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APPLICATION NUMBER:

215358Orig1s008

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

Scemblix (asciminib)

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.

Disclaimer: FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Health Canada (HC) and Switzerland’s Swissmedic. While the conclusions and recommendations expressed herein reflect FDA’s completed review of the application, the applications may still be under review at the other regulatory agencies.

Application Type	Efficacy Supplement (SE-1)
Application Number(s)	NDA 215358, S-008 and S-009
Priority or Standard	Priority
Submit Date(s)	May 29, 2024
Received Date(s)	May 29, 2024
PDUFA Goal Date	November 29, 2024
Division/Office	Division of Hematologic Malignancies 1 (DHMI) Office of Oncology Drugs
Review Completion Date	October 28, 2024
Established Name	Asciminib
Trade Name	Scemblix
Pharmacologic Class	Kinase inhibitor
Code name	ABL-001
Applicant	Novartis Pharmaceuticals Corporation
Formulation(s)	Film coated tablets (20 mg, 40 mg, and 100 mg)
Dosing Regimen	80 mg once daily or 40 mg twice daily
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with newly diagnosed or previously treated Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).
Recommendation on Regulatory Action	Accelerated approval for newly diagnosed CML in CP (S-008) Regular approval for previously treated CML in CP (S-009)
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult patients with: - Newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP). - Previously treated Ph+ CML in CP.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Rachel McMullen, MPH, MHA
Pharmacology/Toxicology Reviewer(s)	Shwu Luan Lee, PhD
Pharmacology/Toxicology Team Leader(s)	Brenda Gehrke, PhD
Office of Clinical Pharmacology Reviewer(s)	Hongfei Zhang, PhD Pharmacometrics: Hongshan Li, PhD
Office of Clinical Pharmacology Team Leader(s)	Ruby Leong, Pharm D Pharmacometrics: Jiang Liu, PhD
Clinical Reviewer	Gulsum Pamuk, MD
Clinical Team Leader	Lori Ehrlich, MD, PhD
Statistical Reviewer	Radhika Avadhani, DrPH
Statistical Team Leader	Jonathon Vallejo, PhD
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSN, ACNP
Cross-Disciplinary Team Leader	Lori Ehrlich, MD, PhD
Division Director (OOD)	Angelo de Claro, MD

Additional Reviewers of Application

OPQ	OPQ Reviewer: Mustafa Guzel, PhD OPQ Team Lead: Rohit Kolhatkar, PhD RBPM: Dahlia Walters
OSI	Anthony Orencia, M.D., Ph.D., F.A.C.P. Min Lu, M.D., M.P.H.,
Other	OOD Safety ADS: Shan Pradhan, MD OOD Safety RPM: Stacie Woods, Pharm D

OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRM=Division of Risk Management

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Project Orbis #129 – Health Canada (Canada) Review team		
Director	(b) (6)	
Clinical Manager (Clinical Evaluation Division – Oncology and Neurology)		
Lead Clinical Reviewer		
Senior Regulatory Affairs Officer		

Project Orbis #129 – Swissmedic (SMC, Switzerland) Review team		
Clinical Assessor	(b) (6)	
Clinical PK Assessor		
Biostatistician		
Risk Management Reviewer		
Regulatory Project Manager		
Project Orbis Coordinators		
Head Clinical Review Unit Oncology		

Glossary

<i>ABL1</i> /ABL1	<i>Italicized</i> : Abelson oncogene; non-italicized: Abelson protein
<i>ABL2</i> /ABL2	<i>Italicized</i> : Abelson related oncogene; non-italicized: Abelson related protein
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
aGFR	adjusted glomerular filtration rate
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AOEs	arterial occlusive events
AP	accelerated phase
AST	aspartate aminotransferase
AUC	area under curve
AUClast	AUC from time zero to the time of the last quantifiable concentration
BC	blast crisis
<i>BCR</i>	breakpoint cluster region
<i>BCR::ABL1</i>	chimeric <i>BCR::ABL1</i> oncogene
BCR::ABL1	BCR::ABL1 oncoprotein with dysregulated ABL1 kinase activity
BID	<i>bis in diem</i> /twice a day
BMA	bone marrow aspirate
BP	blast phase
BP	systolic blood pressure/diastolic blood pressure
BTB	breakthrough therapy designation
CCyR	complete cytogenetic response
cCCyR	confirmed complete cytogenetic response
CFR	Code of Federal Regulations
CHR	complete hematological response
CI	confidence interval

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C _{max}	observed maximum plasma (or serum or blood) concentration following drug administration
CMH	Cochran–Mantel–Haenszel
C _{min}	trough concentration
CL	systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration
CML	chronic myelogenous leukemia
CML-BP	chronic myeloid leukemia in blast phase
CML-CP	chronic myeloid leukemia in chronic phase
COVID-19	coronavirus disease of 2019
CRF	case report form
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
C _{trough} /C _{min}	plasma concentration (measured concentration at the end of a dosing interval at steady state [taken directly before next administration])
CV	coefficient of variation
CYP	cytochrome p450
DMC	data monitoring committee
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
ELN	European Leukemia Net
ELTS	EUTOS Long-Term Survival
EUTOS	European Treatment Outcome Study
FAS	full analysis set
FFS	failure-free survival
FU	follow-up
GI	gastrointestinal
IFN	interferon-alpha
IRT	interactive response technology that includes interactive voice

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	response system and interactive web response system
IS	international standard
IS-TKI	investigator selected-tki
KM	Kaplan-Meier
MCyR	major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
MMR	major molecular response
MC	multicenter
NCCN	National Comprehensive Cancer Network
OL	open label
NDA	new drug application
OS	overall survival
PA	primary analysis
Ph 1/2	phase 1/2
Ph 3	phase 3
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PFS	progression-free survival
Ph+	Philadelphia chromosome positive
Ph+ CML	Philadelphia chromosome-positive chronic myelogenous leukemia
PK	pharmacokinetic(s)
PMC	postmarketing commitment
PMR	postmarketing requirement
PopPK	population PK
PRS-TKI	pre-randomization selected tki
QD	once daily
R	randomized
RQ-PCR	real-time quantitative polymerase chain reaction
SAE	serious adverse event
SD	standard deviation

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SOC	system organ class
sNDA	supplementary new drug application
Tlast	time of last measurable concentration
Tmax	time to reach the maximum concentration after drug administration
TEAE	treatment-emergent adverse event
TFR	treatment-free remission
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
TTF	time to treatment failure
ULN	upper limit of normal
2G	second generation tkis
1L	first-line
2L	second line
3L	third line

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1 Executive Summary

1.1. Product Introduction

Established Name:	Asciminib
Trade Name:	Scemblix
Also Known As:	ABL-001
Therapeutic Class:	Kinase inhibitor
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. 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. Asciminib is currently approved 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).
- Ph+ CML in CP with the T315I mutation.

The Applicant now submits a supplementary New Drug Application (sNDA) to support an indication for the treatment of adult patients with newly diagnosed or previously treated Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).

The Applicant submits an sNDA with results from randomized phase 3 study CABL001J12301 (ASC4FIRST) to support the indication of newly diagnosed CML-CP based on major molecular response (MMR) at 48 weeks. The trial to support the indication of previously treated CML-CP is a single-arm study CABL001AUS08 in patients treated with asciminib as second line therapy and supported by the approved indication for the treatment as third line or higher therapy.

1.2. Conclusions on the Substantial Evidence of Effectiveness

For the treatment of patients with newly diagnosed chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

For the treatment of patients with relapsed or intolerant Ph+ CML in CP, Substantial Evidence of Effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations.

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Information submitted by the Applicant provides substantial evidence for the effectiveness of asciminib for the treatment of adult patients with newly diagnosed or previously treated Ph+ CML in CP. For the indication of the treatment of newly diagnosed CML-CP, the efficacy of asciminib has been established primarily on the results of a single randomized, open-label, active-controlled, multicenter trial in patients with newly diagnosed CML-CP treated with asciminib versus investigator selected TKI (Study CABL001J12301, ASC4FIRST, referred to as study J12301). The recommendation is based on the finding of improved major molecular response (MMR) at 48 weeks in study J12301 to support accelerated approval for an endpoint likely to predict longer term disease control and survival. The current framework for regular approval for a newly diagnosed CML-CP indication requires 5 years of efficacy follow up. Support of the efficacy of asciminib for the newly diagnosed indication was provided by the established activity of asciminib in later lines of therapy for the treatment of CML-CP for which it is already approved.

In study J12301, 405 patients were randomized (1:1) to asciminib or investigator selected tyrosine kinase inhibitors (IS-TKI including imatinib, dasatinib, nilotinib, or bosutinib, selected prior to randomization). Patients were stratified according to EUTOS long-term survival (ELTS) risk group (low, intermediate, high), and pre-randomization selection of TKI (imatinib or 2G TKIs stratum composed of dasatinib, nilotinib, and bosutinib). Patients could receive a TKI for up to 2 weeks prior to randomization for disease control. Patients continued treatment until unacceptable toxicity or treatment failure occurred.

The interim analysis of J12301 included a prespecified assessment of MMR at 48 weeks in all patients and in the imatinib stratum. MMR at 96 weeks in all patients and in the imatinib stratum are key secondary endpoints and were not available at the time of this analysis. Other secondary endpoints include MMR at other scheduled time points, MMR 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 $\leq 0.1\%$ on the International Scale) at 48 weeks was significantly better on the asciminib arm at 68% (95% CI: 61, 74) compared to that in the IS-TKI arm at 49% (95% CI: 42, 56). The treatment difference in MMR rate at 48 weeks was 19% (95% CI: 10, 28; two-sided p value of <0.001 , stratified by the pre-randomization TKI and ELTS risk group). In the imatinib stratum, MMR at 48 weeks was significantly better on the asciminib arm at 69% (95% CI: 59, 78) compared to that in the imatinib stratum at 40% (95% CI: 31, 50). The treatment difference in MMR rate at 48 weeks was 30% (95% CI: 17, 42; two-sided p value of <0.001 , stratified by ELTS risk group). MMR rates at 48 weeks in patients receiving asciminib and IS-TKIs within the other TKIs stratum were 66% (95% CI: 56%, 75%) and 58% (95% CI: 48%, 68%), respectively. This comparison was not statistically tested.

Median time to MMR in patients receiving asciminib was 24 weeks (95% CI: 24 to 25 weeks) and in patients receiving IS-TKIs was 36 weeks (95% CI: 36 to 49 weeks). Exploratory subgroup

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analyses were performed over demographics and baseline disease characteristics. Analyses over subgroups showed a consistent treatment effect favoring asciminib.

The review team recommends accelerated approval for asciminib for the treatment of newly diagnosed Ph+ CML in CP.

For the indication of the treatment of adult patients with previously treated CML-CP, the efficacy of asciminib has been established based on the results of a two randomized, open-label, active-controlled trials: (1) in patients previously treated with two or more TKIs with asciminib versus bosutinib (Study CABL001A2301, ASCEMBL) which led to the approval in third line and (2) in patients with newly diagnosed CML-CP with asciminib versus IS-TKI (study CABL001J12301, ASC4FIRST) submitted to support the frontline indication as reviewed herein. The expansion of the indication to second line was supported by study CABL001AUS08 (referred to as study AUS08), a single arm study of asciminib treatment in patients treated as second line (2L) therapy, and extrapolation by PK/PD modeling.

The interim analysis of AUS08 included a prespecified assessment of MMR at 6 months in patients evaluable for efficacy at that timepoint. At the interim analysis, 71 patients were enrolled in the 2L cohort, and 28 patients were evaluable for efficacy at 6 months having completed the efficacy assessment at that timepoint or discontinued prior to the timepoint. The MMR rate at 6 months was 43% (12/28; 95% CI: 24, 63). For patients who discontinued their prior TKI due to lack of efficacy, the MMR rate at 6 months was 31% (5/16; 95% CI: 11, 59). For patients who discontinued their prior TKI due to lack of tolerability, the MMR rate at 6 months was 58% (7/12; 95% CI: 28, 85). In the patients treated with asciminib as 2L treatment in study AUS08, the MMR rate at 6 months was intermediate to the MMR rate observed in the 1L cohort in study J12301 and the 3L+ cohort in study A2301, as generally expected for this population. The results of AUS08 support activity of asciminib in previously treated CML-CP. PK/PD modeling was also used to support extrapolation for the previously treated CML-CP indication.

The review team recommends regular approval for asciminib for the treatment of previously treated Ph+ CML in CP.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Chronic myeloid leukemia (CML) is a rare myeloproliferative neoplasm characterized by the Philadelphia (Ph) chromosome found in up to 95% of patients. The Ph chromosome results from a reciprocal translocation t(9;22) leading to the chimeric BCR::ABL1 fusion oncogene. Patients with newly diagnosed CML-CP may be treated with imatinib, dasatinib, nilotinib, and bosutinib based on risk scores, preexisting comorbidities and concomitant medications of the patients. Asciminib is an orally administered ABL/BCR-ABL1 tyrosine kinase inhibitor that binds to the myristoyl pocket of BCR-ABL1 protein, currently approved for the treatment of patients with CML in chronic phase previously treated with two or more TKIs.

The recommendation for accelerated approval for asciminib for the treatment of newly diagnosed Ph+ CML in CP is based on the results of a randomized controlled trial evaluating asciminib versus investigator selected TKI (Study CABL001J12301, ASC4FIRST, referred to as study J12301). Supportive efficacy and safety information in this population was provided by the established activity of asciminib in later lines of therapy for the treatment of CML-CP for which it is already approved.

In study J12301, 405 patients were randomized (1:1) to asciminib or investigator selected tyrosine kinase inhibitors (IS-TKI including imatinib, dasatinib, nilotinib, or bosutinib, selected prior to randomization). Patients were stratified according to EUTOS long-term survival (ELTS) risk group (low, intermediate, high), and pre-randomization selection of TKI (imatinib or 2G TKIs stratum composed of dasatinib, nilotinib, and bosutinib). The interim analysis of J12301 included a prespecified assessment of MMR at 48 weeks in all patients and in the imatinib stratum. MMR at 96 weeks in all patients and in the imatinib stratum are key secondary endpoints. At the time of analysis, MMR (defined as BCR-ABL1 ratio $\leq 0.1\%$ on the International Scale) at 48 weeks was significantly better on the asciminib arm at 68% (95% CI: 61, 74) compared to that in the IS-TKI arm at 49% (95% CI: 42, 56). The treatment difference in MMR rate at 48 weeks was 19% (95% CI: 10, 28; two-sided p value of <0.001 , stratified by the pre-randomization TKI and ELTS risk group). In the imatinib stratum, MMR at 48 weeks was significantly better on the asciminib arm at 69% (95% CI: 59, 78) compared to that in the imatinib stratum at 40% (95% CI: 31, 50). The treatment difference in MMR rate at 48 weeks was 30% (95% CI: 17, 42; two-sided p value of <0.001 , stratified by ELTS risk group). MMR rates at 48 weeks in patients receiving asciminib and IS-TKIs within the other TKIs stratum were 66% (95% CI: 56%, 75%) and 58% (95% CI: 48%, 68%), respectively. This comparison was not statistically tested.

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In the randomized study, patients with newly diagnosed CML in CP were treated with either asciminib or IS-TKI. The exposure in the asciminib arm was longer than the IS-TKI arm due to more discontinuations in the IS-TKI arm due to lack of efficacy or dose modifications for toxicity. The overall rate of serious adverse events was lower than in the asciminib arm, though the safety profile differed between the arms and should be considered when choosing the appropriate treatment for a patient based on underlying comorbidities. Serious adverse reactions occurred in 11% of patients who received asciminib. Serious adverse reactions in $\geq 1\%$ included pancreatitis (1%), and musculoskeletal pain (1%). In 200 patients, the most common ($\geq 20\%$) adverse reaction excluding laboratory abnormalities in patients who received asciminib was musculoskeletal pain. The most common select laboratory abnormalities that worsened from baseline in $\geq 20\%$ of patients who received asciminib were lymphocyte count decreased, leukocyte count decreased, platelet count decreased, neutrophil count decreased, calcium corrected decreased, lipase increased, cholesterol increased, uric acid increased, alanine aminotransferase (ALT) increased, alkaline phosphatase (ALP) increased, hemoglobin decreased, and triglycerides increased.

The FDA approach toward approval in CML in CP the newly diagnosed population is to grant accelerated approval when at least 48 weeks of efficacy and safety data is available. For conversion to regular approval, the FDA requires 5 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 J12301 at 48 weeks. The key secondary endpoints of the study are MMR at 96 weeks in all treated patients and in the imatinib stratum. The study will continue for at least 5 years. Therefore, the data from J12301 supports accelerated approval in patients with newly diagnosed CML in CP. A PMR will be issued to obtain an interim study report at 96 weeks and results with at least 5 years of follow up.

The recommendation for regular approval for patients with previously treated CML in CP is based on the established efficacy in patients treated with two or more prior TKIs and supported by patients treated with one prior TKI in study CABL001AUS08 (referred to as study AUS08), a single arm study of asciminib treatment in patients treated as first or second line (2L) therapy, and extrapolation by PK/PD modeling.

The interim analysis of AUS08 included a prespecified assessment of MMR at 6 months in patients evaluable for efficacy at that timepoint. At the interim analysis, 71 patients were enrolled in the 2L cohort, and 28 patients were evaluable for efficacy at 6 months having completed the efficacy assessment at that timepoint or discontinued prior to the timepoint. The MMR rate at 6 months was 43% (12/28; 95% CI: 24, 63). In the patients treated with asciminib as 2L treatment in study AUS08, the MMR rate at 6 months was intermediate to the MMR rate observed in the 1L cohort in study J12301 and the 3L+ cohort in study A2301, as generally expected for this population. Safety in 71 patients treated with asciminib as second line therapy was generally consistent with that observed in other lines of therapy.

The durability of MMR responses and safety in this population supports regular approval for the treatment of patients with previously treated

Scemblix (asciminib)

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 three 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.

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. • In the US, it is estimated that approximately 9280 new cases of CML will be diagnosed and about 1,280 people will die of the malignancy during 2023	CML in chronic phase is a rare, but serious and life-threatening disease.
Current Treatment Options	• Five other 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. • First-line treatment should be based on risk scores, preexisting comorbidities and concomitant medications of the patients. • 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	There is a need for additional effective therapies for patients with CML in CP in newly diagnosed patients and those previously treated.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with two or more prior TKIs or those with T315I-positive CML.	
Benefit	- Study CABL001J12301 (ASC4FIRST) was a randomized (1:1), open-label, active controlled trial of asciminib monotherapy versus IS-TKI, stratified by ELTS risk score and pre-randomization TKI selection (imatinib or 2G TKI). The primary endpoints were MMR at 48 weeks in all patients and in the imatinib stratum. MMR at 48 weeks was 68% (95% CI: 61, 74) in the asciminib arm compared 49% (95% CI: 42, 56) in the IS-TKI arm with a treatment difference of 19% (95% CI: 10, 28 and two-sided p value of <0.001, stratified. In the imatinib stratum, MMR at 48 weeks was 69% (95% CI: 59, 78) in the asciminib arm compared to 40% (95% CI: 31, 50) in the imatinib arm with a treatment difference of 30% (95% CI: 17, 42; two-sided p value of <0.001, stratified. Median time to MMR in patients receiving asciminib was 24 weeks (95% CI: 24 to 25 weeks) and in patients receiving IS-TKIs was 36 weeks (95% CI: 36 to 49 weeks). - Study CABL001AUS08 was a non-randomized, open-label, dose escalation, study of asciminib monotherapy in patients with CML in CP previously treated with one prior TKI. The efficacy population included 28 patients who were evaluable for efficacy at 6 months or discontinued prior to 6 months. The efficacy endpoints of the study included molecular responses at scheduled timepoints. The MMR	The endpoint of MMR at 48 weeks in all patients and in the imatinib stratum support effectiveness in patients with newly diagnosed CML-CP. Asciminib shows a statistically significant and clinically meaningful improvement in MMR at 48 weeks compared to IS-TKI and in the imatinib stratum in this population. The magnitude and duration of major molecular response are clinically meaningful. The endpoint of MMR at 6 months in patients with one prior TKI treatment with the MMR at 96 weeks in patients with two or more prior TKI treatment supports the effectiveness of asciminib for previously treated CML-CP.

Scemblix (asciminib)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	rate at 6 months was 43% (12/28; 95% CI: 24, 63).	
Risk and Risk Management	• In the randomized study of patients with newly diagnosed CML in CP, patients were treated with 80 mg daily asciminib or IS-TKI at the approved dose. • In 200 patients, the most common ($\geq 20\%$) adverse reaction in patients who received asciminib was musculoskeletal pain. • Serious adverse reactions occurred in 11% of patients who received asciminib. Serious adverse reactions in $\geq 1\%$ included pancreatitis (1%), and musculoskeletal pain (1%). No deaths occurred within 30 days after the last dose of the asciminib. • Safety in 71 patients treated with asciminib as second line therapy was generally consistent with that observed in other lines of therapy. • In the pooled safety population of 556 patients, the most common ($\geq 20\%$) adverse reactions in patients who received SCEMBLIX were musculoskeletal pain, rash, fatigue, upper respiratory tract infection, headache, abdominal pain, and diarrhea. • Common select laboratory abnormalities include myelosuppression (decreased lymphocyte count, leukocyte count, platelet count, neutrophil count, and hemoglobin), elevated pancreatic enzymes (lipase and amylase increased), cholesterol increased, and elevated liver enzymes (ALT increased, alkaline phosphatase increased, and AST increased), triglycerides increased, and creatine kinase increased.	The safety profile of asciminib treatment at 80 mg daily for patients with newly diagnosed CML in CP is tolerable and manageable. Safety observed in patients with one prior TKI treatment is consistent with that observed in later lines of treatment. Long-term safety information is needed in this population since asciminib is intended for prolonged use and there may be potential for cumulative toxicity. Risks overall are sufficiently addressed through warnings and precautions in the United States Prescribing Information.

Scemblix (asciminib)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Warnings and precautions include myelosuppression, pancreatic toxicity, hypertension, hypersensitivity, cardiovascular toxicity, and embryo-fetal toxicity, and were updated to include the pooled safety population.	

Scemblix (asciminib)

1.4. Patient Experience Data

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

☐	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)	8.2.6
		☐ Observer reported outcome (ObsRO)	
		☐ Clinician reported outcome (ClinRO)	
		☐ Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify)	
☐	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 myeloproliferative disorder of transformed, hematopoietic progenitor cells characterized by overproduction of immature myeloid cells and mature granulocytes in the spleen, bone marrow, and peripheral blood. The hallmark of CML is the Philadelphia (Ph) chromosome found in up to 95% of patients ([Seong et al 1999](#)). The Ph chromosome results from a reciprocal translocation t(9;22)(q34;q11) which creates a chimeric protein (BCR::ABL1) promoting aberrant cell growth and replication through downstream signaling pathways such as RAS, RAF, JUN kinase, MYC, and STAT ([Jabbour, Kantarjian 2022](#)).

