	**Select one:** X Authored ___ Approved
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Pharmacometrics Team Leader	Lian Ma, PhD	Division of Pharmacometrics/ OCP/OTS	Sections: 6, 18.4	**Select one:** ___ Authored X Approved
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PBPK Reviewer	Manuela Grimstein, PhD	Division of Pharmacometrics/ OCP/OTS	Sections: 6, 18.4	**Select one:** X Authored ___ Approved
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PBPK Team Leader	Xinyuan Zhang, PhD	Division of Pharmacometrics/ OCP/OTS	Sections: 6, 18.4	**Select one:** ___ Authored X Approved
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Genomics Reviewer	Jielin (Jillian) Sun, PhD	Genomics/Division of Translational and Precision Medicine/OCP/OTS	Sections: 6	**Select one:** ___ Authored X Approved
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DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Genomics Team Leader	Rosane Charlab Orbach, PhD	Genomics/Division of Translational and Precision Medicine/OCP/OTS	Sections: 6	**Select one:** ___ Authored _X_ Approved
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QT Reviewer	Nan Zheng, PhD	Division of Pharmacometrics/ OCP/OTS	Sections: 6	**Select one:** ___ Authored _X_ Approved
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Nonclinical Reviewer	Shwu Luan Lee, PhD	OOD/DHOT	Sections: 5, 18.3	**Select one:** _X_ Authored ___ Approved
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Nonclinical Supervisor	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5, 18.3	**Select one:** ___ Authored _X_ Approved
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Nonclinical Deputy Director	Haleh Saber, PhD	OOD/DHOT	Sections: 5, 18.3	**Select one:** ___ Authored _X_ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Haiyan Chen, PhD	Office of Biostatistics/ Division of Biometrics IX	Sections: 8.1 and 8.3	**Select one:** X Authored ___ Approved
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Statistical Team Leader	Jonathon Vallejo, PhD	Office of Biostatistics/ Division of Biometrics IX	Sections: 8.1 and 8.3	**Select one:** X Authored X Approved
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Statistical Division Director	Thomas Gwise, PhD	Office of Biostatistics/ Division of Biometrics IX	Sections: 8.1 and 8.3	**Select one:** ___ Authored X Approved
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Cross-Disciplinary Team Leader (CDTL)	Lori Ehrlich, MD, PhD	OOD/DHM1	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 19.1, 19.2, 19.5	**Select one:** X Authored ___ Approved
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Division Director	R. Angelo de Claro, MD	OOD/DHM1	Sections: All	**Select one:** ___ Authored X Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Office Director	Marc Theoret, MD	OOD	Sections: All	**Select one:** ___ Authored _X_ Approved
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