With a constant worldwide incidence of 1-2 new cases/100,000 per year, the prevalence of CML is steadily increasing due to improved long-term outcomes with tyrosine kinase inhibitor (TKI) treatment ([Senapati et al 2023](#)) ([Jabbour, Kantarjian 2022](#), [ELN 2020](#)). CML mainly affects adult patients with a median age at diagnosis of 57 to 66 years. In the US, it is estimated that approximately 9280 new cases of CML will be diagnosed and about 1,280 people will die of the malignancy during 2023 ([SEER 2024](#), [NCCN 2024](#)).

Clinically, most patients are diagnosed in the chronic phase (CP), characterized by anemia, splenomegaly, and leukocytosis with generally few constitutional symptoms like fatigue, weight loss, malaise, early satiety, and abdominal fullness. Without treatment for around 20% of the patients, the disease may transition into blast phase (BP) ([Faderl et al 1999](#)).

The response to treatment in CML is monitored based on hematological, cytogenetic, and mainly molecular levels of BCR::ABL1 by RQ-PCR test. Molecular responses expressed in % (standardized to an international scale (IS) as the ratio of BCR::ABL1 transcripts to ABL1 transcripts) provide an objective measure of efficacy for guiding treatment and monitoring patients with CML ([Press 2010](#), [Cross et al 2012](#), [Greiner et al 2020](#)). A BCR::ABL1 IS level of > 1% at 12 months is considered a failure of treatment, whereas a BCR::ABL1 IS level of $\leq 0.1\%$ (major molecular response; MMR) at 12 months is considered an optimal response to treatment ([ELN 2020](#), [NCCN 2024](#)).

The FDA's Assessment:

FDA agrees with the Applicant's assessment about the definition, incidence, clinical features of CML, and that response is monitored based on mainly molecular levels of BCR/ABL1 by RQ-PCR. Achievement of major molecular response (MMR) defined as BCR/ABL1 $\leq 0.1\%$ at 12 months is considered optimal response to treatment.

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2.2. Analysis of Current Treatment Options

Table 1 Available Therapies for the Proposed Patient Population

Drug (Dosage) Relevant Indication for CML	Study Design Number of Prior TKIs (CP-CML) No. of participants	Primary Efficacy Results	Warnings and Precautions	Most Common ADRs (of Any Grade)
Imatinib (CML-CP: 400 mg QD) Newly diagnosed adult patients with Ph+ CML-CP	OL, MC, R, Ph3 study No prior TKI N=1106 (randomized 1:1 to imatinib or IFN+Cytarabine)	PFS rate at 84 mo (95% CI): Imatinib 81.2% (78, 85) IFN 60.6% (56, 65) (p<0.001, log-rank test) MMR in subset of patients with CCyR by 12 mo or later (N=333): ¹ Imatinib 59% at 12 mo and 72% at 24 mo.	Edema and severe fluid retention, hematologic toxicity, severe CHF, left ventricular dysfunction, hepatotoxicity, hemorrhage, GI disorders, hypereosinophilic cardiac toxicity, dermatologic toxicities, hypothyroidism, embryofetal toxicity, growth retardation (children and adolescents), TLS, impairments related to driving and using machinery, renal toxicity	≥30%: edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, and abdominal pain
Patients with Ph+ CML in CP, AP, or in BC after failure of IFN therapy (600 mg QD)	Three OL, single-arm Ph2 studies CP after failure of interferon: n=532 AP: n=235 BC: n=260	Complete major cytogenic response: CP: 39%; AP: 16%; BC: 2%		
Nilotinib (1L: 300 mg BID; 2L: 400 mg BID) Adult patients with newly diagnosed Ph+ CML-CP	1L: OL, MC, R, Ph3 study (ENESTnd; NCT00471497) No prior TKI N=846 (randomized 1:1:1 to nilotinib 300 mg BID (n=282), nilotinib 400 mg BID (n=281), or imatinib 400 mg QD (n=283))	1L: MMR at 12 mo (95% CI): Nilotinib 300 mg BID 44% (38.4, 50.3) Imatinib 400 mg QD: 22% (17.6, 27.6) (p<0.0001)	QT prolongation, sudden death, myelosuppression, cardiac and arterial vascular occlusive events, pancreatitis and elevated serum lipase, hepatotoxicity, electrolyte	Non-hematologic ADRs (≥20%): rash, pruritus, nausea, diarrhea, constipation, vomiting, headache, fatigue, pyrexia, arthralgia, pain in extremity, cough,

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Drug (Dosage) Relevant Indication for CML	Study Design Number of Prior TKIs (CP-CML) No. of participants	Primary Efficacy Results	Warnings and Precautions	Most Common ADRs (of Any Grade)
Adult patients with CP and AP Ph+ CML with resistance or intolerance to prior therapy including imatinib	OL, uncontrolled, MC, Ph2 study (NCT00109707, EUDRACT: 2004-001483-51) 1 prior TKI (100% imatinib) (imatinib-resistant or -intolerant CML) N=321	Unconfirmed MCyR : 51% (95% CI: 46 , 57)	abnormalities, TLS, hemorrhage, fluid retention, effects on growth and development (pediatrics), total gastrectomy, embryofetal toxicity, lactose, monitoring laboratory tests, , monitoring of BCR-ABL transcript levels.	nasopharyngitis, and night sweats Hematologic ADRs: myelosuppression, thrombocytopenia, neutropenia, and anemia
Dasatinib (100 mg QD) Adult patients with newly diagnosed Ph+ CML-CP	1L: OL, MC, R, Ph3 study (DASISION; NCT00481247) No prior TKI N= 519 (dasatinib 100 mg QD (n=259) or imatinib 400 mg QD (n=260)	1L: cCCyR within 12 mo (95% CI): Dasatinib 100 mg QD: 76.8% (71.2, 81.8) Imatinib 400 mg QD: 66.2% (60.1, 71.9) (p=0.007) MMR at 12 mo (95% CI): ¹ Dasatinib 100 mg QD: 52.1% (45.9, 58.3) Imatinib 400 mg QD: 33.8% (28.1, 39.9) (p<0.0001)	Myelosuppression and bleeding events, fluid retention, cardiovascular toxicity, pulmonary arterial hypertension, QT prolongation, severe dermatologic reactions, TLS, embryofetal toxicity, effects on growth and development (pediatrics), hepatotoxicity	≥15%: myelosuppression, fluid retention events, diarrhea, headache, skin rash, hemorrhage, dyspnea, fatigue, nausea, and musculoskeletal pain
Adult patients with CP, AP, or myeloid or lymphoid BP Ph+ CML with resistance or intolerance to prior therapy including imatinib	Phase 3, OL, R study (NCT00123474, EUDRACT: 2005-001294-99) 1 prior TKI (100% imatinib) N=670	MCyR at 6 mo: Dasatinib 100 mg or 140 mg QD (n=247): 51.8% (95% CI: 45.4, 58.2) Dasatinib 50 mg or 70 mg BID (n=251): 49.0% (95% CI: 42.7, 55.4)		

Version date: February 9, 2024 (ALL NDA/ BLA reviews)

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

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Drug (Dosage) Relevant Indication for CML	Study Design Number of Prior TKIs (CP-CML) No. of participants	Primary Efficacy Results	Warnings and Precautions	Most Common ADRs (of Any Grade)
		MMR 2 years: Dasatinib 100 mg QD: 34%		
Bosutinib (1L: 400 mg QD; 2L: 500 mg QD) Adult patients with newly diagnosed Ph+ CML-CP	1L: 2-arm, OL, MC, Ph3, R, superiority study (BFORE; NCT02130557) No prior TKI N=536 (268 in each arm; bosutinib 400 mg QD vs. imatinib 400 mg QD)	1L: MMR at 12 mo (95% CI): Bosutinib 400 mg QD: 47% (41, 53) Imatinib 400 mg QD: 36% (30, 42) OR=1.57 (95% CI: 1.10, 2.22). (2-sided p- value=0.0200)	GI toxicity, myelosuppression, hepatic toxicity, cardiovascular toxicity, fluid retention, renal toxicity, embryofetal toxicity	≥20%: diarrhea, abdominal pain, vomiting, nausea, rash, fatigue, hepatic dysfunction, headache, pyrexia, decreased appetite, RTI, and constipation
Adult patients with CP, AP, and BP Ph+ CML with resistance or intolerance to prior therapy	Single-arm, OL, MC, Ph1/2 study (NCT00261846) 1 prior TKI (imatinib only): N=262 ≥2 TKIs (imatinib and at least 1 additional TKI): N=112	MCyR at Wk 24 (95% CI): 1 prior TKI: 40.1% (34.1, 46.3) MCyR by Wk 24 (95% CI): ≥2 TKIs: 25.9% (18.1, 35.0)		

¹ Not the primary endpoint

Sources: Imatinib: [Gleevec USPI \(2022\)](#), [Glivec SmPC \(2023\)](#) Nilotinib: <https://www.clinicaltrialsregister.eu/ctr-search/search?query=2004-001483-51>, [Tasigna USPI \(2021\)](#), [Tasigna SmPC \(2023\)](#);
Dasatinib:<https://www.clinicaltrialsregister.eu/ctr-search/trial/2005-001294-99/results>, [NCT00123474 \(ClinicalTrials.gov\)](#), [Sprycel USPI \(2023\)](#), [Sprycel SmPC \(2022\)](#); Bosutinib: [Bosulif USPI \(2023\)](#), [Bosulif SmPC \(2023\)](#)

The Applicant's Position:

The introduction of the TKI imatinib in 2001, the first drug targeting an oncogenic mutation, revolutionized the treatment of patients with CML. This was followed by the approval of several second-generation (2G) adenosine triphosphate (ATP)-binding site TKIs including dasatinib, nilotinib, bosutinib ([Sweet et al 2023](#)).

TKI in current use: in routine medical practice, these ATP-binding TKIs are used interchangeably in all lines of treatment of CML-CP irrespective of the approved line of treatment. Although TKI treatment has improved the survival rates for patients with CML, and patients with optimal treatment response may expect near-normal life expectancy ([García-Gutiérrez](#), [Hernández-](#)

Scemblix (asciminib)

[Boluda 2019](#) and [Jabbour, Kantarjian 2022](#)), the requirement of chronic therapy for CML has underlined the importance of treatment selection for newly-diagnosed patients. The primary aims of treatment in this population are to achieve early optimal responses to prevent disease progression, maintain quality of life, sometimes to achieve TFR in selected patients, and reduce the likelihood of serious and irreversible side effects. It is also crucial to choose the appropriate TKI option for second-line (2L) treatment for those who develop resistance or intolerance to 1L treatment with similar considerations ([Cortes, Lang 2021](#)).

The personalized approach to selection of treatment for CML is reflected in international CML treatment guidelines ([ELN 2020, NCCN 2024](#)). There is currently no single standard of care for patients with newly diagnosed CML-CP ([Table 1](#)). Approximately 50% of newly-diagnosed patients in clinical practice are treated with imatinib and the remaining 50% with one of the 2G TKIs (internal market research conducted via (b) (4) and IQVIA in the US and EU in June 2023; [Campbell et al 2019](#)).

The selection of the 1L treatment option is based on individual patient need and preference, disease characteristics (Sokal, Hasford, EUTOS or ELTS), pre-existing comorbidities, and concomitant medications, as well as the individual treatment goal ([Saglio, Jabbour 2018, NCCN 2024, ELN 2020](#)). In elderly patients or newly-diagnosed patients with low-risk score, imatinib is more frequently selected. From an efficacy perspective, imatinib is less potent than 2G TKIs, delivering lower cytogenetic and molecular response rates (e.g. MMR rates at 12 months of 22% to 37%) in many comparative studies against 2G TKIs ([Saglio et al 2010, Kantarjian et al 2010, Hochhaus et al 2016, Cortes, Kantarjian 2016, Cortes 2018](#)). The 2G TKIs are more frequently used in younger patients, in patients with high-risk score, and in an attempt to attain TFR. However, the use of 2G TKIs is often limited by their serious, and sometimes irreversible, adverse events, including severe organ dysfunction ([Hochhaus et al 2016, ELN 2020, NCCN 2024](#)). Similar to that in 1L, selection of the TKI to be used in 2L also needs to be based on a number of considerations including patient and disease characteristics, comorbidities and prior therapy safety profile (history of intolerance and/or treatment related complications with 1L treatment). For patients treated with imatinib in 1L a 2G TKI is used in 2L, while for patients treated with a 2G TKI in 1L an alternate 2G TKI is recommended ([NCCN 2024](#)). However, on exhaustion of 2G TKI options or in case of comorbidities precluding the use of 2G TKIs, imatinib use in later lines is also seen in medical practice ([Mauro et al 2023](#)). In patients with no BCR::ABL1 kinase domain mutations, there is no clear recommendation for any particular TKI in 2L. Treatment sequencing in CML is very much personalized to the patient, and either imatinib or any of the 2G TKIs are used irrespective of line of treatment.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that patients with newly diagnosed chronic phase (CP)-CML are treated with imatinib or one of the second-generation tyrosine kinase inhibitors (TKIs) (dasatinib, nilotinib, or bosutinib). First-line (1L) treatment should be based on risk scores (Sokal, Hasford, EUTOS or ELTS), preexisting comorbidities and concomitant medications of the

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patients. The treatment of choice is based on similar criteria in second-line (2L) treatment.

FDA agrees with the Applicant's assessment of safety and efficacy of currently approved TKIs for patients with newly diagnosed CP-CML based on the prescribing information for the approved TKIs and the published literature.

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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant’s Position:

Asciminib (Scemblix®, ABL001) was initially approved on 29-Oct-2021 for the treatment of adult patients with Ph+ CML in CP, previously treated with two or more TKIs under accelerated approval, and for the treatment of adult patients with Ph+ CML in CP harboring the T315I mutation under regular approval. Regular approval for the treatment of adult patients with Ph+ CML-CP, previously treated with two or more TKIs was subsequently granted on 22-Oct-2022.

The purpose of this current submission is to seek approval for asciminib for the treatment of adult patients with newly-diagnosed or previously-treated Ph+ CML-CP.

The FDA’s Assessment:

FDA confirms the Applicant’s assessment. The current approval for asciminib is for CML-CP previously treated with two or more tyrosine kinase inhibitors (TKIs), known as third line (3L) treatment. The proposed indication for the treatment of patients with newly diagnosed or previously treated CML-CP would include second line (2L) treatment.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant’s Position:

A summary of key interactions with the FDA regarding asciminib development relevant to this supplemental NDA is provided in [Table 2](#).

Table 2 Key FDA Interactions

Type of Interaction	Date	Purpose
Pre-Phase III Type B Meeting	22-Jan-2021	Discuss development of asciminib as a single agent for patients with newly diagnosed Ph+ CML-CP
Pre-sNDA Type C meeting	26-Jun-2023	Obtain agreement regarding the planned sNDA package and the proposed indication of newly-diagnosed and previously-treated patients with Ph+ CML-CP. The rationale for applying for a broader indication than the population studied in controlled studies was discussed.
Type C Meeting	07-Dec-2023	(b) (4)

NDA Multi-disciplinary Review and Evaluation sNDA 215358, S-008

Scemblix (asciminib)

Type of Interaction	Date	Purpose
Preliminary BTDA Advice teleconference (J12301)	21-Feb-2024	Obtain agreement that the primary analysis results of Study J12301 are appropriate to support a BTDA request for asciminib in newly-diagnosed Ph+ CML-CP.
Pre-sNDA Type B Meeting	04-Mar-2024	Obtain agreement that the primary analysis results of Study J12301 were considered adequate to support the sNDA submission and agreed with the proposed plan for inclusion of clinical data from Study AUS08 as part of the sNDA. FDA also agreed with the proposed RTOR and Project Orbis plans.
BTDA granted	07-May-2024	BTDA granted for the treatment of adult patients with newly-diagnosed Ph+ CML-CP.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of key FDA interactions regarding development of asciminib in CML. This sNDA submission was administratively split into 2 sNDAs, S-008 for newly diagnosed CML in CP and S-009 for previously treated CML in CP (inclusive of 2L and later).

Scemblix (asciminib)

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 for clinical sites. In Study CABL001J12301 (briefly referred to as J12301) 8 (4%) patients in the asciminib arm and 10 (4.9%) patients in the investigator-selected TKI (IS-TKI) arm were enrolled in the US. Inspection of 2 international clinical sites was requested because there was insufficient domestic data and most experience with asciminib has been at ex-US sites. Therefore, it was planned to include ex-US sites in the OSI inspections to verify the quality of conduct of the study. OSI inspected two foreign clinical investigators (one in Canada, site #1002; one in Czech Republic, site #2080) and the Applicant. These sites were chosen because they contained sufficient numbers of patients in safety and efficacy populations, and they had outliers in safety and efficacy outcomes. OSI review team concluded that study CABL001J12301 appeared to have been conducted adequately and the study data from the inspected clinical investigator sites were considered acceptable.

4.2. Product Quality

The Applicant did not submit any new product quality information. Asciminib drug product is provided as film-coated tablets containing 20 mg, 40 mg, or 100 mg of asciminib per tablet.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable. Response was monitored based on molecular levels of BCR/ABL1 by RQ-PCR at an Applicant-designated laboratory.

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5 Nonclinical Pharmacology/Toxicology

The Applicant's Position:

No new information is provided in the current application for nonclinical pharmacology/toxicology.

5.1. Executive Summary

The FDA concurs that no new nonclinical pharmacology/toxicology data were submitted to the current efficacy supplement for NDA 215358 (S-008). The pharmacology/toxicology data to support the approval and labeling of asciminib were previously reviewed in the initial NDA submission. The 2-year carcinogenicity study of asciminib in rats was reviewed and the USPI was updated under the previous supplement to NDA 215358 (S-007) approved on August 7, 2024.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

Reference is made to NDA 215358/S-007 prior approval supplement containing updates to the proposed USPI, which include a nonclinical safety update of the 2-year rat carcinogenicity study. The prior approval supplement is currently under review, with a user fee goal date of 06-Dec-2024.

The FDA's Assessment:

The FDA has completed the review of the 2-year carcinogenicity study in rats and updated the USPI; NDA 215358/S-007 was approved on August 7, 2024.

X

X

Primary Reviewer

Supervisor

Scemblix (asciminib)

6 Clinical Pharmacology

6.1. Executive Summary

The FDA’s Assessment:

SCEMBLIX (asciminib) is a kinase inhibitor that is currently approved 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 Ph+ CML in CP with the T315I mutation. The recommended dosages are 80 mg once daily (QD) or 40 mg twice daily (BID) for patients with Ph+ CML-CP and 200 mg BID for patients with Ph+ CML in CP harboring the T315I mutation. Asciminib should be taken orally and avoid food for at least 2 hours before and 1 hour after taking SCEMBLIX.

The Applicant submitted this efficacy supplement (S008) to support the application for the use of asciminib monotherapy in the treatment of adult patients with newly diagnosed or previously treated Ph+ CML-CP. Specifically, the Applicant is seeking the approval of an indication in a broad population of newly diagnosed or previously treated patients, regardless of the number of prior TKIs, including those in second line (2L) of treatment.

The clinical pharmacology sections of this supplement were supported by PK data from patients with newly diagnosed Ph+ CML-CP from Study J12301, population PK and exposure-response analyses, and PK-pharmacogenomic analyses. The clinical pharmacology review focused on the appropriateness of the proposed dosages of 80 mg QD and 40 mg BID for the first line (1L) indication and the PK/PD modeling to support extrapolation to the 2L indication. The potential for genetic variants in UGT2B7 and UGT2B17 to impact the PK of asciminib was also evaluated.

Recommendations:

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

Review issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from: Newly diagnosed Ph+ CML-CP: Study J12301 demonstrated statistically significant meaningful improvements in major molecular response (MMR)

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	at 48 weeks for asciminib 80 mg QD vs. investigator-selected TKIs in patients with newly diagnosed Ph+ CML-CP. 2L Ph+ CML-CP: - Study CABL001AUS08 (AUS08), ongoing, Phase 2, single arm dose escalation study of asciminib in patients with 2L Ph+ CP-CML. In the 14 patients with 6-month follow-up, MMR was observed in 8/14 patients (57.1%) administered asciminib 80 mg QD. - Supportive PK/PD modeling: PK/PD modeling was used to support extrapolation to the 2L setting based on asciminib 1L and 3L+ data as well as borrowing the difference between the 1L and 2L effect on the model parameters from the nilotinib exposure-efficacy analysis and applying the differences to simulate the time-course of <i>BCR::ABL1</i> transcript levels. The predicted MMR rates of asciminib 80 mg QD or 40 mg BID in the 2L setting ranged from 54 – 63% at Week 48 and 66 – 74% at Week 96, which fell within MMR rates for the 1L and 3L settings and were generally consistent with the observed MMR of 57% at the 6-month follow-up.
General dosing instructions	The proposed dosages of 40 mg BID or 80 mg QD are acceptable for patients with newly diagnosed or previously treated Ph+ CML-CP per the following rationale: - The observed efficacy/safety results from pivotal Study J12301 supports 80 mg QD in newly diagnosed Ph+ CML-CP. - The observed efficacy/safety results from supportive Study AUS08 supports 80 mg QD in 2L Ph+ CMLCP. - Original approval for the indication of previously treated with two or more TKIs in patients with Ph+ CML-CP based on data from the pivotal Study A2301.

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	The recommended dosages are 80 mg QD or 40 mg BID. - Population PK simulation shows similar PK exposures between 80 mg QD and 40 mg BID dosing regimens. Similar efficacy is expected for 40 mg BID (e.g., similar AUC, lower C_{max} and higher C_{min}). - The supportive PK/PD modeling predicted MMR rates at 48 and 96 weeks that fell within those for the 1L (Study J12301) and 3L (Study A2301) settings and were generally consistent with the observed preliminary MMR from Study AUS08 in the 2L setting.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The proposed dosing is the same as the current recommendations in the approved USPI. Exploratory analysis suggests that polymorphic variants in <i>UGT2B7</i> and <i>UGT2B17</i> do not have a clinically significant impact on the PK of asciminib and no dosage adjustment is needed.
Labeling	There are no additional updates in clinical pharmacology sections.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

An integrated assessment of PK data from clinical studies, dedicated clinical pharmacology studies in healthy subjects and studies in participants with Ph+ CML-CP along with the results of pharmacometric analyses providing in-depth interpretation of PK and PD data of asciminib were presented in the original SCP. The original SCP consisted of basic PK properties of asciminib, PBPK modeling, population PK (PopPK) analyses (using data from participants with Ph+ CML-CP/AP in Study X2101 and participants with 3L+ Ph+ CML-CP in Study A2301), and exposure-efficacy and exposure-safety relationships including exposure-QTc relationships in participants with CML.

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Additional asciminib PK data in participants with Ph+ CML-CP from Study J12301 are provided in the current submission. Furthermore, the PopPK analyses were updated to include data from participants with CML-BP and Ph+ ALL in Study X2101, as well as data from 3 additional studies: Study J12301, the Phase I hepatic impairment study CABL001A2103, and the Phase I renal impairment study CABL001A2105. Exposure-response analyses including pooled data of participants with CML from Studies J12301, A2301, and X2101 were also provided.

The FDA's Assessment:

The PK data from patients with newly diagnosed Ph+ CML-CP from Study J12301 were generally consistent with previous characterization of the pharmacology and clinical pharmacokinetics of asciminib. The updated population PK modeling in the current submission did not identify any additional significant covariates on the PK of asciminib. See Appendix 19.4.2 for details.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

The recommended dose of asciminib is a total daily dose of 80 mg, taken either as 80 mg QD or 40 mg BID which was approved by FDA in patients with Ph+ CML-CP, previously treated with two or more TKIs ([Scemblix USPI 2021](#)). The proposed dose of 80 mg QD for participants with newly-diagnosed Ph+ CML-CP in Study J12301 was based on clinical experience in participants with Ph+ CML-CP in Studies X2101 (multiple doses including 80 mg QD) and A2301 (40 mg BID, equivalent to a total daily dose of 80 mg) and the PK/PD modeling based exposure-response and exposure-safety analyses [CO-Section 4.1].

Data from Study J12301 confirmed that the benefit/risk profile of 80 mg QD in 1L is not different from that of 40 mg BID assessed in 3L+ in Study A2301. In addition, the updated PK/PD modeling further confirmed that the benefit/risk for 80 mg QD is comparable to that seen with the 40 mg BID dose, and hence asciminib 80 mg QD and 40 mg BID can be used interchangeably [CO-Section 4.1].

The FDA's Assessment:

The FDA agrees with the Applicant's proposed dosages of 40 mg BID or 80 mg QD for patients with newly diagnosed or previously treated Ph+ CML-CP based on the following rationale:

- Results of pivotal Study J12301 demonstrated favorable benefit/risk profile of asciminib 80 mg QD in patients with newly diagnosed Ph+ CML-CP as compared to investigator-selected TKIs arm and imatinib stratum.
- The observed efficacy/safety results from supportive Study AUS08 supports 80 mg QD in 2L Ph+ CML-CP.

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- Original approval for the indication of previously treated with two or more TKIs in patients with Ph+ CML-CP based on data from Study A2301. The recommended dosages are 80 mg QD or 40 mg BID.
- Population PK simulation shows similar PK exposures between 80 mg QD and 40 mg BID dosing regimens (Table 35). Similar efficacy is expected for 40 mg BID (e.g., similar AUC, lower C_{max} and higher C_{min}).
- PK/PD modeling was used to support extrapolation to the 2L setting based on asciminib 1L (n=197 from Study J12301) and 3L+ (n=150 from Study A2301) data as well as borrowing the difference between the 1L and 2L effect on the model parameters from the nilotinib exposure-efficacy analysis and applying the differences to simulate the time-course of BCR::ABL1 transcript levels. In summary, the PK/PD model was a 3-compartment model representing quiescent leukemic stem cells (q), proliferating bone marrow cells (p), and resistant cells (r) developed using data from 430 patients with Ph+ CML-CP to describe the time-course of BCR::ABL1 transcript levels. Drug kill of the p cells by asciminib was characterized by an E_{max} model. The potential influences of the number of previous TKI treatments (i.e., line of treatment) and patient's baseline and disease characteristics (including ELTS risk group) were investigated. The extrapolation of longitudinal BCR::ABL1 transcript levels to asciminib in the 2L setting utilized the difference in the p, r and E_{max} parameters between nilotinib as first and second line treatments. The predicted MMR rates of asciminib 80 mg QD or 40 mg BID in the 2L setting ranged from 54 – 63% at Week 48 and 66 – 74% at Week 96, which fell within MMR rates for the 1L and 3L settings and were generally consistent with the observed MMR of 57% at the 6-month follow-up (Week 48 MMR not reached yet).

See Appendix 19.4.2 and 19.4.3 for details of the population PK and E-R analyses.

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, ethnicity), drug-drug interactions with asciminib as a victim or as a perpetrator, or in special populations (hepatic or renal impairment) [SCP-Section 3.2, Section 3.3, Section 5.1.2].

The FDA's Assessment:

The updated population PK modeling in the current submission did not identify any additional significant covariates on the PK of asciminib. There are no additional recommendations for therapeutic individualization of asciminib for the proposed indication.

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6.2.2.3. Outstanding Issues

The Applicant's Position:

None

The FDA's Assessment:

There are no outstanding issues at this time.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General characteristics of asciminib PK in terms of bioavailability, absorption, food effect, dose proportionality, distribution, metabolism, and excretion were detailed in the original submission. No new information is provided in support of the current application.

The new PK data of asciminib in Study J12301 is in line with the overall PK profile of asciminib previously reported in the original submission. Data showed that the plasma concentrations of asciminib increased rapidly after oral administration of asciminib 80 mg QD with a median Tmax of 2.0 hr. The geo-mean of peak plasma concentration of asciminib (Cmax) was 1470 ng/mL (CV% geo-mean: 38.2%), geo-mean of AUClast was 8590 ng*hr/mL (CV% geo-mean: 42.2%; note: Tlast was 12 hr post-dose). The trough concentrations (Ctrough) of asciminib were similar throughout the visits (geo-mean range: 160-182 ng/mL) [CO-Section 3.0].

Using the updated final PopPK model, simulated PK metrics for the 40 mg BID and 80 mg QD dosing regimens were obtained. Overall, the simulated mean AUC0-24h values were comparable between the two regimens, while the mean Cmax and Cmin at steady state of 80 mg QD were 1.62-fold and 0.71-fold of that of 40 mg BID, respectively. These simulated metrics based on the updated dataset were consistent with the results of the simulation carried out in the original PopPK analysis (Table 35, [CO-Section 3.0]).

Additionally, based on the new PopPK analysis, no correlation between clearance and number of prior TKIs (irrespective of prior TKI use and/or no prior TKI use) was observed, thus suggesting that asciminib PK is consistent across lines of treatment [CO-Section 3.1.1].

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of the general pharmacology and pharmacokinetic characteristics of asciminib.

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6.3.2. Clinical Pharmacology Questions

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

Data

The Applicant's Position:

Yes. Results from Studies J12301, A2301, and X2101 provide evidence of positive benefit-risk and support the efficacy claim of asciminib 80 mg total daily dose in adult participants with Ph+ CML-CP. While the clinical pharmacology evaluation does not include a direct assessment of benefit-risk, the exposure-response models provide the following exposure-efficacy and safety relationships.

In participants with newly diagnosed Ph+ CML-CP, a predicted 70% Week-48 MMR rate is achieved based on the participant's dosing history in Study J12301, and an enhanced MMR rate of 75% is predicted in uninterrupted dosing situation. Higher MMR rates are achieved when patients maintained uninterrupted dosing; dose interruptions are predicted to lead to lower MMR rates, highlighting the importance of treatment compliance. The asciminib 80 mg QD and 40 mg BID regimens are predicted to result in comparable MMR rates across treatment lines and timepoints [Exposure-efficacy report-Section 7].

The model-based analysis that characterized the longitudinal BCR::ABL1 by treatment lines (1L, 2L or 3L+) is suitable for extrapolation across lines of asciminib treatment in CML-CP. In the 2L, the total daily dose of 80 mg administered either as once-daily (80 mg QD) or twice-daily (40 mg BID) is predicted to achieve a Week-48 MMR rate of 54-63% and a Week-96 MMR rate of 66-74% [Exposure-efficacy report-Section 7] ([Table 38](#)). This predicted MMR rate is in alignment with the preliminary emerging data available from the ongoing Study AUS08 in a cohort of participants with 2L Ph+ CML-CP ([Section 8.1.4](#))

The probability of occurrence of all safety events was lower for newly-diagnosed than for pretreated participants with Ph+ CML. The higher event probability in pretreated participants is expected, given the persistent side effects of prior TKIs, increased incidence of cross-intolerance, and evolution of their disease characteristics including resistant mutations due to prolonged exposure to other TKIs [Exposure-safety report-Section 9].

Over the range of exposure for 1L participants, the probability of grade ≥ 3 lipase increase was low and ranged from 5.8-11.2%, indicating a slight positive relationship between asciminib exposure and probability of grade ≥ 3 lipase increase. The probability of occurrence of all other safety events is unlikely to increase with increased exposure of asciminib. Comparable exposure was reached with the 40 mg BID and 80 mg QD asciminib doses, and no association was observed between exposure and most safety events, indicating the interchangeability of these two dosing regimens with respect to their safety profile [Exposure-safety report-Section 9].

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The FDA's Assessment:

FDA generally agrees with the Applicant that the clinical pharmacology program provides supportive evidence of the effectiveness of asciminib in the proposed patient population. 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 anti-leukemic activity of single-agent asciminib was demonstrated irrespective of dose level (i.e. across total daily doses of 20 to 400 mg) and prior lines of therapy received ([Table 38](#)) [PopPK report-Table 5-1].

The FDA's Assessment:

FDA agrees with the Applicant that the proposed dosages of 80 mg QD or 40 mg BID 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.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

The Applicant's Position:

Based on the assessment of intrinsic factors, no dose adjustment or change in regimen is required based on demographics (age, gender, weight, race, ethnicity), genotypes (UGT2B7 and UGT2B17 genotypes), or in special populations (i.e. hepatic and renal impairment) [SCP-Section 5.1.2].

The FDA's Assessment:

FDA agrees with the Applicant's assessment that no additional or different dosage adjustment or management strategy is required based on intrinsic factors.

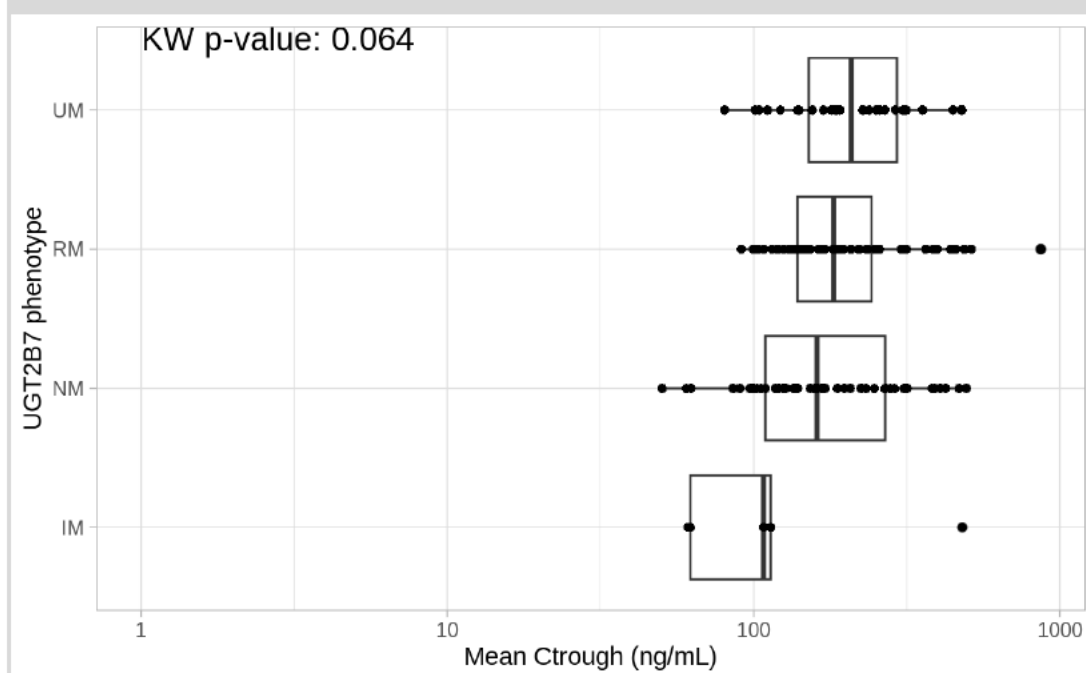
UGT2B7 and UGT2B17 genotype status and asciminib PK

Asciminib is mainly metabolized by polymorphic UGTs (UGT2B7: ~28%, UGT2B17: ~16%, UGT1A3/4: ~14%) and CYP3A4 (~35%). The Applicant performed an exploratory study to examine the impact of germline *UGT2B7* and *UGT2B17* genotype status on the PK of asciminib in blood. The study utilized samples collected during Study J12301. Whole blood for *UGT* genotyping (PharmacoScan gene chip) was collected at baseline from patients in the asciminib arm. Asciminib C_{through} levels were measured in pre-dose samples collected at weeks 2, 4, 12, 24, and 48, and the average C_{through} value for each patient was used for analysis. *UGT* genotype data from

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151 patients were available for analysis (149 patients had genotype data for both *UGT2B7* and *UGT2B17* [98.7%], and 2 extra patients had only *UGT2B17* genotype data [100.0%]). C_{trough} data were available for 145 patients (97.3%) out of the 149 genotyped for *UGT2B7* and *UGT2B17*, and for 147 patients (97.4%) out of the 151 with *UGT2B17* genotype data. *UGT2B7* and *UGT2B17* phenotypes were inferred from genotypes using the PharmacoScan software. Mean asciminib C_{trough} levels were similar between *UGT2B7* phenotype categories (Kruskal-Wallis test, p -value = 0.064; Figure 1). Likewise, mean asciminib C_{trough} levels were similar between *UGT2B17* phenotype categories (Kruskal-Wallis test, p -value = 0.762; Figure 2). In conclusion, the results from this exploratory analysis suggest that polymorphic variants in *UGT2B7* and *UGT2B17* do not have a significant clinical impact on the PK of asciminib.

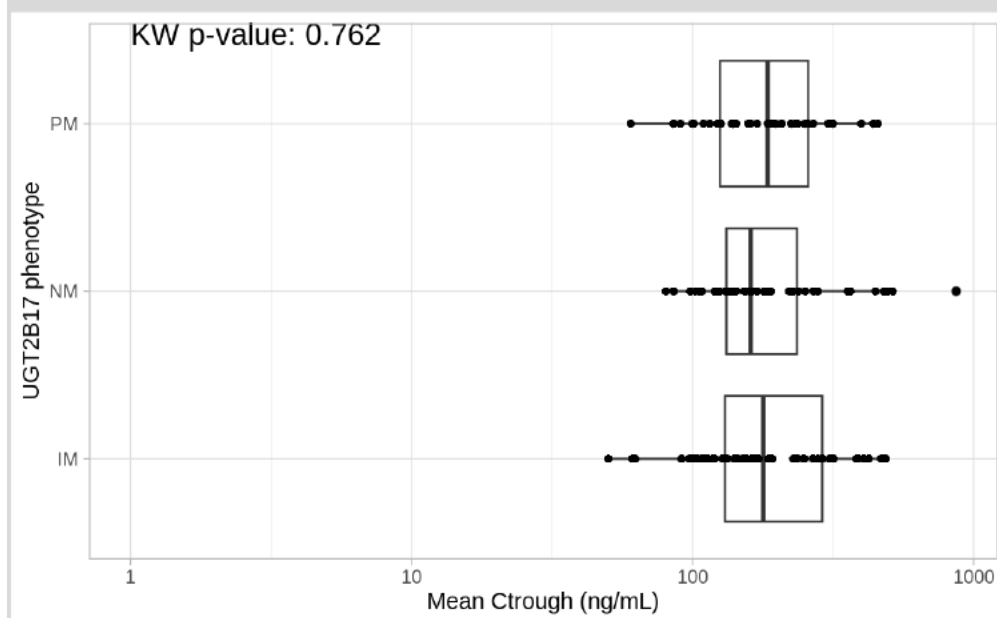
Figure 1 Asciminib mean C_{trough} by *UGT2B7* phenotype



Source: Applicant's Exploratory UGT Genotype PK Analyses Report, Figure 4-2.

IM: intermediate metabolizer, $n = 5$. NM: normal metabolizer, $n = 57$. RM: rapid metabolizer, $n = 55$. UM: ultrarapid metabolizer, $n = 28$. Observed *UGT2B7* diplotypes: *1a/*1a ($n = 9$), *1a/*1b ($n = 6$), *1a/*1c ($n = 6$), *1a/*1d ($n = 10$), *1a/*2a ($n = 21$), *1a/*2g ($n = 1$), *1a/*3 ($n = 3$), *1b/*1b ($n = 1$), *1b/*1c ($n = 1$), *1b/*1d ($n = 1$), *1b/*2a ($n = 4$), *1b/*3 ($n = 3$), *1c/*1d ($n = 5$), *1c/*2a ($n = 11$), *1d/*1d ($n = 4$), *1d/*2a ($n = 16$), *1d/*2g ($n = 3$), *2a/*2a ($n = 28$), *2a/*2g ($n = 6$), *2a/*3 ($n = 3$), *2g/*2g ($n = 1$), and *3/*3 ($n = 2$).

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Figure 2 Asciminib mean C_{trough} by UGT2B17 phenotype

Source: Applicant's Exploratory UGT Genotype PK Analyses Report, Figure 4-4.

IM: intermediate metabolizer, n = 64. NM: normal metabolizer, n = 42. PM: poor metabolizer, n = 41. Observed *UGT2B17* diplotypes: *1/*1 (n = 41), *1a/*2 (n = 59), *1a/hapB (n = 1), *2/*2 (n = 41), and *2/hapB (n = 5).

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:

Food consumption decreases asciminib bioavailability, with a high-fat meal having a higher impact on asciminib PK than a low-fat meal. Asciminib AUC_{inf} is decreased by 62.3% with a high-fat meal and by 30% with a low-fat meal compared to the fasted state. Food consumption should be avoided for at least 2 hours before and 1 hour after taking asciminib [SCP-Section 5.1.3.1].

Asciminib as a victim or perpetrator of DDI, both regarding enzymes and transporters, was assessed and described in the original submission. Since the original approval the prescribing information has been updated with new information on DDI. No new information is provided in support of the current application.

The FDA's Assessment:

FDA has no additional comments or recommendations for alternative dosing or management strategies based on extrinsic factors.

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X

X

Primary Reviewer

Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

All studies pertinent to the evaluation of efficacy and/or safety are summarized in [Table 3](#). The clinical pharmacology studies in healthy participants with asciminib were provided in the original application, no new information is provided in support of the current application.

Table 3 Listings of Clinical Studies Relevant to this sNDA

Study Identity/ NCT No. / No. of Centers and Countries/ Data cut-off	Study Design	Regimen/ Schedule/(N=Participant enrolled; n=Participants in the Safety pool)	Study Endpoints (applicable for this application)	Treatment Duration	Study Population
Study J12301: Controlled Study to Support Efficacy and Safety					
CABL001J12301/ NCT04971226/ 116 centers in 29 countries/ 28-Nov-2023 (Week 48 after Last participant first visit)	Ph3, multi-center, open-label, randomized study of oral asciminib versus Investigator selected TKI in participants with newly diagnosed Ph+ CML-CP	Asciminib 80 mg QD Imatinib 400 mg QD 2G-TKI: Nilotinib 300 mg BID Dasatinib 100 mg QD Bosutinib 400 mg QD (N=405, n=200).	Primary: MMR at Week 48: asciminib vs. IS-TKI, and asciminib vs. imatinib (as PRS-TKI). For other secondary efficacy, safety, PRO and biomarker endpoints refer to Table 4 .	Participants in the study will continue to receive the assigned treatment until the End of Study (5 years from randomization date of last participant first treatment), or until premature discontinuation due to treatment failure, disease progression or intolerance or due to Investigator or participant decision.	Adult, treatment-naive participants with newly-diagnosed Ph+ CML-CP (within 3 months of diagnosis)

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Study Identity/ NCT No. / No. of Centers and Countries/ Data cut-off	Study Design	Regimen/ Schedule/(N=Participant enrolled; n=Participants in the Safety pool)	Study Endpoints (applicable for this application)	Treatment Duration	Study Population
Supportive Studies in the Safety Pool					
CABL001A2301/ NCT03106779/ 88 centers in 25 countries/ 22-Mar-2023 (End of treatment CSR)	Ph3, randomized, open-label, active- controlled (bosutinib), multi- center study.	Asciminib 40 mg BID Bosutinib 500 mg QD (N=233, n=156) *	Safety: AE type, frequency, and severity; changes in laboratory values outside of pre-determined ranges. Complete details for safety assessment were provided in the original submission.	Participants are treated up to end of study treatment period defined as up to 96 weeks after the last participant receives the first dose or up to 48 weeks after the last participant has switched to asciminib treatment whichever is longer unless participants have discontinued treatment earlier.	Adult participants with Ph+ CML-CP, previously treated with at least 2 prior TKIs, with treatment failure or intolerance to most recent TKI.
CABL001X2101/ NCT02081378/ 18 centers in 10 countries/ 14-Mar-2023 (Final CSR)	Ph1, multicenter, open-label, dose escalation study	Asciminib 10, 20, 40, 80, 150, 160, 200, 280 mg BID and 40, 60 80, 120, 160, 200 mg QD as single agent or in combination with imatinib, nilotinib, or dasatinib* (N=326; n=200).	Safety: AE type, frequency, and severity; changes in laboratory values outside of pre-determined ranges, following treatment with asciminib as single agent. Complete details for safety assessment were provided in the original submission.	Participants are treated up to end of treatment period defined as when all patients enrolled had been followed for at least 64 weeks in the study (corresponding approximately to Cycle 16) or had discontinued from treatment, whichever occurred first.	Adult participants with Ph+ CML or Ph+ ALL, who had relapsed, were refractory to, or intolerant to at least two prior TKIs.
*Only CML-CP/AP participants who received asciminib monotherapy are included in the asciminib safety pool.					

The FDA's Assessment:

FDA agrees with the summary of the clinical studies presented in Table 3 above. The proposed USPI includes safety and efficacy data from Study CABL001J12301. Warnings and Precautions sections of the proposed USPI is based on the Asciminib Safety Pool (N=556)

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which consists of 200 patients from Study CABL001J12301, 156 patients from Study CABL001A2301, and 200 patients from Study CABL001X2101.

The Applicant also provided safety and efficacy information from Study CABL001AUS08 which is an ongoing phase 2, US multi-center, open label, single arm dose escalation study in patients with Philadelphia chromosome positive CML in CP receiving asciminib monotherapy as 2L or 1L treatment. The primary endpoint of this study is MMR rate at 12 months with key efficacy assessments of molecular responses at various timepoints. Six-month interim efficacy results in 28 patients who used asciminib as 2L therapy were evaluated to support the previously treated Philadelphia chromosome positive CML in CP indication. Safety in 71 patients treated in 2L was also evaluated.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant's Description:

Efficacy claims are based on the results of the primary analysis of the Phase III registration Study J12301, performed when all randomized participants (n=405) had been on study treatment for at least 48 weeks or had discontinued earlier; this corresponded to a data cut-off date of 28-Nov-2023.

8.1.1. Study J12301

Study Design

The Applicant's Description:

Study J12301 is an ongoing Phase III, multicenter, open-label, randomized study of oral asciminib 80 mg QD versus IS-TKI in adult participants with newly-diagnosed Ph+ CML-CP, designated to characterize efficacy, safety, and tolerability, and to assess the PK profile of asciminib.

Study Location: Conducted across 116 centers (including 16 centers in USA) in 29 countries worldwide.

Choice of Control Group: The selection of the TKI in the IS-TKI arm was at the physician's discretion based on disease characteristics, comorbidities and participant preference. The choice of use of any of the currently approved TKIs for newly-diagnosed Ph+ CML-CP in the IS-TKI arm is reflective of the standard of care in clinical practice and minimizes the risk of excluding any group of participants, based on Investigator and/or participant preference, or participant age group, risk category, or specific comorbidities [SCE-Section 1.2.1].

Diagnostic Criteria: Per European Leukemia Network (ELN) criteria ([Hochhaus et al 2020](#)).

Dose Selection/Rationale: Described in [Section 6.2.2.1](#).

Study Treatments and Treatment Assignment: Participants were assigned to one of the 2 treatment arms (Arm 1: asciminib 80 mg QD or Arm 2: IS-TKI (imatinib 400 mg QD, nilotinib 300 mg BID, dasatinib 100 mg QD, or bosutinib 400 mg QD) in a 1:1 ratio. Randomization was stratified based on ELTS risk group (low vs. intermediate vs. high) and the PRS-TKI. Enrollment into each stratum i.e imatinib vs. 2G TKI [nilotinib or dasatinib or bosutinib] was controlled at approximately 50% vs. 50%, respectively, to achieve a balance across treatment arms for baseline disease characteristics, prognostic factors, and comorbidities and to reflect standard of care

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treatment used in the study population. No crossover of study treatment and no change of study treatment within the IS-TKI arm was allowed ([Figure 3](#)) [Study J12301 PA CSR-Section 9.4].

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 treatment arms. Blinding of study treatment would have been very complex and could have increased the likelihood of dosing errors in the study. To minimize the potential impact of the knowledge of treatments, the randomization list was kept strictly confidential. No aggregate statistical analyses by treatment arm were performed prior to database lock; however, an independent data monitoring committee (DMC) reviewed unblinded safety data.

Dose Modification, Dose Discontinuation: For participants who did not tolerate the protocol-specified asciminib dosing schedule, dose interruptions and/or reductions were either recommended or mandated to allow participants to continue study treatment. The criteria for dose modification were based on the dose modification guidelines for each toxicity. Dose escalation beyond 80 mg QD for asciminib was not permitted. Dose modifications of the IS-TKI were at the Investigator's discretion and in accordance with institutional practice and local prescribing information [Study J12301 PA CSR-Section 9.4.4].

Administrative Structure: Study J12301 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 DMC, comprising of two physicians with appropriate disease area qualifications and one statistician. The DMC reviewed the unblinded safety data starting approximately 6 months after the first participant had started study treatment. Subsequent reviews were conducted every 4 months until the primary analysis [Study J12301 PA CSR-Appendix 16.1.4].

Procedures and Schedule: The efficacy assessments included assessment of molecular, cytogenetic, and hematological response in all randomized participants.

Peripheral blood samples were collected from all participants at screening and every 4 weeks until Week 12 and subsequently every 12 weeks until the end of study treatment for analysis of *BCR::ABL1* level via RQ-PCR by a Novartis designated laboratory. Bone marrow aspirates for cytogenetic analyses were performed at screening and upon treatment failure. Hematologic response was assessed by complete blood count and physical examination at each visit [Study J12301 PA CSR-Section 9.5.2].

Safety assessments consisted of collecting all AEs and SAEs, with their severity and relationship to study drug; monitoring of hematology, blood chemistry, coagulation, pregnancy, hepatitis marker specimens; and regular assessments of vital signs, ECOG performance status, ECG; and physical examination (including body weight and height). For all women of childbearing potential, a serum pregnancy test (serum β -HCG) was performed as specified in the assessment schedule

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[Study J12301 PA CSR-Appendix 16.1.1-Protocol-Table 8-1] and urine pregnancy tests were to be performed at home every 4 weeks if serum pregnancy test (Serum β -HCG) was not performed [Study J12301 PA CSR-Section 9.5.3].

Concurrent Medications: In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the participant were allowed, except as specifically prohibited. Concomitant use of hydroxyurea for urgent control of high cell counts during the first 2 weeks of study treatment was allowed. For participants treated with asciminib, the use of bisphosphonates regardless of indication, and anticancer treatments of newly-diagnosed solid cancers (e.g. prostate cancer) that would not impact the level of minimal residual disease of participants was allowed. Use of CYP3A4/5 and CYP2C9 substrates with narrow therapeutic index, strong CYP3A4 inducers, substrates of OATP1B, BCRP or both transporters, and drugs with "Known risk", "Possible risk", or "Conditional risk of Torsades de Pointes" were allowed with caution and with close monitoring to ensure participant safety. For participants treated with IS-TKI, the Investigator was to follow the respective local label for specific directions regarding other drugs that were contra-indicated with the assigned study treatment [Study J12301 PA CSR-Section 9.4.5]

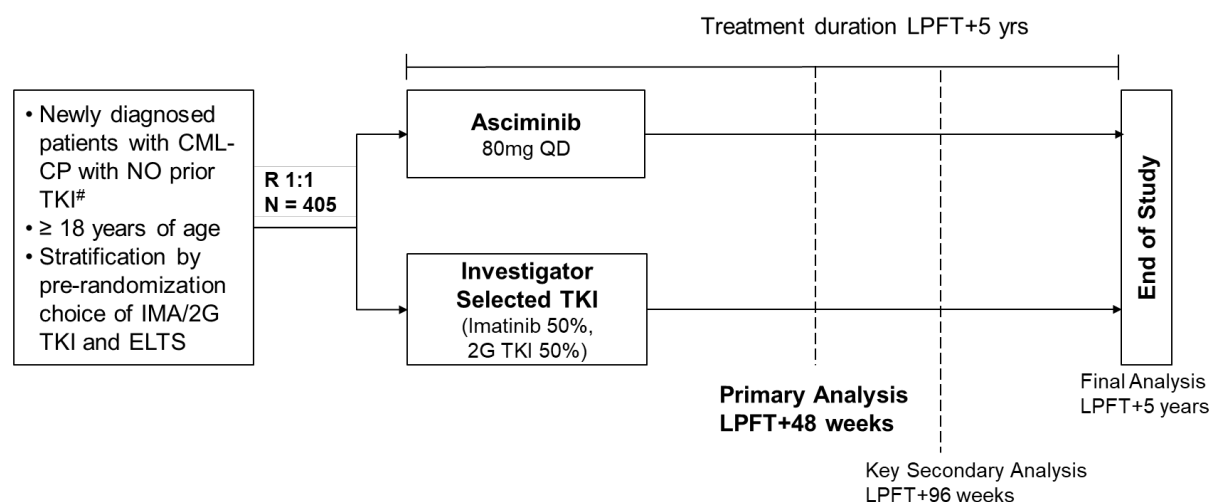
Treatment Compliance: was assessed by the Investigator and/or study personnel at each visit using tablet counts (if applicable at the visit), and information provided by the participant. This information was captured in the source document at each visit. All study treatment dispensed and returned was recorded in the Drug Accountability Log. Total daily dose of study treatment administered with start and end date was collected on the dedicated eCRF page. Remote treatment administration compliance was assessed by off-site healthcare professionals, and information provided to the Investigator and/or study personnel [Study J12301 PA CSR-Section 9.4.3.4].

Rescue Medication: No rescue medication was allowed.

Participant Completion, Discontinuation, or Withdrawal: Participants are planned to continue to receive their assigned treatment until the End of Study, or until premature discontinuation due to treatment failure, disease progression, or intolerance or due to Investigator or participant decision. The End of Study will occur 5 years from the last participant first treatment in the study. Participants who discontinue study treatment prematurely due to any reason are followed up for survival and progression until the End of Study [Study J12301 PA CSR-Section 9.1].

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Figure 3 Study Design of Study J12301



#: Either imatinib, or nilotinib, or dasatinib or bosutinib for ≤ 2 weeks is allowed. No other treatment with TKIs prior to randomization is permitted.

Source: [Study J12301 PA CSR-Figure 9-1]

The FDA's Assessment:

FDA agrees with the Applicant's description of the trial design of the phase 3, CABL001J12301 study.

Eligibility Criteria

The Applicant's Description:

Adult participants with newly-diagnosed Ph+ CML-CP (diagnosed within 3 months of enrollment) were eligible for entry. For urgent disease control hydroxyurea and anagrelide or either imatinib or nilotinib, or dasatinib or bosutinib for a period of ≤ 2 weeks prior to randomization were allowed. Treatment with other anticancer agents including other TKIs prior to randomization was not permitted. No TKI other than the study treatment was to be used post-randomization [Study J12301 PA CSR-Section 9.3].

The FDA's Assessment:

FDA agrees with the Applicant's description of the eligibility criteria of the CABL001J12301 study.

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Study Endpoints

The Applicant's Description:

The primary and other relevant study objectives, endpoints, and statistical analyses pertaining to the Week 48 analyses are presented in [Table 4](#) [Study J12301 PA CSR-Section 8 and Section 9.7].

Robustness and appropriateness of primary efficacy endpoints

MMR is recognised as the most relevant surrogate of long-term outcome and clinical benefit in patients with Ph+ CML-CP. MMR at 12 months is endorsed as key milestone for achieving optimal response with treatment guidelines ([ELN 2020](#), [NCCN 2024](#)) recommending a switch in treatment for most patients not being able to achieve this level of response. Evidence of MMR being a clinically relevant endpoint that is predictive of superior long-term clinical outcomes (PFS, OS), durable long-term cytogenetic remissions, and low rate of disease progression in Ph+ CML-CP has been substantively established ([ELN 2020](#), [NCCN 2024](#), [Hughes et al 2010](#), [Hochhaus et al 2017](#)). Additionally, MMR at 12 months is also associated with a higher likelihood of achieving DMR, which is an important criteria for determining TFR eligibility ([NCCN 2024](#)). The rapid achievement of DMR indicates the effective depletion of disease burden in patients with CML and association of DMR with lack of disease progression and superior long-term outcomes has been shown ([Cortes 2018](#), [Dulucq, Mahon 2016](#), [Branford 2016](#)). Furthermore, sustained DMR is a necessary prerequisite for attempting TFR, which is increasingly selected as a goal of treatment for patients newly diagnosed with CML.

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Table 4 Relevant Objectives, Endpoints and Statistical Analyses, Pertaining to the Week 48 Analyses of Study J12301

Primary objectives ¹	Endpoint	Statistical methodology (analysis set)
To compare proportion of participants in MMR - Asciminib vs. IS-TKI - Asciminib vs. IS-TKI among participants with imatinib as PRS-TKI	MMR at Week 48 (Y/N)	- 1-sided CMH test stratified by ELTS risk groups and PRS-TKI (imatinib vs. 2G-TKI) (FAS) - 1-sided CMH test stratified by ELTS risk groups (FAS _{IMA}) Response rates and Clopper-Pearson 95% CIs; Stratified MH common treatment differences and 95% CIs
Secondary objectives	Endpoint	Statistical methodology (analysis set)
Efficacy: To compare additional efficacy parameters - Asciminib vs. IS-TKI - Asciminib vs. IS-TKI among participants with imatinib as PRS-TKI - Asciminib vs. IS-TKI among participants with 2G-TKI as PRS-TKI	- MMR at all scheduled time points (except Weeks 48 and 96) - MMR by all scheduled time points - Following at and by all scheduled time points: - MR4.0 and MR 4.5 - CHR - BCR-ABL1 $\leq$ 1% - CCyR by Weeks 48 - Duration of MMR, MR4.0, MR 4.5 - Time to first MMR, first MR4.0, first MR 4.5 - Other time-to-event endpoints: TTF, PFS, OS, FFS, EFS	<u>MMR/MR4.0/MR4.5</u> : BCR::ABL $\leq$ 1% and CHR: Per primary endpoints above (FAS, FAS _{IMA} , and FAS _{2GTKI}) <u>CyR</u> : Frequency and % of responders (2-sided 95% CI based on Clopper-Pearson methodology) <u>Duration of MMR/MR4.0/MR4.5</u> : KM estimates (respective MMR, MR4.0, or MR4.5 Responder set) <u>Time to first MMR/MR4.0/MR4.5</u> : Competing risk analysis, KM estimate (FAS, FAS _{IMA} , and FAS _{2GTKI}) <u>Other time-to-event endpoints</u> : TTF, PFS, and OS: KM estimate. Stratified log-rank tests and Cox regression models for treatment comparison. FFS and EFS: Competing risk analysis (FAS, FAS _{IMA} , and FAS _{2GTKI})
Safety: To characterize the safety and tolerability of - Asciminib vs. IS-TKI	AE type, frequency, and severity; changes in laboratory values to outside pre-determined ranges; clinically notable ECGs; other safety data (vital signs, physical examination).	Descriptive statistical analysis (Safety set)
¹ Study was to be declared positive if either of the primary objectives was met. Source: [Study J12301 PA CSR-Table 8-1 and Section 9.7]		

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The FDA's Assessment:

FDA agrees with the Applicant's description of the study endpoints of the phase 3, CABL001J12301 study.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The planned Statistical Analysis Plan was agreed upon with FDA and finalized prior to conduct of any analysis and is described in [Table 4](#). The primary and supplemental estimands are summarized in [SCE-Section 1.2.1]

Analysis sets used were defined as:

- The **Full Analysis Set (FAS)** comprised all participants to whom study treatment was assigned by randomization.
- The **IMA Full Analysis Set (FAS_{IMA})** comprised all participants from the FAS, whose PRS-TKI was imatinib.
- The **2G TKI Full Analysis Set (FAS_{2G TKI})** comprised all participants from the FAS, whose PRS-TKI was a 2G TKI (nilotinib, dasatinib, or bosutinib).
- For duration of MMR, the **MMR Responder Set, IMA MMR Responder Set, and 2G TKI MMR Responder Set** were used, which comprised the subset of participants from the FAS, FAS_{IMA}, or FAS_{2G TKI}, respectively, who achieved MMR at any time.
- For duration of MR4.0, the **MR4.0 Responder Set, IMA MR4.0 Responder Set, and 2G TKI MR4.0 Responder Set** was used, which comprised the subset of participants from the FAS, FAS_{IMA}, or FAS_{2G TKI}, respectively, who achieved MR4.0 at any time.
- For duration of MR4.5, the **MR4.5 Responder Set, IMA MR4.5 Responder Set, and 2G TKI MR4.5 Responder Set** was used, which comprised the subset of participants from the FAS, FAS_{IMA}, or FAS_{2G TKI}, respectively, who achieved MR4.5 at any time.
- The **Safety Set** comprised of all participants who received at least one dose of any study treatment.

Following the intent-to-treat principle, participants were analyzed according to the treatment arm and stratum they were assigned to at randomization. Efficacy of asciminib was assessed overall compared with all IS-TKIs as well as within each pre-randomization stratum of participants with imatinib (formally tested) and 2G TKIs (not formally tested) separately [CO-Section 4.1.2].

Criteria for response and relapse:

Major Molecular response: MMR: $BCR::ABL1$ (IS) $\leq 0.1\%$,

Deep Molecular Response: MR4.0: $BCR::ABL1$ (IS) $\leq 0.01\%$ or, **MR4.5:** $BCR::ABL1$ (IS) $\leq 0.0032\%$.

Cytogenetic response: CCyR: No Ph-positive metaphases

CHR: Defined as all of the following present for ≥ 4 weeks: complete normalization of peripheral blood counts with leukocyte count $<10 \times 10^9/L$, platelet count $<450 \times 10^9/L$, basophils

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<5%, no blasts and promyelocytes in peripheral blood, myelocytes + metamyelocytes <5% in peripheral blood, and no evidence of extramedullary disease, including spleen and liver [CO-Table 4-2].

Efficacy analyses terminology [CO-Section 4.1.2]:

- ASC^{IMA} – refers to participants randomized to the asciminib arm, within the stratum of participants with imatinib as their PRS-TKI
- ASC^{2G}-refers to participants randomized to the asciminib arm, within the stratum of participants with 2G TKI as their PRS-TKI
- IS-TKI^{IMA}-refers to participants randomized to the IS-TKI arm, within the stratum of participants with imatinib as their PRS-TKI
- IS-TKI^{2G}-refers to participants randomized to the IS-TKI arm, within the stratum of participants with 2G TKI as their PRS-TKI

Datasets: The datasets used to derive the tables and figures for Study J12301 are provided in Module 5.3.5.1 and datasets used for the summary documents including Exposure-Response and PopPK report are provided in Module 5.3.5.3 of this application.

Handling of missing assessments for primary analysis

Participants with missing RQ-PCR evaluation at the Week 48 visit were imputed as MMR responders if they had non-missing RQ-PCR evaluations at both Week 36 and Week 60 visits, and both met the MMR criteria (BCR::ABL1 levels (IS) $\leq 0.1\%$), assuming that MMR was maintained between Week 36 and Week 60. If RQ-PCR evaluations were performed at unscheduled visits closer to the Week 48 visit (before or after), these were taken into account for the imputation. Otherwise, participants with missing RQ-PCR evaluations at Week 48 were considered as non-responders [Study J12301 PA CSR-Section 9.7.3.4]

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Protocol Amendments

The Applicant's Description:

The study protocol was amended on 2 occasions ([Table 5](#)).

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Table 5 Protocol Amendments

Version and date	Summary of key changes
Amendment 01 09-May-2022	To further clarify requirements for eligibility, dose administration, and pregnancy testing in view of the comparator arm being approved TKIs selected by Investigators. BCR-ABL ≤ 1% added as a secondary endpoint. Details added on remote procedures that could be implemented in case of a Public Health emergency that limited or prevented on-site study visits.
Amendment 02 15-May-2023	To clarify dose modification guidelines for hepatotoxicity with asciminib and dose discontinuation rule as applicable to both treatment arms.
Source: [Study J12301 PA CSR-Section 9.8.1]	

Changes to Planned Analysis: There were no changes to the protocol-specified analyses.

The FDA’s Assessment:
FDA agrees with the Applicant’s description of the amendments of the phase 3, CABL001J12301 study.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant’s Position:

Study J12301 has been conducted in accordance with the CFR governing the protection of human participants (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. Written informed consent was obtained from each participant or legally acceptable representative of the participant, before conducting any study-specific procedures. The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board.

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 ([Appendix 19.2](#)).

The FDA’s Assessment:
A summary of the financial disclosure information is presented in Appendix 19.2. There were

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896 investigators. One investigator at one site had financial disclosures for research grants and an investigator-initiated trial. Investigators at this site enrolled ^(b)₍₆₎ patients. With the small number of patients enrolled at this site, the enrollment of patients by this investigator is not expected to bias the outcome of the study results.

Patient Disposition

Data:

Table 6 Disposition of Study J12301 (Full Analysis Set)

Disposition/Reason	Asciminib			Investigator Selected TKI		
	Imatinib Stratum N=101 n (%)	2G TKI Stratum N=100 n (%)	All Asciminib N=201 n (%)	Imatinib Stratum N=102 n (%)	2G TKI Stratum N=102 n (%)	All Comparators N=204 n (%)
Participants randomized						
Randomized	101 (100)	100 (100)	201 (100)	102 (100)	102 (100)	204 (100)
Treated*	100 (99.0)	100 (100)	200 (99.5)	100 (98.0)	101 (99.0)	201 (98.5)
Not treated	1 (1.0)	0	1 (0.5)	2 (2.0)	1 (1.0)	3 (1.5)
Reason for not being treated						
Subject Decision	1 (1.0)	0	1 (0.5)	0	1 (1.0)	1 (0.5)
Adverse Event	0	0	0	1 (1.0)	0	1 (0.5)
Screen Failure	0	0	0	1 (1.0)	0	1 (0.5)
Treatment Ongoing #	85 (84.2)	88 (88.0)	173 (86.1)	63 (61.8)	77 (75.5)	140 (68.6)
Discontinued From Treatment	15 (14.9)	12 (12.0)	27 (13.4)	37 (36.3)	24 (23.5)	61 (29.9)
< Week 48	11 (10.9)	8 (8.0)	19 (9.5)	27 (26.5)	12 (11.8)	39 (19.1)
≥Week 48 and < Week 96	4 (4.0)	4 (4.0)	8 (4.0)	10 (9.8)	11 (10.8)	21 (10.3)
≥Week 96	0	0	0	0	1 (1.0)	1 (0.5)
Reason for discontinuation						
Unsatisfactory Therapeutic Effect	6 (5.9)	6 (6.0)	12 (6.0)	21 (20.6)	10 (9.8)	31 (15.2)
Treatment Failure Per ELN	6 (5.9)	4 (4.0)	10 (5.0)	16 (15.7)	8 (7.8)	24 (11.8)
Confirmed Loss Of MMR	0	1 (1.0)	1 (0.5)	0	0	0
Other	0	1 (1.0)	1 (0.5)	5 (4.9)	2 (2.0)	7 (3.4)
Adverse Event	6 (5.9)	5 (5.0)	11 (5.5)	11 (10.8)	10 (9.8)	21 (10.3)
Progressive Disease	2 (2.0)	0	2 (1.0)	3 (2.9)	1 (1.0)	4 (2.0)

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Disposition/Reason	Asciminib			Investigator Selected TKI		
	Imatinib Stratum N=101 n (%)	2G TKI Stratum N=100 n (%)	All Asciminib N=201 n (%)	Imatinib Stratum N=102 n (%)	2G TKI Stratum N=102 n (%)	All Comparators N=204 n (%)
Protocol Deviation	1 (1.0)	0	1 (0.5)	1 (1.0)	1 (1.0)	2 (1.0)
Subject Decision	0	1 (1.0)	1 (0.5)	1 (1.0)	1 (1.0)	2 (1.0)
Pregnancy	0	0	0	0	1 (1.0)	1 (0.5)
< Week 48						
Adverse Event	5 (5.0)	4 (4.0)	9 (4.5)	9 (8.8)	5 (4.9)	14 (6.9)
Unsatisfactory Therapeutic Effect	4 (4.0)	3 (3.0)	7 (3.5)	14 (13.7)	5 (4.9)	19 (9.3)
Treatment Failure Per ELN	4 (4.0)	2 (2.0)	6 (3.0)	10 (9.8)	5 (4.9)	15 (7.4)
Other	0	1 (1.0)	1 (0.5)	4 (3.9)	0	4 (2.0)
Progressive Disease	2 (2.0)	0	2 (1.0)	3 (2.9)	1 (1.0)	4 (2.0)
Subject Decision	0	1 (1.0)	1 (0.5)	0	0	0
Protocol Deviation	0	0	0	1 (1.0)	1 (1.0)	2 (1.0)
≥Week 48 and < Week 96						
Unsatisfactory Therapeutic Effect	2 (2.0)	3 (3.0)	5 (2.5)	7 (6.9)	5 (4.9)	12 (5.9)
Treatment Failure Per ELN	2 (2.0)	2 (2.0)	4 (2.0)	6 (5.9)	3 (2.9)	9 (4.4)
Confirmed Loss Of MMR	0	1 (1.0)	1 (0.5)	0	0	0
Other	0	0	0	1 (1.0)	2 (2.0)	3 (1.5)
Adverse Event	1 (1.0)	1 (1.0)	2 (1.0)	2 (2.0)	4 (3.9)	6 (2.9)
Protocol Deviation	1 (1.0)	0	1 (0.5)	0	0	0
Pregnancy	0	0	0	0	1 (1.0)	1 (0.5)
Subject Decision	0	0	0	1 (1.0)	1 (1.0)	2 (1.0)
≥Week 96						
Adverse Event	0	0	0	0	1 (1.0)	1 (0.5)
Participants who have entered Survival Follow-up	13 (12.9)	7 (7.0)	20 (10.0)	28 (27.5)	20 (19.6)	48 (23.5)
Participants who have discontinued from study	5 (5.0)	4 (4.0)	9 (4.5)	11 (10.8)	4 (3.9)	15 (7.4)

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Disposition/Reason	Asciminib			Investigator Selected TKI		
	Imatinib	2G TKI	All	Imatinib	2G TKI	All
	Stratum	Stratum	Asciminib	Stratum	Stratum	Comparators
	N=101	N=100	N=201	N=102	N=102	N=204
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Ongoing at the time of the data cut-off date.

* One participant stratified to imatinib as PRS-TKI received nilotinib as actual treatment. Hence this participant is considered in imatinib stratum for efficacy analysis and in 2G TKI treated for safety analysis.

Source: [Study J12301 PA CSR-Table 14.1-1.1]

The Applicant's Position:

The FAS consisted of all 405 randomized participants (Table 6). Four participants (1 in the asciminib arm and 3 in the IS-TKI arm) never received any study treatment. Of 201 participants receiving IS-TKIs, 99 received imatinib, 49 received nilotinib, 42 received dasatinib, and 11 received bosutinib, respectively [CO-Section 4.1.3.2].

Asciminib vs. IS-TKI (FAS): As of the data cut-off date, the proportion of participants who discontinued study treatment was lower in the asciminib arm (13.4%) compared to the IS-TKI arm (29.9%). Overall, treatment discontinuations were predominantly due to lack of efficacy or AEs; both were less frequent in the asciminib arm than in the IS-TKI arm (unsatisfactory therapeutic effect: 6.0% vs. 15.2%; AE: 5.5% vs. 10.3%). Among treatment discontinuations due to unsatisfactory therapeutic effect the majority were due to treatment failure per ELN criteria 2020 (5.0% in the asciminib arm vs. 11.8% in the IS-TKI arm) (Table 6).

A similar trend was observed for study treatment discontinuations (overall and for individual reasons) in the FAS_{IMA} and FAS_{2G TKI}, with the proportions of participants with study treatment discontinuations being lower in the asciminib arm compared to the IS-TKI arm (Table 6).

The FDA's Assessment:

FDA confirms the Applicant's position. One patient in the asciminib arm was not treated because of subject decision, and three patients in the IS-TKI arm were not treated because of subject decision, adverse event, and screen failure (one for each).

Treatment discontinuation due to various reasons was less frequent with asciminib vs. IS-TKIs (4.5% vs. 7.4%). The most frequent reasons for treatment discontinuation in both arms were unsatisfactory therapeutic effect (6% vs. 15.2%) and adverse event (5.5% vs. 10.3%).

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Protocol Violations/DeviationsData:**Table 7 Protocol Deviations of Study J12301 (Full Analysis Set)**

Protocol deviation category	Asciminib			Investigator Selected TKI		
	Imatinib Stratum N=101 n (%)	2G TKI Stratum N=100 n (%)	All Asciminib N=201 n (%)	Imatinib Stratum N=102 n (%)	2G TKI Stratum N=102 n (%)	All Comparators N=204 n (%)
Any protocol deviation	45 (44.6)	50 (50.0)	95 (47.3)	40 (39.2)	58 (56.9)	98 (48.0)
Other	27 (26.7)	37 (37.0)	64 (31.8)	31 (30.4)	41 (40.2)	72 (35.3)
Selection criteria not met	17 (16.8)	13 (13.0)	30 (14.9)	8 (7.8)	17 (16.7)	25 (12.3)
Treatment deviation	13 (12.9)	9 (9.0)	22 (10.9)	5 (4.9)	11 (10.8)	16 (7.8)
Subject not withdrawn as per protocol	0	3 (3.0)	3 (1.5)	1 (1.0)	5 (4.9)	6 (2.9)
Prohibited concomitant medication	1 (1.0)	1 (1.0)	2 (1.0)	0	2 (2.0)	2 (1.0)

Numbers (n) represent counts of participants.

Source: [Study J12301 PA CSR -Table 14.1-2.1.1.1, Table 14.1-2.1.1.2, Table 14.1-2.1.1.3]

The Applicant's Position:

Overall, the proportion of participants with protocol deviations (PDs) was similar in the asciminib arm (47.3%) compared to the IS-TKI arm (48.0%) (Table 7). There were 3 participants (1 participant in the asciminib arm and 2 participants in the IS-TKI arm) who discontinued study treatment due to PD. None of the PDs resulted in exclusion of data from the analyses and there was no impact on the primary and secondary endpoints due to these PDs [Study J12301 PA CSR-Section 10.2].

Overall, the PDs specific to the COVID-19 pandemic were comparable between the asciminib and IS-TKI arms (8.5% vs. 11.8%). The majority of these deviations were assessment/procedure not done, visit done outside of study site, missed visit, and assessment/procedure changed due to COVID-19. The frequency and nature of the COVID-19 related PDs in imatinib and 2G TKI strata were similar to that reported overall [Study J12301 PA CSR-Section 10.2.1].

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Protocol deviations were similar in the asciminib arm compared to the IS-TKI arm (47.3% vs. 48%). Protocol deviation category of "Other" was less frequent with asciminib (31.8% vs. 35.3%). Protocol deviation categories of "Selection criteria not met" and "Treatment deviation" were more frequent with asciminib compared to

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IS-TKIs, respectively, 14.9% vs. 12.3% and 10.9% vs. 7.8%. The protocol deviations were considered to be unlikely to bias the study in favor of the study drug.

Table of Demographic Characteristics

Data:

Table 8 Demographics and Baseline Characteristics of Study J12301 (Full Analysis Set)

Baseline Characteristic Categories/ Statistics	Asciminib			Investigator Selected TKI		
	Imatinib Stratum N=101	2G TKI Stratum N=100	All Asciminib N=201	Imatinib Stratum N=102	2G TKI Stratum N=102	All Comparators N=204
Age (years)						
Mean (SD)	55.8 (13.70)	45.7 (15.37)	50.8 (15.38)	55.1 (15.04)	46.3 (16.18)	50.7 (16.20)
Median	56.0	43.0	52.0	54.5	43.0	50.5
Min-Max	21.0-79.0	18.0-76.0	18.0-79.0	20.0-86.0	19.0-83.0	19.0-86.0
Age group -n (%)						
18-< 65 years	69 (68.3)	86 (86.0)	155 (77.1)	70 (68.6)	85 (83.3)	155 (76.0)
65-< 75 years	24 (23.8)	12 (12.0)	36 (17.9)	22 (21.6)	12 (11.8)	34 (16.7)
≥75 years	8 (7.9)	2 (2.0)	10 (5.0)	10 (9.8)	5 (4.9)	15 (7.4)
Sex -n (%)						
Male	62 (61.4)	69 (69.0)	131 (65.2)	65 (63.7)	60 (58.8)	125 (61.3)
Female	39 (38.6)	31 (31.0)	70 (34.8)	37 (36.3)	42 (41.2)	79 (38.7)
Race -n (%)						
White	63 (62.4)	45 (45.0)	108 (53.7)	66 (64.7)	44 (43.1)	110 (53.9)
Black or African American	1 (1.0)	1 (1.0)	2 (1.0)	1 (1.0)	1 (1.0)	2 (1.0)
Asian	37 (36.6)	53 (53.0)	90 (44.8)	34 (33.3)	56 (54.9)	90 (44.1)
Unknown	0	1 (1.0)	1 (0.5)	1 (1.0)	1 (1.0)	2 (1.0)
Ethnicity -n (%)						
Hispanic/Latino	1 (1.0)	3 (3.0)	4 (2.0)	2 (2.0)	5 (4.9)	7 (3.4)
Not Hispanic/Latino	95 (94.1)	90 (90.0)	185 (92.0)	86 (84.3)	92 (90.2)	178 (87.3)
Unknown	1 (1.0)	1 (1.0)	2 (1.0)	0	3 (2.9)	3 (1.5)
Not Reported	4 (4.0)	6 (6.0)	10 (5.0)	14 (13.7)	2 (2.0)	16 (7.8)
BMI (kg/m²)						
n	100	100	200	100	101	201
Mean (SD)	26.4 (5.85)	25.0 (4.82)	25.7 (5.39)	26.2 (4.25)	24.4 (4.61)	25.3 (4.51)

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Baseline Characteristic Categories/ Statistics	Asciminib			Investigator Selected TKI		
	Imatinib Stratum N=101	2G TKI Stratum N=100	All Asciminib N=201	Imatinib Stratum N=102	2G TKI Stratum N=102	All Comparators N=204
Median	25.4	24.5	24.9	26.1	22.9	24.9
Q1-Q3	22.3-28.8	21.6-28.1	22.1-28.5	23.5-28.4	21.3-26.7	22.1-27.9
Min-Max	13.6-51.2	16.8-42.9	13.6-51.2	17.5-38.6	16.6-40.1	16.6-40.1
Framingham estimated 10-year CVD risk categories						
n (%)						
Low (estimated risk <10%)	41 (40.6)	68 (68.0)	109 (54.2)	40 (39.2)	72 (70.6)	112 (54.9)
Intermediate (estimated risk between 10% and 20%)	21 (20.8)	11 (11.0)	32 (15.9)	29 (28.4)	15 (14.7)	44 (21.6)
High (estimated risk ≥20%)	39 (38.6)	21 (21.0)	60 (29.9)	33 (32.4)	15 (14.7)	48 (23.5)
CCI estimated 10-year probability of survival (%)						
n	100	100	200	99	102	201
Mean (SD)	53.6 (31.69)	71.9 (27.80)	62.7 (31.12)	56.4 (33.61)	72.1 (28.90)	64.3 (32.21)
Median	53.4	90.1	77.5	77.5	90.1	77.5
Q1-Q3	21.4-77.5	53.4-90.1	53.4-90.1	21.4-90.1	53.4-90.1	53.4-90.1
Min-Max	0.0-90.1	0.0-90.1	0.0-90.1	0.0-90.1	0.0-90.1	0.0-90.1
ECOG performance status -n (%)						
0	85 (84.2)	85 (85.0)	170 (84.6)	83 (81.4)	87 (85.3)	170 (83.3)
1	16 (15.8)	15 (15.0)	31 (15.4)	18 (17.6)	15 (14.7)	33 (16.2)
Missing	0	0	0	1 (1.0)	0	1 (0.5)
ELTS Score (IRT)						
Low	62 (61.4)	60 (60.0)	122 (60.7)	64 (62.7)	61 (59.8)	125 (61.3)
Intermediate	30 (29.7)	26 (26.0)	56 (27.9)	30 (29.4)	27 (26.5)	57 (27.9)
High	9 (8.9)	14 (14.0)	23 (11.4)	8 (7.8)	14 (13.7)	22 (10.8)
Pre-randomization selection TKI (IRT)						
Imatinib stratum	101 (100)	0	101 (50.2)	102 (100)	0	102 (50.0)
2G TKI stratum	0	100 (100)	100 (49.8)	0	102 (100)	102 (50.0)
Reason for TKI selection						
Local practice / guidelines clinical experience	33 (32.7)	42 (42.0)	75 (37.3)	29 (28.4)	46 (45.1)	75 (36.8)

Scemblix (asciminib)

Baseline Characteristic Categories/ Statistics	Asciminib			Investigator Selected TKI		
	Imatinib Stratum N=101	2G TKI Stratum N=100	All Asciminib N=201	Imatinib Stratum N=102	2G TKI Stratum N=102	All Comparators N=204
Risk category	23 (22.8)	13 (13.0)	36 (17.9)	24 (23.5)	18 (17.6)	42 (20.6)
Age	13 (12.9)	16 (16.0)	29 (14.4)	16 (15.7)	15 (14.7)	31 (15.2)
Other	14 (13.9)	13 (13.0)	27 (13.4)	20 (19.6)	11 (10.8)	31 (15.2)
Treatment objective	9 (8.9)	15 (15.0)	24 (11.9)	6 (5.9)	6 (5.9)	12 (5.9)
Co-morbidities	9 (8.9)	1 (1.0)	10 (5.0)	6 (5.9)	6 (5.9)	12 (5.9)
Missing	0	0	0	1 (1.0)	0	1 (0.5)

Source: [Study J12301 PA CSR-Table 14.1-4.1]

The Applicant's Position:

The demographic characteristics of the study population were well balanced between treatment arms, both overall and within each stratum. The study population was representative of the intended target population. Of note, compared to participants in the 2G TKI stratum, participants in the imatinib stratum were older in age, had a lower proportion of participants in the ELTS high-risk group, had a higher proportion of participants in the high-risk category for Framingham score, and had a higher proportion of participants with CCI ≥ 5 . This is reflective of medical practice where there is preferential use of imatinib in patients with similar demographic profile: older patients, in patients with cardiovascular comorbidities and patients in the low ELTS risk group (Table 8) (NCCN 2024).

The FDA's Assessment:

FDA agrees with the Applicant's assessment. There were more male patients than female patients in both the asciminib and IS-TKI arms. FDA notes that Black or African American patients are significantly underrepresented compared to patients with CML-CP in the US. There was also underrepresentation of Hispanic or Latino patients in both arms. In the US, 81% of CML patients identify as White, 12% as Black or African American, 4% as Other, and 3% as Asian (Sobieski et al. 2022). In addition, the majority of study subjects were enrolled at ex-US sites. As Black or African American and Hispanic/Latino patients with CML are underrepresented in study CABL001J12301, FDA plans to issue a PMC to determine whether asciminib shows a similar safety and efficacy profile in these racial and ethnic groups.

Demographics were well balanced between arms.

Scemblix (asciminib)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)Data:**Table 9 Disease History of Study J12301 (Full Analysis Set)**

Disease history	Asciminib			Investigator Selected TKI		
	Imatinib Stratum N=101	2G TKI Stratum N=100	All Asciminib N=201	Imatinib Stratum N=102	2G TKI Stratum N=102	All Comparators N=204
Time since initial diagnosis of CML to randomization (Weeks)						
n	101	100	201	101	102	203
Mean (SD)	5.38 (2.388)	5.38 (2.567)	5.38 (2.472)	5.56 (2.710)	5.15 (2.847)	5.35 (2.780)
Median	5.00	5.07	5.00	5.00	4.57	4.71
Min-Max	1.9-12.3	1.9-16.1	1.9-16.1	1.4-14.9	1.3-12.3	1.3-14.9
Time since initial diagnosis of CML to first hydroxyurea / anagrelide (Weeks)						
n	66	76	142	57	77	134
Mean (SD)	0.93 (1.694)	0.86 (1.908)	0.89 (1.806)	0.77 (1.286)	0.73 (1.443)	0.74 (1.374)
Median	0.14	0.14	0.14	0.14	0.14	0.14
Min-Max	0.1-8.9	0.1-14.3	0.1-14.3	0.1-7.1	0.1-9.1	0.1-9.1
Time since initial diagnosis of CML to any TKI (Weeks)						
n	101	100	201	100	101	201
Mean (SD)	5.02 (2.488)	5.19 (2.694)	5.10 (2.587)	5.60 (2.747)	5.07 (2.835)	5.33 (2.797)
Median	4.86	4.86	4.86	5.00	4.29	4.71
Min-Max	0.3-12.3	0.1-16.1	0.1-16.1	1.4-14.9	0.7-12.4	0.7-14.9
Prior use of TKI before randomization-n (%)						
No	85 (84.2)	92 (92.0)	177 (88.1)	99 (97.1)	95 (93.1)	194 (95.1)
Yes	16 (15.8)	8 (8.0)	24 (11.9)	3 (2.9)	7 (6.9)	10 (4.9)
Length of exposure (Weeks)-Mean (SD)	1.94 (0.654)	1.64 (0.388)	1.84 (0.587)	1.71 (0.497)	1.94 (1.302)	1.87 (1.094)
Prior use of antineoplastic therapy before randomization-n (%)						
No	27 (26.7)	24 (24.0)	51 (25.4)	44 (43.1)	22 (21.6)	66 (32.4)
Yes	74 (73.3)	76 (76.0)	150 (74.6)	58 (56.9)	80 (78.4)	138 (67.6)

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	Asciminib			Investigator Selected TKI		
	Imatinib Stratum N=101	2G TKI Stratum N=100	All Asciminib N=201	Imatinib Stratum N=102	2G TKI Stratum N=102	All Comparators N=204
Disease history						
Length of exposure (Weeks)-Mean (SD)	5.48 (9.899)	5.29 (3.200)	5.39 (7.292)	5.08 (4.237)	4.68 (2.788)	4.84 (3.463)
Any extramedullary involvement-n(%)						
No	95 (94.1)	93 (93.0)	188 (93.5)	96 (94.1)	93 (91.2)	189 (92.6)
Yes	6 (5.9)	7 (7.0)	13 (6.5)	4 (3.9)	9 (8.8)	13 (6.4)
Unknown	0	0	0	2 (2.0)	0	2 (1.0)
Location of extramedullary involvement-n(%)						
Spleen	6 (5.9)	7 (7.0)	13 (6.5)	4 (3.9)	9 (8.8)	13 (6.4)
Source: [Study J12301 PA CSR-Table 14.1-4.5]						

The Applicant's Position:

The disease history and other baseline characteristics of the study population were well balanced between treatment arms, both overall and within each stratum (Table 9).

Characteristics of bone marrow (BM) aspirate analysis at baseline were well balanced between the two treatment arms, both overall and within the imatinib stratum and 2G TKI stratum. The mean blasts and mean blasts + promyelocytes in bone marrow were both similar for participants between the two treatment arms. More than 90% of participants did not have additional chromosomal abnormalities in Ph+ metaphases or Ph- metaphases for either of the arms [CO-Section 4.1.3.1].

The FDA's Assessment:

FDA agrees with the Applicant's position. More patients in the asciminib arm used prior TKIs compared to the IS-TKI arm (11.9% vs. 4.9%). However, the length of exposure (1.8 weeks in the asciminib arm and 1.9 weeks in the IS-TKI arm) was too short to influence the treatment outcomes at week 48. Other baseline characteristics were well balanced between the arms.

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

Treatment compliance was assured by the Investigator and/or study personnel. The majority of participants received study treatment at the planned dose. The median RDI was 100.0% (range: 49.9% - 100%) for the asciminib arm and was 99.7% (range: 23.8% 100.2%) for the IS-TKI arm [Study J12301 PA CSR-Section 10.6.2].

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Overall, 94.0% of participants in the asciminib arm compared to 95.5% of participants in the IS-TKI arm required concomitant medications and the nature of concomitant medications was similar in participants across the two treatment arms [Study J12301 PA CSR-Section 10.5.2].

Three participants (1.5%) in the asciminib group and 4 participants (2.0%) in the IS-TKI group overall received hydroxycarbamide and one participant (1.0%) in the 2GTKI group received anagrelide [Study J12301 PA CSR-Section 10.5.3].

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Treatment compliance, use of concomitant medications, and use of rescue medications was similar between the arms. Use of concomitant medications (hydroxyurea, anagrelide, imatinib) with asciminib was not associated with any specific TEAEs.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)Data:**Table 10 Primary Efficacy Results of Study J12301**

	FAS		FAS _{IMA} (imatinib stratum)	
	Asciminib N=201	IS-TKI N=204	Asciminib N=101	IS-TKI N=102
MMR at Week 48				
Response-n (%)	136 (67.66)	100 (49.02)	70 (69.31)	41 (40.20)
(95% CI)	(60.72, 74.07)	(41.97, 56.10)	(59.34, 78.10)	(30.61, 50.37)
Common treatment difference (%)	18.88 (9.59, 28.17)		29.55 (16.91, 42.18)	
95% CI)				
CMH 1-sided test p-value	<.001		<.001	
CMH 1-sided test adjusted p-value	<.001		<.001	

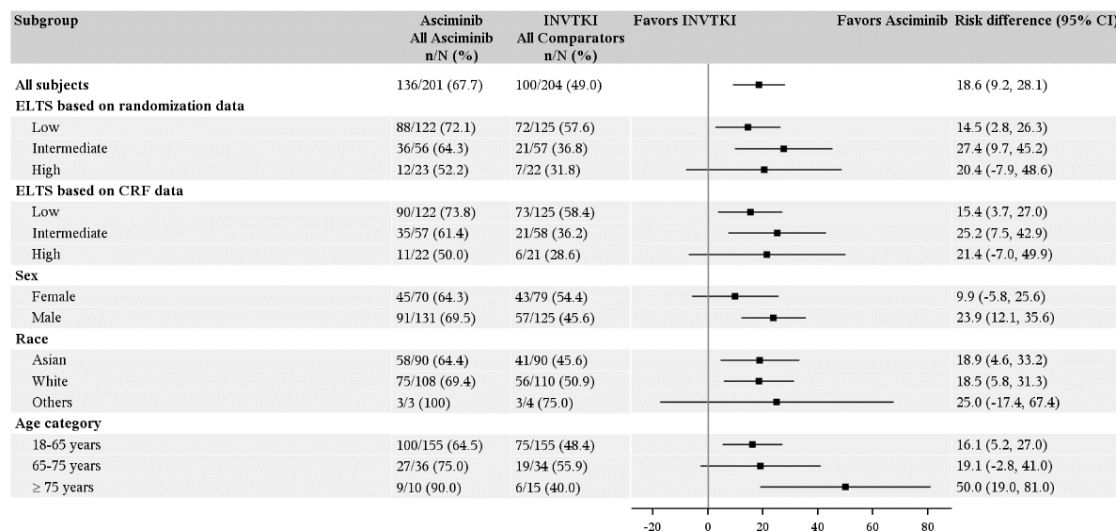
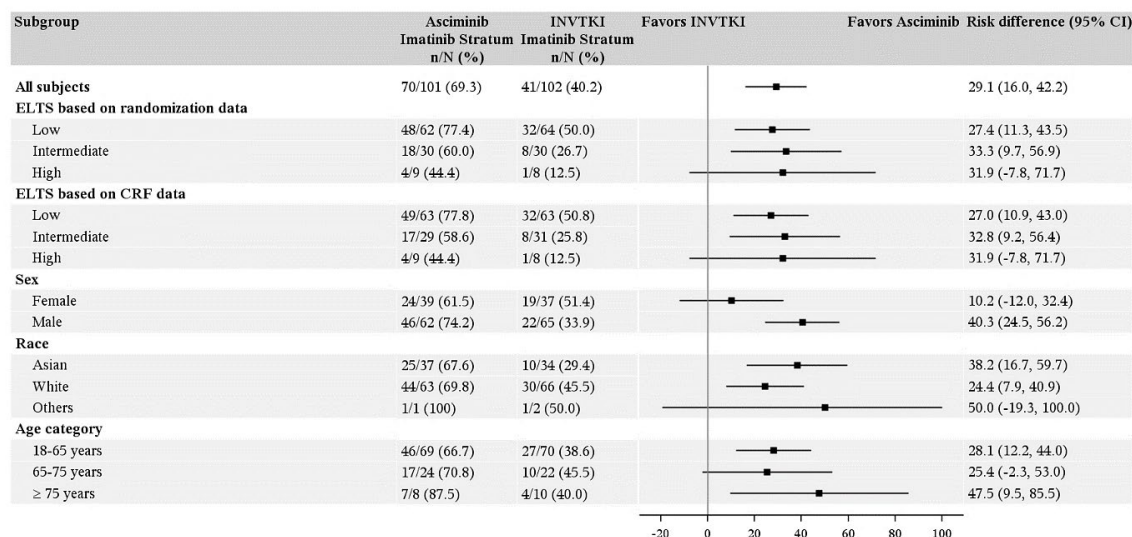
Source: [CO-Table 4-3, CO-Table 4-4]

Participants without PCR assessment at Week 48 are considered non-responders unless they are in MMR at both Week 36 and Week 60. One and 2 participants in the asciminib arm and in the Investigator Selected TKI arm, respectively, are imputed as responders.

Common treatment difference and common risk difference are synonymous. For FAS, the common treatment difference and its 95% CI estimated using the Mantel-Haenszel method after stratifying for (1) pre-randomization selected TKI, and (2) baseline ELTS risk groups (both IRT data). For FAS_{IMA} and FAS_{2GTKI} they are stratified with baseline ELTS risk groups.

Cochran–Mantel–Haenszel 1-sided test stratified by the same stratification factors. Adjusted 1-sided p-value calculated based on the graphical gatekeeping procedure.

Scemblix (asciminib)

Figure 4 Forest Plot of Risk Difference with 95% CI for MMR at Week 48 from Subgroup Analysis of Study J12301**Full Analysis Set****Imatinib Full Analysis Set**

n: The number of participants who responded; N: The total number of participants in the subgroup and treatment arm; INVTKI: Investigator Selected TKI.

95% Wald CI for Risk Difference. Risk Difference is Asciminib vs. INVTKI.

Source: [Study J12301-PA-CSR-Figure 14.2-1.7.1, Figure 14.2-1.7.2]

Scemblix (asciminib)

The Applicant's Position:

The study met both its primary objectives (as described in [Table 10](#)) and was declared positive. Clinically relevant and highly statistically significant improvements in the primary endpoint of MMR rate at Week 48 were observed in participants treated with asciminib vs. participants treated with IS-TKI overall (imatinib, nilotinib, dasatinib, or bosutinib), and vs. participants with imatinib as their pre-randomization selected-TKI (PRS-TKI).

MMR at Week 48 -Asciminib vs. IS-TKI: Superiority was demonstrated for asciminib 80 mg QD compared to IS-TKI, in the overall participants and within the stratum of participants who had imatinib as their PRS-TKI, for the primary endpoint of MMR at Week 48 while on study treatment without meeting any treatment failure criteria (as per [ELN 2020](#) criteria) and without treatment discontinuation. The MMR rate at Week 48 was 67.7% in the asciminib arm compared to 49.0% in the IS-TKI arm. The common treatment difference in the MMR rate was 18.88%, which was clinically meaningful and highly statistically significant (95% CI: 9.59, 28.17; one-sided adjusted p-value: <0.001, per the CMH one-sided test, stratified by both ELTS risk group and PRS-TKI (imatinib vs. 2G TKI) ([Table 10](#)).

Results of the predefined sensitivity analysis of MMR rate at Week 48 (without imputation) of the primary objectives were consistent with the primary results. The MMR rate at Week 48 (without imputation) was 67.2% in the asciminib arm and 48.0% in the IS-TKI arm with the common treatment difference in the MMR rate of 19.37% (95% CI: 10.09, 28.64) [SCE-Section 3.2.1.1].

Two supplemental analyses of MMR rate at Week 48 (FAS) 1) stratified with PRS-TKI and ELTS category from eCRF [asciminib arm vs. IS-TKI arm: 67.7% vs. 49.0%, common treatment difference: 18.51% (95% CI: 9.26, 27.75) 2) after excluding 3 participants from the IS-TKI arm (Imatinib stratum): one randomized by mistake, one had an atypical transcript at screening and was in MMR at baseline, and one participant had typical and atypical transcript at screening [asciminib arm vs. IS-TKI arm: 67.7% vs. 49.3%, common treatment difference: 18.73% (95% CI: 9.39, 28.07)] were consistent with those from the primary analysis indicating no significant impact on the interpretation of the primary efficacy results [SCE-Section 3.2.1.1].

Multivariate analyses indicated a consistent treatment effect of asciminib compared to IS-TKI, independent of the demographic and prognostic variables tested [CO-Section 4.1.4.1.1]. Subgroup analyses for rate of MMR at Week 48 (FAS) demonstrated a robust and consistent treatment effect in favour of asciminib across all demographic and prognostic subgroups, including ELTS risk group (low, intermediate, high) ([Figure 4](#)).

MMR at Week 48-ASC^{IMA} vs. IS-TKI^{IMA}: Within the imatinib stratum, superiority was demonstrated for asciminib 80 mg QD compared to IS-TKI for the primary endpoint of MMR at Week 48 ([Table 10](#)). Results of sensitivity analysis of MMR rate at Week 48 without imputation, were consistent with the primary results confirming robustness of the results. The results of the multivariate

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analysis indicate a consistent treatment effect favoring ASC^{IMA} vs. IS-TKI^{IMA}, independent of the demographic and prognostic variables tested [CO-Section 4.1.4.1.2].

The FDA's Assessment:

FDA confirms that the primary results and associated subgroup results are correct. FDA notes that the overall treatment effect on MMR at Week 48 is a difference of 18.88%, while the difference in the imatinib stratum is 29.55%. As noted below in the Applicant's efficacy results of secondary endpoints, this difference was 8.17% for the 2nd generation TKI stratum. This was expected a priori, as all of the 2nd generation TKIs included were approved based on an improvement in response rates as compared to imatinib in randomized trials.

Given this heterogeneity of treatment effect, the overall estimate should not be considered to be representative of the comparative effectiveness of asciminib versus any of the comparators. The associated subgroup estimates should be considered more reliable for understanding the benefit of asciminib over imatinib or 2nd generation TKIs.

The MMR rate at 48 weeks for imatinib is 40.20%. A recent trial in patients with newly-diagnosed CP-CML to support an approval was BFORE, which randomized patients 1:1 to bosutinib or imatinib. The MMR rate at 48 weeks for imatinib was 37% in BFORE, as reported in the bosutinib USPI. Response rates to imatinib in earlier trials are lower (22% for MMR at 12 months as reported in the nilotinib USPI and 33.8% for MMR at any time as reported in the dasatinib USPI). Such comparisons are limited by potential differences in populations and other uncontrolled confounders.

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 as no data integrity concerns were found. The data were submitted on April 30, 2024 (Data as of 11/28/2023) under \\CDSESUB1\evsprod\NDA215358\0109. The review team was able to replicate the primary and secondary efficacy results, safety results, and key demographic results. No inconsistencies were identified.

Efficacy Results – Secondary and other relevant endpoints

Data:

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Table 11 Summary of Other Secondary Efficacy Results of Study J12301

	FAS		FAS _{IMA}		FAS _{2G^{TKI}}	
	Asciminib N=201	IS-TKI N=204	Asciminib N=101	IS-TKI ^{IMA} N=102	Asciminib N=100	IS-TKI ^{2G^{TKI}} N=102
MMR rate at Week 48						
Response-n (%)				66 (66.00)	59 (57.84)	
(95% CI) ^a				(55.85, 75.18)	(47.66, 67.56)	
Common treatment difference (%) (95% CI) ^b					8.17 (-5.14, 21.47)	
CMH 1-sided test adjusted p-value ^c					NA	
MMR rate by Week 48						
n (%) (95% CI)	140 (69.65) (62.79, 75.92)	104 (50.98) (43.90, 58.03)	71 (70.30) (60.39, 78.98)	45 (44.12) (34.29, 54.29)	69 (69.00) (58.97, 77.87)	59 (57.84) (47.66, 67.56)
Common treatment difference (%) (95% CI)	18.92 (9.78, 28.07)		26.65 (14.06, 39.25)		11.16 (-1.92, 24.25)	
Time to MMR						
KM median time to first MMR (Weeks) (95% CI)	24.3 (24.1, 24.6)	36.4 (36.1, 48.6)	24.1 (24.0, 24.6)	48.6 (36.1, 59.6)	24.3 (24.1, 35.6)	36.1 (24.4, 48.1)
EMR (BCR::ABL1 Ratio (%IS)≤10% at 12 weeks)						
n (%) (cumulative categories)	180 (89.6)	143 (70.1)	89 (88.1)	61 (59.8)	91 (91.0)	82 (80.4)
Common treatment difference (%) (95% CI)	19.68 (12.32, 27.04)		28.75 (17.64, 39.85)		10.57 (1.24, 19.90)	
BCR::ABL1 ≤ 1% rate at Week 48						
n (%) (95% CI)	175 (87.06) (81.62, 91.37)	148 (72.55) (65.88, 78.55)	85 (84.16) (75.55, 90.67)	63 (61.76) (51.61, 71.21)	90 (90.00) (82.38, 95.10)	85 (83.33) (74.66, 89.98)
Common treatment difference (%) (95% CI)	14.78% (7.44, 22.12)		22.86% (11.52, 34.20)		6.66% (-2.36, 15.68)	

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	FAS		FAS _{IMA}		FAS _{2GTKI}	
	Asciminib N=201	IS-TKI N=204	Asciminib N=101	IS-TKI ^{IMA} N=102	Asciminib N=100	IS-TKI ^{2GTKI} N=102
BCR::ABL1 ≤ 1% rate by Week 48						
n (%) (95% CI)	186 (92.54) (87.99, 95.76)	157 (76.96) (70.57, 82.55)	92 (91.09) (83.76, 95.84)	71 (69.61) (59.71, 78.33)	94 (94.00) (87.40, 97.77)	86 (84.31) (75.78, 90.76)
Common treatment difference (%) (95% CI)	15.85% (9.30, 22.40)		22.00% (11.95, 32.06)		9.67% (1.45, 17.89)	
MR 4.0 rate at Week 48						
n (%) (95% CI)	78 (38.81) (32.03, 45.92)	42 (20.59) (15.26, 26.79)	43 (42.57) (32.79, 52.81)	15 (14.71) (8.47, 23.09)	35 (35.00) (25.73, 45.18)	27 (26.47) (18.22, 36.13)
Common treatment difference (%) (95% CI)	18.38% (9.96, 26.79)		28.22% (16.81, 39.63)		8.49% (-3.58, 20.56)	
MR4.0 rate by Week 48						
n (%) (95% CI)	82 (40.80) (33.93, 47.93)	45 (22.06) (16.57, 28.38)	46 (45.54) (35.60, 55.76)	16 (15.69) (9.24, 24.22)	36 (36.00) (26.64, 46.21)	29 (28.43) (19.94, 38.22)
Common treatment difference (%) (95% CI)	18.91 (10.30, 27.52)		30.22 (18.61, 41.83)		7.54 (-4.77, 19.86)	
Time to MR4.0						
KM median time to first MMR (Weeks) (95% CI)	60.1 (48.6, 84.3)	NE (72.9, NE)	48.6 (37.0, 60.1)	NE (72.9, NE)	84.3 (59.0, NE)	NE (64.0, NE)
MR 4.5 rate at Week 48						
n (%) (95% CI)	34 (16.92) (12.01, 22.83)	18 (8.82) (5.31, 13.59)	18 (17.82) (10.92, 26.70)	5 (4.90) (1.61, 11.07)	16 (16.00) (9.43, 24.68)	13 (12.75) (6.96, 20.81)
Common treatment difference (%) (95% CI)	8.2% (1.78, 14.62)		13.13% (4.69, 21.56)		3.24% (-6.34, 12.83)	
MR4.5 rate by Week 48						

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	FAS		FAS _{IMA}		FAS _{2GTKI}	
	Asciminib N=201	IS-TKI N=204	Asciminib N=101	IS-TKI ^{IMA} N=102	Asciminib N=100	IS-TKI ^{2GTKI} N=102
n (%) (95% CI)	40 (19.90) (14.61, 26.10)	24 (11.76) (7.69, 17.00)	22 (21.78) (14.18, 31.10)	6 (5.88) (2.19, 12.36)	18 (18.00) (11.03, 26.95)	18 (17.65) (10.81, 26.45)
Common treatment difference (%) (95% CI)	8.26 (1.26, 15.25)		16.15 (7.01, 25.29)		0.33 (-10.03, 10.69)	

Participants without PCR assessment at Week 48 are considered non-responders unless they are in MMR at both week 36 and week 60. For FAS, 1 and 2 participants in asciminib arm and in Investigator Selected TKI arm, respectively, are imputed as responders. For FAS_{IMA}, 1 participant each in the asciminib arm and the Investigator Selected TKI arm were imputed as responders, for FAS_{2GTKI}, 0 participant in the asciminib arm and 1 participant in the Investigator Selected TKI arm were imputed as responders.

a Clopper-Pearson 95% CI.

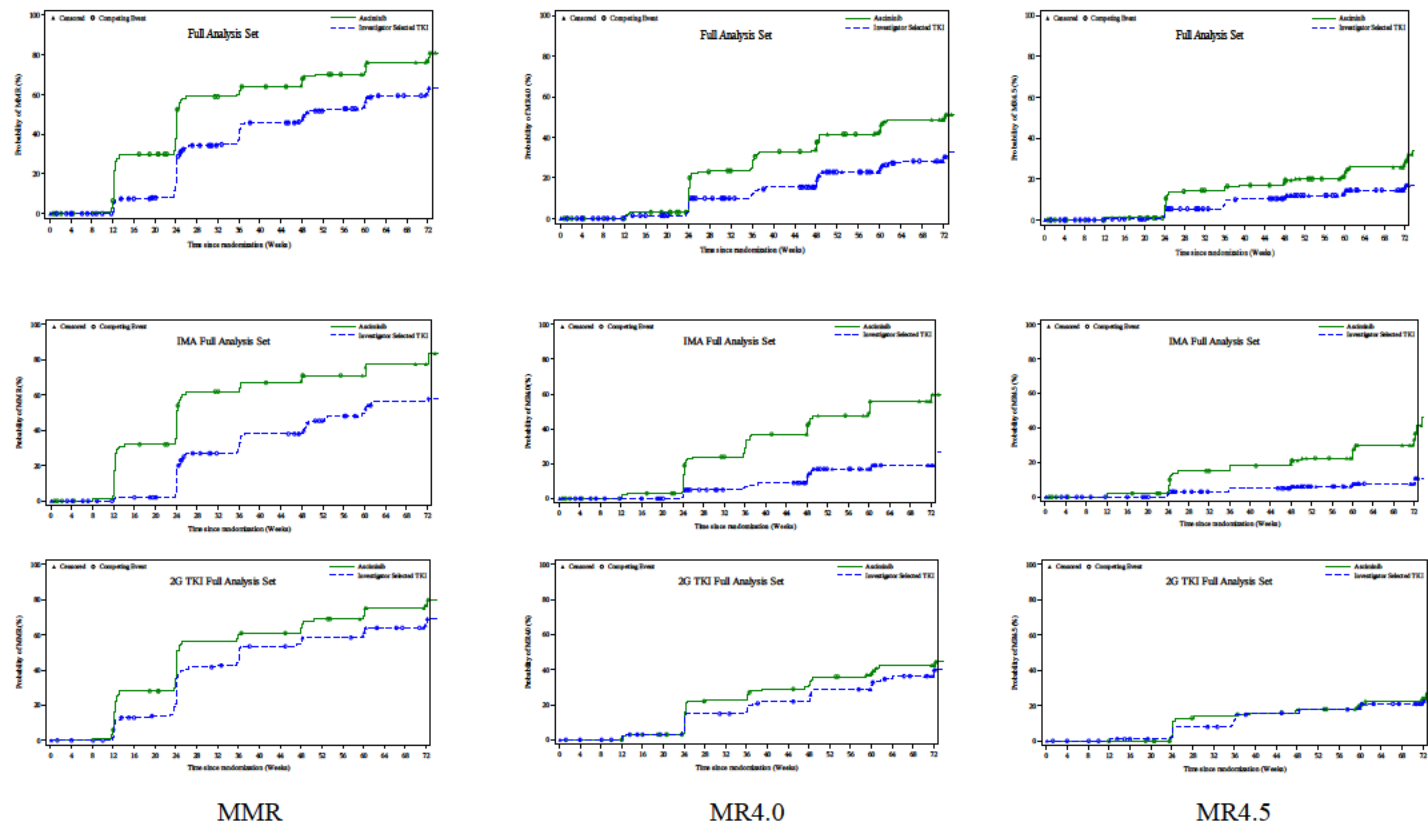
b Common treatment difference and common risk difference are synonymous. For FAS, the common treatment difference and its 95% CI estimated using the Mantel-Haenszel method after stratifying for (1) pre-randomization selected TKI, and (2) baseline ELTS risk groups (both IRT data). For FAS_{IMA} and FAS_{2GTKI} they are stratified with baseline ELTS risk groups.

c Adjusted 1-sided p-value calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted p-value is less than or equal to 2.5%.

Source: [CO-Table 6-2] [SCE Table 6-1]

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Figure 5 Cumulative Incidence Function of Time to MMR, MR4.0, MR4.5 of Study J12301 (FAS, FAS_{IMA}, FAS_{2G TKI})

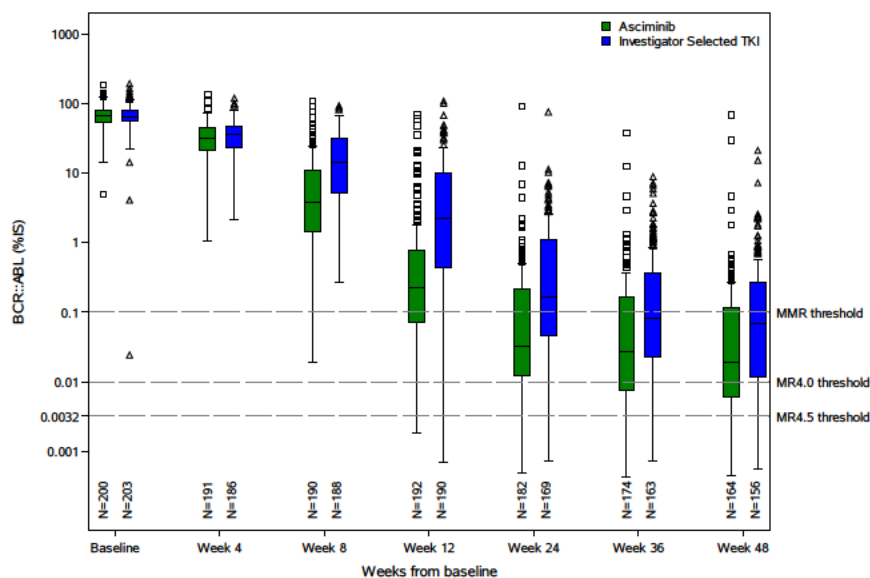


Source: [CO-Figure 6-4]

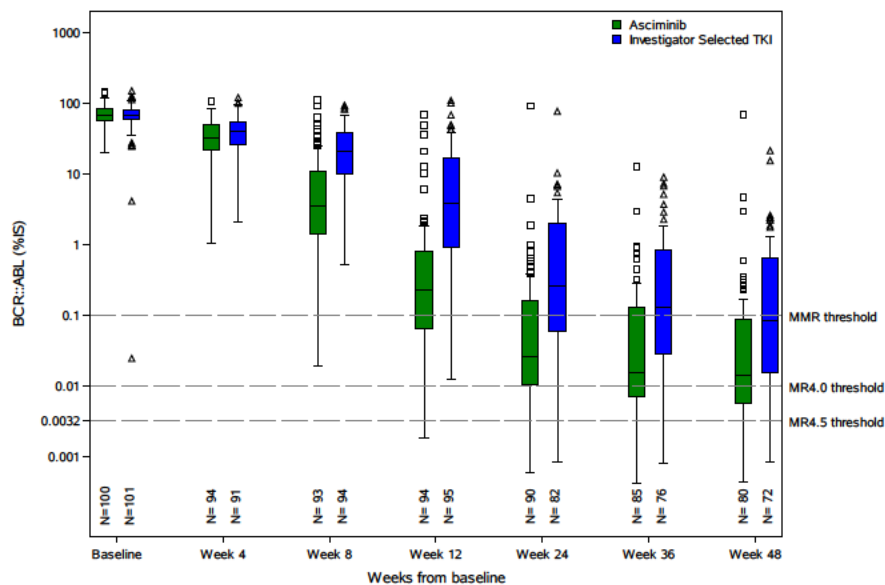
Scemblix (asciminib)

Figure 6 BCR::ABL1 ratio (%IS) Summary Plot Over Time of Study J12301

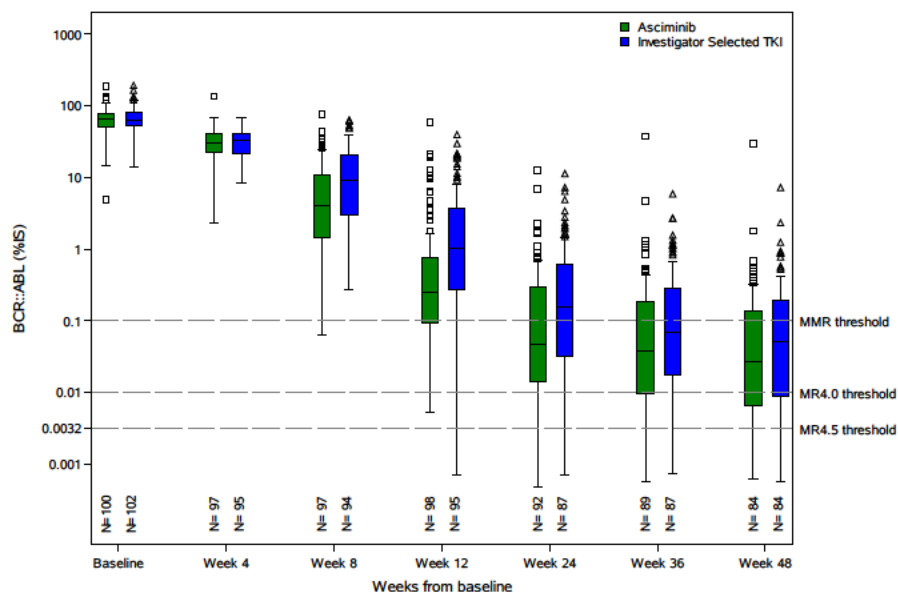
FAS



FASIMA



Scemblix (asciminib)

FAS₂GTKI

N: number of participants with available assessments.

Squares and triangles denote outliers

Source: [Study J12301 PA CSR-Figure 14.2-2.2.3]

The Applicant's Position:

MMR at Week 48-ASC^{2G} vs. IS-TKI^{2G}: Within the 2G TKI stratum, the MMR rate at Week 48 in the asciminib arm was numerically higher at 66.0% compared to 57.8% in the IS-TKI arm. The common treatment difference in the MMR rate was 8.17% (95% CI: -5.14, 21.47) (not powered). A numerically higher treatment effect in favor of asciminib was observed across all demographic and prognostic subgroups, including all ELTS risk categories. Results of the predefined sensitivity analyses (without imputation) were consistent with the analysis of MMR rate at Week 48 in FAS₂GTKI with imputation, thereby confirming robustness of the results [CO-Section 4.1.4.2.1].

MMR at and by all scheduled data collection time points: MMR at and by scheduled data collection time points: A higher rate of MMR was achieved in participants in the asciminib arm (overall and within the imatinib and 2G TKI strata) compared to participants in the IS-TKI arm at or by each scheduled timepoint assessed, with clinically meaningful differences starting to be observed from Week 12 onwards. The results are consistent across the imatinib and 2G TKI strata, favouring asciminib [CO-Section 4.1.4.2.1].

The MMR rate at and by each scheduled time point (Weeks 12, 24, 36, and 48) was higher for the asciminib arm compared to the IS-TKI arm, with clinically meaningful differences starting as early as Week 12 (MMR rate at Week 12: 29.9% in the asciminib arm compared to 7.4% in the IS-

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TKI arm, with an estimated common treatment difference of 22.55% (95% CI: 15.32, 29.79)). This clinically meaningful difference in MMR rate favoring participants in the asciminib arm persisted through Week 48 ([Table 11](#)) [CO-Section 4.1.4.2.1].

MR2.0 (BCR::ABL1 $\leq 1\%$) at and by all scheduled data collection time points: A higher rate of MR2.0 was achieved in participants in the asciminib arm (overall and within the imatinib and 2G TKI stratum) compared to participants in the IS-TKI arm **at** or **by** each scheduled timepoint assessed, with clinically meaningful differences starting to be observed from as early as Week 8 onwards. The results are consistent across the imatinib and 2G TKI strata, favouring asciminib [CO-Section 4.1.4.2.1].

The MR2.0 rate at and by each scheduled time point (Weeks 12, 24, 36 and 48) was higher for the asciminib arm compared to the IS-TKI arm, with clinically meaningful differences starting as early as Week 8 (MR2.0 rate at Week 8: 15.4% in the asciminib arm compared to 2.9% in the IS-TKI arm, with an estimated common treatment difference of 12.52% (95% CI: 7.02, 18.03)) which persisted through Week 48 ([Table 11](#)) [SCE-Table 3-13] [CO-Section 4.1.4.2.1].

Time to MMR: The probability of achieving MMR earlier, as early as Week 12, was higher in the asciminib arm compared to the IS-TKI arm overall (probability of achieving MMR by Week 48: 66.5% vs. 46.3%), and within the imatinib stratum (by Week 48: 69.1% vs. 38.0%) and the 2G TKI stratum (by Week 48: 64.0% vs. 54.5%) ([Figure 5](#)).

MMR was achieved faster in participants randomized to the asciminib arm compared to the IS-TKI arm overall (KM estimated median time to first MMR: 24.3 weeks vs. 36.4 weeks) and the trends were similar across the imatinib (24.1 weeks vs. 48.6 weeks) and the 2G TKI strata (24.3 weeks vs. 36.1 weeks) ([Table 11](#)).

EMR (BCR::ABL1 (IS) $\leq 10\%$ at Week 12): A higher number of participants in the asciminib arm achieved EMR compared to the IS-TKI arm (overall and within each stratum). EMR indicates an optimal response to TKI therapy and has been shown to correlate with good prognosis (improved OS and PFS) ([Table 11](#)).

Deep molecular response (MR4.0/MR4.5): A higher rate of MR4.0 and MR4.5 was achieved in participants in the asciminib arm (overall and within the imatinib and 2G TKI stratum) compared to participants in the IS-TKI arm **at** and **by** each scheduled timepoint assessed, with clinically meaningful differences starting to be observed from Week 24. The results are consistent across the imatinib and 2G TKI strata, favouring asciminib ([Table 11](#)).

Time to MR4.0/MR4.5: MR4.0/MR4.5 was achieved faster in participants treated with asciminib compared to IS-TKI, and the results were similar within the imatinib and 2G TKI strata. Median time to first MR4.0 was 60.1 weeks in the asciminib arm and not reached in the IS-TKI arm [CO-Section 4.1.4.2.1].

BCR::ABL1 ratio (% IS) kinetics: Summary plots over time of number of participants achieving EMR, MR2.0, MMR, MR4.0 and MR4.5 in FAS, FAS_{IMA}, and FAS_{2GTKI} showed that higher proportion

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of participants in the asciminib arm achieved these thresholds earlier and as compared to participants in the IS-TKI arm. Overall and within each stratum, on average, participants in the asciminib arm had lower $BCR::ABL1$ levels as compared to participants in the IS-TKI arm, and from Week 12 onwards, the graphical comparison of medians at each timepoint for the asciminib vs. IS-TKI arm showed clinically meaningful difference (for FAS and FAS_{IMA}) and a numerically higher difference (for FAS_{2GTKI}) in favor of asciminib [CO-Section 4.1.4.2.2] ([Figure 6](#)).

CHR: By Week 48, CHR was achieved in 94.5% of participants in the asciminib arm and 94.1% in the IS-TKI arm, with no clinical difference. A trend of earlier CHR being achieved in the asciminib arm before Week 8 was noted. Similar results were observed within the imatinib stratum (ASC^{IMA} vs. IS-TKI^{IMA}: 90.10% vs. 93.14%) and within the 2G TKI stratum (ASC^{2G} vs. IS-TKI^{2G}: 99.0% vs. 95.1%) [CO-Section 4.1.4.2.2].

CCyR by Week 48: During the course of the study, cytogenetic assessment was not mandatory and only performed if clinically indicated (e.g., treatment failure). As a result, very few participants (n =2) had the cytogenetic assessment performed by Week 48 [Study J12301-PA-CSR-Section 11.3.3.1].

The FDA's Assessment:

FDA agrees with the results presented above. FDA focused on the validation of key primary results for MMR at Week 48.

FDA notes that the MMR rate at 12 months for the 2GTKI stratum is 57.84% in the control arm. This is higher than the response rates reported in the corresponding USPI's for these products. For instance, bosutinib yielded a 47% MMR rate at 12 months and nilotinib yielded a 44% MMR rate at 12 months. The USPI for dasatinib reports an MMR rate at any time of 52.1%.

Dose/Dose Response

The Applicant's Position:

Exposure-response analyses are described in [Section 19.4.3](#).

The FDA's Assessment:

Refer to the Clinical Pharmacology review in Section 19.4.2 and the FDA's assessment therein.

Durability of Response

Data

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Table 12 Duration of Response in Study J12301

Duration of first MMR among subjects who achieved MMR (MMR responder set)						
	Asciminib N=157	IS-TKI N=119	Asciminib^{IMA} N=77	IS-TKI^{IMA} N=52	Asciminib^{2GTki} N=80	IS-TKI^{2GTki} N=67
Number of participants who lost response	2	1	1	1	1	0
KM estimated probability (%) of remaining in response (95% CI)						
48 weeks after achieving MMR	97.8 (91.6-99.5)	98.9 (92.7-99.8)	97.1 (80.9-99.6)	97.2 (81.9-99.6)	98.2 (88.0, 99.7)	100.0 (100.0-100.0)
Duration first MR 4.0 among subjects who achieved MR 4.0 (MR 4.0 responder set)						
	Asciminib N=97	IS-TKI N=55	Asciminib^{IMA} N=53	IS-TKI^{IMA} N=18	Asciminib^{2GTki} N=44	IS-TKI^{2GTki} N=37
Number of participants who lost response	3	1	2	0	1	1
KM estimated probability (%) of remaining in response (95% CI)						
48 weeks after achieving MR4.0	95.3 (85.8-98.5)	97.2 (81.9-99.6)	94.9 (80.9, 98.7)	100.0 (100.0-100.0)	96.7 (78.6-99.5)	96.6 (77.9-99.5)
Duration first MR 4.5 among subjects who achieved MR 4.5 (MR 4.5 responder set)						
	Asciminib N=56	IS-TKI N=31	Asciminib^{IMA} N=31	IS-TKI^{IMA} N=8	Asciminib^{2GTki} N=25	IS-TKI^{2GTki} N=23
Number of participants who lost response	1	1	1	0	0	1
KM estimated probability (%) of remaining in response (95% CI)						
48 weeks after achieving MR4.0	97.2 (81.9-99.6)	100.0 (100.0-100.0)	94.7 (68.1-99.2)	NE (NE-NE)	100.0 (100.0-100.0)	100.0 (100.0-100.0)
Source: [Study J12301 PA CSR-Table 14.2-1.4.1, Table 14.2-1.4.2, Table 14.2-1.4.3, Table 14.2-2.7.1, Table 14.2-2.7.2, Table 14.2-2.7.3, Table 14.2-2.11.1, Table 14.2-2.11.2, Table 14.2-2.11.3].						

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The Applicant's Position:

The majority of participants who achieved MMR/MR4.0/MR4.5 continued to maintain their response at the time of their last molecular assessment, suggesting a sustained treatment effect of asciminib. Results of ASC^{IMA} vs. IS-TKI^{IMA} and ASC^{2G} vs. IS-TKI^{2G} were similar to results of asciminib vs. IS-TKI (Table 12) [CO-Section 4.1.4.2].

The FDA's Assessment:

The FDA agrees with the results presented above. FDA focused on the validation of key primary results for MMR at Week 48. Therefore, all other results have not been completely validated.

Persistence of Effect

The Applicant's Position:

Treatment with asciminib should continue, until unacceptable toxicity or treatment failure occurs.

Time to treatment failure (TTF): The KM probability of experiencing treatment failure by data cut-off was lower in the asciminib arm as compared to participants in the IS-TKI arm (FAS) (overall and within strata) [CO-Section 4.1.4.2.3].

Event free survival (EFS) and failure free survival (FFS): The proportion of participants with an EFS event was approximately 2-times lower in the asciminib arm compared to the IS-TKI arm (12.4% vs. 24.5%). The probability of EFS and FFS was higher in participants in the asciminib arm as compared to participants in the IS-TKI arm (overall and within each stratum) [CO-Section 4.1.4.2.3].

Progression free survival (PFS)/ Overall survival (OS) were immature at the time of this report. PFS events occurred in 2.5% of participants in the asciminib arm and 3.9% of participants in the IS-TKI arm. There were no on-treatment deaths in either treatment arm; 2/201 (1.0%) participants in the asciminib arm and 3/204 (1.5%) participants in the IS-TKI arm died during the study [CO-Section 4.1.4.2.3].

The FDA's Assessment:

FDA agrees with the results presented above. FDA focused on the validation of key primary results for MMR at Week 48. Therefore, all other results have not been completely validated.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

The Applicant's Position:

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Patient-related outcomes data were collected in Study J12301. However, no formal statistical analysis was performed and only descriptive summaries are provided in the CSR [Study J12301 PA CSR-Section 11.5].

The FDA's Assessment:

FDA agrees with the Applicant's assessment that the patient-related outcomes data were collected in this study, but no formal statistical analysis was conducted, and only descriptive summaries are provided. This is in line with the exploratory nature of the analysis.

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 confirms the Applicant's assessment.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

Efficacy results for the newly diagnosed Philadelphia chromosome positive CML in chronic phase indication was provided by study CABL001J12301. Study CABL001J12301 is a phase 3, multi-center, open-label, randomized study of asciminib versus IS-TKIs in participants with newly diagnosed Ph+ CP-CML. The primary endpoint of MMR at 48 weeks was considered appropriate as it reflects an endpoint likely to predict longer term disease control and survival and represents an acceptable depth and duration of response in the newly diagnosed setting. FDA agrees that the open-label design is appropriate given the differences in treated regimens and given the primary endpoint was assessed by central lab determined BCR-ABL1 levels and therefore not likely to be subject to measurement bias. The review team recommends that this indication receives accelerated approval.

The Applicant also requested the Philadelphia chromosome-positive CML in CP, previously treated with two or more TKIs indication to be updated to previously treated Philadelphia chromosome-positive CML in CP indication to be inclusive of second line treatment. Efficacy results for the initial approval in 3L+ treatment was provided by study CABL001A2301 which was a phase 3, multi-center, open-label, randomized study of asciminib vs. bosutinib in patients with Philadelphia chromosome-positive CML in CP, previously treated with two or more TKIs. Study CABL001AUS08 is an ongoing phase 2, US multi-center, open label, single arm dose escalation study in patients with Philadelphia chromosome positive CML in CP receiving asciminib monotherapy as 2L or 1L treatment. The primary endpoint of this study is MMR rate at 12 months with secondary endpoints of molecular responses at other time points. For the

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previously treated Philadelphia chromosome-positive CML in CP indication, 6-month interim efficacy results in 28 patients using asciminib as 2L treatment were evaluated and found acceptable. See summary results at the interim analysis in Section 8.1.4. The review team recommends that the previously treated Philadelphia chromosome positive CML in CP indication receives regular approval.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position:

Efficacy claims for the proposed indication are based on the results of the primary analysis of the Phase III registration Study J12301.

Preliminary clinical data from Study CABL001AUS08 (ASC2ESCALATE, hereafter referred to as Study AUS08), an ongoing Phase II, US multi-center, open label, single arm dose escalation study of asciminib 80 mg QD single agent in 2L Ph+ CML-CP, are available and have been included as agreed with US FDA [CO-Section 1.0].

The demographic, disease history and other baseline characteristics of the study population in the 2L cohort in Study AUS08 are representative of participants with Ph+ CML-CP in the 2L setting.

As of the cut-off date for this analysis (22-Mar-2024), preliminary efficacy data from Study AUS08 (2L cohort; N=43) was analyzed for 14 participants who were evaluable for the 6 months efficacy assessment with the remaining 29 participants ongoing on study not having achieved this milestone yet. The analysis showed achievement of MR2.0 and MMR for asciminib in 12/14 (85.7%) (95% CI: 57.2, 98.2) and 8/14 (57.1%) (95% CI: 28.9, 82.3) participants respectively at 6 months. The MR4.0 rate was achieved in 4/14 participants (28.6%; 95% CI: 8.4, 58.1) at 6 months [CO-Section 4.2.2].

The FDA's Assessment:

FDA confirms the Applicant's position. Also, refer to Sections 8.1.2 and 8.1.3.

During the review, updated safety and efficacy information was provided on August 30, 2024, for Study AUS08 from interim analysis 2 (IA2) with a data cutoff of June 28, 2024. At IA2, 71 patients were enrolled in the 2L cohort, and 28 patients were evaluable for efficacy at 6 months having completed the efficacy assessment at that timepoint or discontinued prior to the timepoint.

Of the 28 patients evaluable at 6 months, 25 patients completed the 6-month visit, 1 patient had an unscheduled visit at day 145 which was considered to be the 6-month assessment, and 2 patients discontinued prior to the 6-month visit (1 due to an adverse event, 1 due to patient decision). The median age was 48 years with 25% of patients ≥65 years, 54% were male, and 93% were White. The reason for discontinuing the prior TKI was lack of efficacy in 16 (57%) patients and lack of tolerability in 12 (43%) patients.

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The MMR rate at 6 months was 43% (12/28; 95% CI: 24, 63). For patients who discontinued their prior TKI due to lack of efficacy, the MMR rate at 6 months was 31% (5/16; 95% CI: 11, 59). For patients who discontinued their prior TKI due to lack of tolerability, the MMR rate at 6 months was 58% (7/12; 95% CI: 28, 85).

In the patients treated with asciminib as 2L treatment in this study, the MMR rate at 6 months was intermediate to the MMR rate observed in the 1L cohort in study J12301 and the 3L+ cohort in study A2301, which would be generally expected for this population. See Section 6.2.2.1 for discussion of PK/PD modeling used to support extrapolation to the 2L indication.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

The efficacy evaluation for this indication is based on the primary analysis from Study J12301.

This study met both primary objectives. The MMR rate at Week 48 in the asciminib arm vs. the IS-TKI arm in the overall population (FAS) was 67.7% vs. 49.0% and within the imatinib stratum (FAS_{IMA}) was 69.3% vs. 40.2%. The common treatment difference in the MMR rates (per the CMH one-sided test) between asciminib and IS-TKI were 18.88% (95% CI: 9.59, 28.17; $p < 0.001$) (FAS) and 29.55% (95% CI: 16.91, 42.18; $p < 0.001$) (FAS_{IMA}), which were both considered clinically meaningful and highly statistically significant.

For both the overall population (FAS) and for the imatinib stratum (FAS_{IMA}), the subgroup analysis for rate of MMR at Week 48 demonstrated a robust and consistent treatment effect in favor of asciminib across all demographic and prognostic subgroups, including ELTS risk group (low, intermediate, high). Results of multivariate analyses also indicated a consistent treatment effect in favor of asciminib compared to IS-TKI, independent of the demographic and prognostic variables tested.

The efficacy of asciminib was further demonstrated by other secondary efficacy endpoints of the study with data across all endpoints consistently favoring asciminib and showing an overall positive efficacy data for asciminib vs. the standard of care treatments.

Higher and favorable rates with faster, sustained, and deeper molecular responses were observed generally in participants with asciminib treatment compared to the IS-TKIs, for molecular response (at and by all time-points).

Within the 2G TKI stratum, the MMR rate at Week 48 in the asciminib arm was numerically higher than in the IS-TKI arm (66.0% vs. 57.8%) with the common treatment difference in the MMR rate being 8.17% (95% CI: -5.14%, 21.47%) (not powered) per the CMH one-sided test. A numerically higher treatment effect in favor of asciminib was observed across all demographic and prognostic subgroups, including all ELTS risk categories.

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Of note, the MMR rate at 12 months for asciminib was observed to be even better than what was predicted as part of the protocol design. This trend in improved MMR rates were also seen for the 2G TKIs including comparing with what was previously seen in literature, which could be attributed to the current much improved understanding of CML disease management.

MMR was achieved faster overall and within each stratum, as early as Week 12. MMR was achieved faster in participants in the asciminib arm compared to the IS-TKI arm (median time to first MMR: 24.3 weeks vs. 36.4 weeks). The same trend was observed within the imatinib stratum (24.1 weeks vs. 48.6 weeks) and within the 2G TKI stratum (24.3 weeks vs. 36.1 weeks).

Loss of MMR was rare in both treatment arms. All participants who achieved MMR continued to remain in MMR at the time of their last molecular assessment except 1 participant who had confirmed loss of MMR in the asciminib arm, suggesting a sustained treatment effect of asciminib.

A higher rate of EMR ($BCR::ABL1 \leq 10\%$ at Week 12), and a higher rate of MR2.0 ($BCR::ABL1 \leq 1\%$) **at** and **by** all scheduled timepoints from as early as Week 8 which persisted through Week 48, were also achieved in participants in the asciminib arm compared to the IS-TKI arm, overall and within each stratum.

Deep molecular response was achieved with higher rates of MR4.0 and MR4.5 (overall and within each stratum) observed in participants in the asciminib arm **at** and **by** all scheduled timepoints from as early as Week 24 which persisted through Week 48. Probability of achieving MR4.0/MR4.5 earlier, as early as Week 24, was higher in the asciminib arm compared to the IS-TKI arm (overall and within each stratum). Median time to first MR4.0 was 60.1 weeks in the asciminib arm and not reached in the IS-TKI arm. The majority of participants in the asciminib and the IS-TKI arm who achieved MR4.0 (96.9% vs. 98.2%)/MR4.5 (98.2% vs. 96.8%) continued to remain in MR4.0/MR4.5 at the time of their last molecular assessment, further suggesting a sustained treatment effect of asciminib.

Overall Summary

Approval in the 3L+ setting: Asciminib is approved for treatment of patients previously treated with at least two prior TKIs based on Study A2301 ([Rea et al 2021](#), [Hochhaus et al 2023](#)).

Benefit/risk profile in the 1L setting: Data from Study J12301 now shows compelling evidence supporting the efficacy claim of asciminib in adult patients with Ph+ CML-CP in the 1L setting.

Clinical extrapolation of efficacy of asciminib in 2L: Based on an established response rate in 1L (from current Study J12301) and in 3L+ (from the previous Study A2301), efficacy of asciminib in 2L can be established by extrapolation. Taking into account historical data generated for the other TKIs, leading to approvals in the 2L setting and subsequently in the 1L setting, the indication of asciminib is proposed to be extended to previously treated patients including the 2L setting. The 2L Ph+ CML-CP treatment landscape includes the same TKIs as 1L, and the response rate for asciminib in 3L+ is comparable to that seen in 2L with 2G TKIs:

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- The 2L Ph+ CML-CP treatment landscape is composed of imatinib and 2G TKIs (dasatinib, nilotinib and bosutinib), as it is the case in the 1L setting. Since Study J12301 demonstrates the superiority of asciminib against the IS-TKIs of imatinib and 2G TKIs in 1L Ph+ CML-CP, a similar trend of response could be expected in 2L.
- Furthermore, the response rate observed with asciminib in the 3L+ population (MMR by 2 years: 41%; [Hochhaus et al 2023](#)) is even better than the response rate seen in pivotal studies with 2G TKIs in 2L (MMR by 2 years: 28 to 38%; nilotinib, [Kantarjian et al 2011](#); dasatinib, [Shah et al 2010](#); bosutinib, [Gambacorti-Passerini et al 2014](#)).

Considering the above and also the fact that higher efficacy of TKIs is seen in earlier lines compared to later lines, it can be concluded that asciminib would be effective and compare favorably to other TKIs in 2L Ph+ CML-CP.

Modeling based estimated efficacy in 2L extrapolation data: Furthermore, model-based analysis of asciminib based on 1L and 3L+ data as well as the nilotinib 1L and 2L modeling data used for extrapolation across lines of asciminib treatment in CML-CP was able to successfully show high predicted MMR rates for asciminib in 2L and as expected, in-between the MMR rates demonstrated in 1L and 3L+ clinical studies: a 48-week MMR rate in the range of 54-63% and a 96-week MMR rate of 66-74% was estimated for asciminib in 2L. Thus, asciminib is expected to be highly efficacious as a 2L treatment for Ph+ CML-CP.

Interim preliminary results from Study AUS08: The demographic, disease history and other baseline characteristics of the study population are representative of participants with Ph+ CML-CP in the 2L setting. Available clinical data from Study AUS08 shows preliminary robust efficacy of asciminib in 2L Ph+ CML-CP with MR2.0 and MMR for asciminib in 12/14 (85.7%) (95% CI: 57.2, 98.2) and 8/14 (57.1%) (95% CI: 28.9, 82.3) participants respectively at 6 months. This efficacy data in 2L is trending to validate the clinical extrapolation that efficacy rates in 2L can be estimated to be between the observed rates in 1L and 3L+ and is also in alignment with the data predicted by the 2L modeling approach. Within the limitation of the small dataset this preliminary data seems to compare favorably with historical data from 2G TKIs in 2L, where 25% to 50% rate of MCyR by 6 months, and ~ 7-11% MMR rate at 6 months have been reported ([Gambacorti-Passerini et al 2014](#)).

The FDA's Assessment:

Refer to the FDA's Assessment in Section 8.1.3.

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8.2. Review of Safety

The Applicant's Position:

The key safety data in support of this application is from the registration Study J12301 (N=401 treated participants; 200 in the asciminib treatment group and 201 in the IS-TKI treatment group).

The safety evaluation of asciminib monotherapy to establish the overall safety profile of asciminib, is based on data from 556 participants with Ph+ CML in a pooled analysis across 3 clinical studies: Study J12301 (1L), n=200; Study A2301 (3L+), n=156, and Study X2101, n=200. This Safety pool was pre-agreed with FDA. The pooling strategy supports the proposed indication covering the overall disease population, i.e. adult participants with Ph+ CML-CP, irrespective of line of therapy. Participants harboring the T315I mutation were also included.

All safety analyses were performed on the Safety Set. The Safety Set includes all participants who received at least one dose of study treatment in Studies J12301, A2301, and X2101. Participants were analyzed according to the study treatment received. In Studies J12301 and A2301, treatment received is defined as the randomized treatment if the participant took at least one dose of asciminib or comparator TKI. Participants who switched treatment were not included.

The FDA's Assessment:

FDA agrees with the Applicant's position of the safety database for asciminib. Warnings and Precautions sections of the proposed USPI is based on the Asciminib Safety Pool (N=556). The Asciminib Safety Pool consists of patients treated with asciminib in three studies: 200 patients in study CABL001J12301 (1L), 156 patients in study CABL001A2301 (3L+), and 200 patients in study CABL001X2101.

The analyses in this review are based on study CABL001J12301 with a data cut-off date of 28 November 2023. Safety analyses of the interim results from the 2L cohort of 71 patients in study CABL001AUS08 with a data cut-off date of 28 June 2024 have also been performed and included in relevant sections of the review.

8.2.1. Safety Review Approach

The Applicant's Position:

A comprehensive assessment of safety data relevant to the use of asciminib as monotherapy in participants with CML is provided in the subsequent sections below ([Section 8.2.4](#)).

Individual safety data from Study J12301 (N=401 treated participants; 200 in the asciminib arm and 201 in the IS-TKI arm) is also summarized in comparison to IS-TKIs (all comparators:

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imatinib, nilotinib, dasatinib or bosutinib), imatinib and 2G TKIs and is essential for a thorough benefit-risk assessment of asciminib vs. the current therapies (imatinib and the 2G TKIs).

Additionally, long-term safety from Studies A2301 and X2101 are included in the Safety pool.

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 in participants with Ph+ CML-CP. This safety population is also considered appropriate for the detection and characterization of common AEs and to provide guidance on toxicity management in the intended population.

The FDA's Assessment:

As the Asciminib Safety Pool (N=556) includes safety data related to a larger patient population of patients using asciminib, Warnings & Precautions section of the label 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 CABL001J12301 (safety set of 200 patients in the asciminib arm and 201 in the IS-TKI arm). Interim safety data from 71 patients treated with asciminib as 2L treatment in study CABL001AUS08 have also been analyzed to support the previously treated Ph+ CP-CML indication.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 13 Duration of Exposure to Study Drug (Safet Set)

Duration of exposure (weeks)	Study J12301						Safety Pool All Asciminib N=556
	Asciminib			Investigator Selected TKI			
	Imatinib Stratum N=100	2G TKI Stratum N=100	All Asciminib N=200	Imatinib N=99	2G TKI N=102	All Comparators N=201	
Mean (SD)	61.00 (20.521)	74.21 (19.558)	67.60 (21.064)	53.32 (22.075)	69.32 (21.985)	61.43 (23.392)	132.05 (113.627)
Median	60.93	75.21	69.79	56.29	71.43	64.29	83.29
Min-Max	0.7-107.7	5.9-105.1	0.7-107.7	2.7-99.0	1.3-103.1	1.3-103.1	0.1-439.0
Duration of exposure categories							
< 8 weeks	4 (4.0)	1 (1.0)	5 (2.5)	5 (5.1)	3 (2.9)	8 (4.0)	29 (5.2)
8-< 16 weeks	2 (2.0)	1 (1.0)	3 (1.5)	1 (1.0)	3 (2.9)	4 (2.0)	14 (2.5)
16-< 24 weeks	2 (2.0)	3 (3.0)	5 (2.5)	8 (8.1)	2 (2.0)	10 (5.0)	27 (4.9)
24-< 48 weeks	4 (4.0)	3 (3.0)	7 (3.5)	13 (13.1)	4 (3.9)	17 (8.5)	45 (8.1)
48-< 96 weeks	87 (87.0)	84 (84.0)	171 (85.5)	71 (71.7)	83 (81.4)	154 (76.6)	205 (36.9)
96-< 144 weeks	1 (1.0)	8 (8.0)	9 (4.5)	1 (1.0)	7 (6.9)	8 (4.0)	30 (5.4)
144-< 192 weeks	0	0	0	0	0	0	64 (11.5)
≥192 weeks	0	0	0	0	0	0	142 (25.5)
Patient-Treatment-Years	116.9	142.2	259.1	101.2	135.5	236.7	1407.1
Source: [SCS Appendix 1-Table 1-2]							

Scemblix (asciminib)

The Applicant's Position:

A pooled analysis of 556 participants contributed to the main analysis for safety of asciminib. Exposure to asciminib in Studies J12301, A2301 and X2101 was considered appropriate by Novartis to allow for an adequate assessment of the safety of asciminib in participants who are representative of the intended target population.

In Study J12301, the median duration of exposure to study drug was marginally longer in the asciminib treatment group (69.79 weeks) compared to the IS-TKI treatment group (64.29 weeks) ([Table 133](#)). Within the IS-TKI treatment group, the median duration of exposure was 56.29 weeks for imatinib and 71.43 weeks for 2G TKI. The difference in exposure between imatinib and 2G TKI is due in part to the recruitment dynamics wherein recruitment in the 2G TKI stratum was completed early. After enrollment of the 2G TKI stratum was completed, all participants were entered into the imatinib stratum during the last 3 months. As a result, the imatinib stratum has lower exposure as well as shorter follow-up [CO-Section 5.1.1.3].

In the **All Asciminib Safety Pool**, the median duration of exposure (83.3 weeks, range: 0.1 to 439.0) and the total exposure (1407.1 patient-years) is considered adequate for a comprehensive safety assessment for asciminib across the different lines of treatment ([Table 133](#)).

The FDA's Assessment:

FDA agrees with the Applicant's assessment that the duration of exposure to asciminib is adequate considering that the dual primary endpoints are MMR at 48 weeks with asciminib versus IS-TKI and MMR at 48 weeks with asciminib versus imatinib (both within the stratum of patients with imatinib as their pre-randomization selected TKI).

Relevant characteristics of the safety population:

The Applicant's Position:

Overall, the demographics and baseline characteristics in the All Asciminib Safety Pool were representative of the targeted patient population of newly-diagnosed and previously-treated Ph+ CML-CP.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Asciminib Safety Pool (N=556) included sufficient number of patients to reflect the demographic and baseline characteristics of newly diagnosed and previously treated Ph+ CP-CML patients.

Adequacy of the safety database:

The Applicant's Position: Details are provided in [Section 8.2](#).

The FDA's Assessment:

The size of the safety database is adequate to provide a reasonable estimate of the adverse

Scemblix (asciminib)

reactions, and the duration of treatment is adequate to allow assessment of adverse reactions over time for the indicated populations.

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 datasets 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 Events

The Applicant's Position:

The safety of asciminib was evaluated based on:

- Frequency, type, and severity of AEs (graded as per NCI CTCAE version 5.0 for Study J12301, and version 4.03 for Studies A2301 and X2101) and study drug relationship. (Note: grade 5 events were collected in Studies J12301 and A2301 and were derived for Study X2101 based on events with a fatal outcome, and incorporated in the Asciminib Safety Pool).
- Frequency of deaths, SAEs, AESIs, and ADRs.
- Changes in laboratory parameters, with particular attention to grade 3 or 4 laboratory abnormalities, ECG changes, and vital signs.

Adverse events were coded using MedDRA version 26.1 for Study J12301, and the same version was applied to all studies in the All Asciminib Safety Pool regardless of the individual study MedDRA versions.

Participants were questioned about AEs at each clinical visit. In addition, AEs could also be detected when reported by the participants 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 and other TKIs were also analyzed. These Adverse events of special interest (AESIs) were identified by grouping AEs that are of scientific and medical concern specific to asciminib and/or are related to class risks of other TKIs.

Scemblix (asciminib)

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Adverse events were assessed by frequency (i.e., events per patient). Additional grouped 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.

Adverse events in study CABL001AUS08 were graded as per CTCAE version 5.0 and they were coded using MedDRA version 27.0.

Routine Clinical Tests

The Applicant's Position:

Refer [Section 8.1.1](#) for safety assessment in Study J12301. The nature and timing of the clinical monitoring of participant safety was considered adequate for the expected toxicities associated with the study treatments.

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

The Applicant's Position

In Study J12301, overall, asciminib showed a markedly favorable safety profile compared to IS-TKIs including imatinib and 2G TKIs ([Table 20](#)).

In order to account for any differences in duration of exposure in Study J12301, analyses of exposure-adjusted incidence rate (EAIR) of AEs were also performed to compare the AE incidence between the treatment groups. The EAIR of AEs showed a similar distribution with regards to the most frequent adverse events, and the differences between treatment groups were also consistent with the results from the unadjusted AE incidence rates. Hence, the EAIR for events is not discussed in detail in this document [SCS-Section 2] [CO-Section 5.1.2.1.3].

In the **All Asciminib Safety Pool**, the safety profile is consistent to that seen in Study J12301 ([Table 20](#)). No new or worsening safety concerns were identified in the All Asciminib Safety Pool and the safety findings were overall consistent with the known safety profile of asciminib. The differences, if any, between the asciminib treatment group in Study J12301 and the All Asciminib Safety Pool are expected due to the larger number of heavily pre-treated participants with resistant or intolerant disease, leading to heavier burden of baseline co-morbidities in Studies A2301 and X2101, unlike the participants in Study J12301.

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Detailed description of the All Asciminib Safety Pool will not be presented specifically for each of the sections in this document. However, pooled data in this document is presented in the outputs both in-text and additional details can be found in the [SCS-Section 2.0].

Deaths

Data

Scemblix (asciminib)

Table 14 All Deaths by System Organ Class and Preferred Term (Safety Set)

	Study J12301						Safety Pool All Asciminib N=556
	Asciminib			Investigator Selected TKI			
	Imatinib Stratum N=100	2G TKI Stratum N=100	All Asciminib N=200	Imatinib N=99	2G TKI N=102	All Comparators N=201	
Primary system organ class							
Primary reason (preferred term)							
Number of subjects who died	1 (1.0)	1 (1.0)	2 (1.0)	3 (3.0)	0	3 (1.5)	28 (5.0)
Study indication	0	0	0	1 (1.0)	0	1 (0.5)	10 (1.8)
Other	0	0	0	0	0	0	16 (2.9)
Bronchogenic carcinoma with hepatic and grancionar metastasis	0	1 (1.0)	1 (0.5)	0	0	0	1 (0.2)
Complications after HSCT	1 (1.0)	0	1 (0.5)	0	0	0	1 (0.2)
Cor pulmonale	0	0	0	1 (1.0)	0	1 (0.5)	0
Metastatic gastric malignancy	0	0	0	1 (1.0)	0	1 (0.5)	0
Cardiac disorders	0	0	0	1 (1.0)	0	1 (0.5)	4 (0.7)
Cardiac arrest	0	0	0	0	0	0	1 (0.2)
Cardiac disorder	0	0	0	0	0	0	1 (0.2)
Cardiac failure	0	0	0	0	0	0	1 (0.2)
Myocardial infarction	0	0	0	0	0	0	1 (0.2)
Cor pulmonale	0	0	0	1 (1.0)	0	1 (0.5)	0
General disorders and administration site conditions	0	0	0	0	0	0	3 (0.5)
Death	0	0	0	0	0	0	1 (0.2)

Scemblix (asciminib)

	Study J12301						Safety Pool
	Asciminib			Investigator Selected TKI			
	Imatinib Stratum N=100	2G TKI Stratum N=100	All Asciminib N=200	Imatinib N=99	2G TKI N=102	All Comparators N=201	
Primary system organ class							
Primary reason (preferred term)							
General physical health deterioration	0	0	0	0	0	0	1 (0.2)
Multiple organ dysfunction syndrome	0	0	0	0	0	0	1 (0.2)
Infections and infestations	0	0	0	0	0	0	4 (0.7)
COVID-19	0	0	0	0	0	0	1 (0.2)
COVID-19 pneumonia	0	0	0	0	0	0	1 (0.2)
Pneumonia	0	0	0	0	0	0	1 (0.2)
Pneumonia aspiration	0	0	0	0	0	0	1 (0.2)
Injury, poisoning and procedural complications	1 (1.0)	0	1 (0.5)	0	0	0	1 (0.2)
Post procedural complication	1 (1.0)	0	1 (0.5)	0	0	0	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.0)	1 (0.5)	1 (1.0)	0	1 (0.5)	1 (0.2)
Metastatic bronchial carcinoma	0	1 (1.0)	1 (0.5)	0	0	0	1 (0.2)
Metastatic gastric cancer	0	0	0	1 (1.0)	0	1 (0.5)	0
Nervous system disorders	0	0	0	0	0	0	3 (0.5)
Cerebral disorder	0	0	0	0	0	0	1 (0.2)
Haemorrhagic stroke	0	0	0	0	0	0	1 (0.2)
Ischaemic stroke	0	0	0	0	0	0	1 (0.2)
Psychiatric disorders	0	0	0	0	0	0	1 (0.2)

Scemblix (asciminib)

	Study J12301						Safety Pool All Asciminib N=556
	Asciminib			Investigator Selected TKI			
	Imatinib Stratum N=100	2G TKI Stratum N=100	All Asciminib N=200	Imatinib N=99	2G TKI N=102	All Comparators N=201	
Primary system organ class							
Primary reason (preferred term)							
Completed suicide	0	0	0	0	0	0	1 (0.2)
Vascular disorders	0	0	0	0	0	0	1 (0.2)
Embolism arterial	0	0	0	0	0	0	1 (0.2)
Numbers (n) represent counts of subjects. MedDRA version 26.1							
Source: [SCS Appendix 1-Table 2-5]							

Scemblix (asciminib)

The Applicant’s Position:

In Study J12301, as of the 28-Nov-2023 data cut-off date, there were no on-treatment deaths (i.e. death occurring during the treatment period and up to 30 days after the end of treatment) reported in any of the treatment groups. Overall, 5 (1.25%) participants subsequently died post the on-treatment period: 2 (1.0%) from the asciminib treatment group and 3 participants (1.5%) from the IS-TKI treatment group. The reasons for deaths are provided in Table 14, further details can be found in [SCS-Section 2.3].

The FDA’s Assessment:

FDA agrees with the Applicant’s assessment of death due to adverse events. In Study CABL001J12301, no excess mortality within 30 days of initiation of treatment was observed with asciminib. FDA analysis showed that two deaths in the asciminib arm, and three deaths in the IS-TKI arm in study CABL001J12301 occurred 30 days after last dose of drug. The two deaths 30 days after the last dose of asciminib were caused by post procedural complication and metastatic bronchial carcinoma. The three deaths 30 days after the last dose of IS-TKI occurred with imatinib and were caused by disease indication, cor pulmonale, and metastatic gastric malignancy, respectively. FDA assesses that based on the death summaries provided the causality between asciminib and deaths seems to be not related (Table 15).

Table 15 Summary of death narratives >30 days after last dose of asciminib in study CABL001J12301

USUBJID	Preferred term for death	Summary of death
(b) (6)	Post procedural complication (asciminib 80 mg qd)	The patient received allogeneic hematopoietic stem cell transplant 105 days after the last dose of asciminib. The last dose of asciminib was received on Day 218 and the patient died on Day 411 due to complications of hematopoietic stem cell transplant. The relationship is evaluated as being not related.
(b) (6)	Metastatic bronchial carcinoma (asciminib 80 mg qd)	The patient was a smoker (106 pack years). The patient received the last dose of asciminib on Day 168 and treatment was permanently discontinued due to hepatotoxicity on Day 195. The CT scan on Day 198 showed bronchogenic carcinoma with liver and lymph node metastases and the patient was diagnosed with metastatic bronchial carcinoma. The patient died on Day 209. The relationship is evaluated as being not related.

Source: FDA review, created from CSR.

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There were no on-treatment deaths or deaths >30 days after last dose of asciminib in study CABL001AUS08.

Serious Adverse Events

Data

Scemblix (asciminib)

Table 16 Serious Adverse Events by System Organ Class (Safety Set)

Primary system organ class	Study J12301													
	Asciminib						Investigator Selected TKI						Safety Pool	
	Imatinib		2G TKI		All		Imatinib		2G TKI		All		All	
	Stratum		Stratum		Asciminib		Stratum		Stratum		Comparators		Asciminib	
	N=100		N=100		N=200		N=99		N=102		N=201		N=556	
	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 (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of subjects with at least one event	13 (13.0)	10 (10.0)	9 (9.0)	7 (7.0)	22 (11.0)	17 (8.5)	12 (12.1)	10 (10.1)	20 (19.6)	14 (13.7)	32 (15.9)	24 (11.9)	152 (27.3)	119 (21.4)
Gastrointestinal disorders	2 (2.0)	1 (1.0)	3 (3.0)	2 (2.0)	5 (2.5)	3 (1.5)	2 (2.0)	2 (2.0)	2 (2.0)	2 (2.0)	4 (2.0)	4 (2.0)	28 (5.0)	19 (3.4)
Musculoskeletal and connective tissue disorders	3 (3.0)	3 (3.0)	1 (1.0)	0	4 (2.0)	3 (1.5)	1 (1.0)	0	0	0	1 (0.5)	0	11 (2.0)	9 (1.6)
Infections and infestations	1 (1.0)	0	2 (2.0)	2 (2.0)	3 (1.5)	2 (1.0)	3 (3.0)	3 (3.0)	7 (6.9)	3 (2.9)	10 (5.0)	6 (3.0)	40 (7.2)	33 (5.9)
Nervous system disorders	2 (2.0)	1 (1.0)	1 (1.0)	1 (1.0)	3 (1.5)	2 (1.0)	0	0	1 (1.0)	0	1 (0.5)	0	19 (3.4)	13 (2.3)
Hepatobiliary disorders	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	2 (1.0)	2 (1.0)	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)	6 (1.1)	6 (1.1)
Injury, poisoning and procedural complications	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	2 (1.0)	2 (1.0)	0	0	0	0	0	0	14 (2.5)	11 (2.0)
Investigations	2 (2.0)	2 (2.0)	0	0	2 (1.0)	2 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	2 (1.0)	2 (1.0)	7 (1.3)	7 (1.3)
Psychiatric disorders	2 (2.0)	1 (1.0)	0	0	2 (1.0)	1 (0.5)	0	0	0	0	0	0	8 (1.4)	6 (1.1)

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Primary system organ class	Study J12301													
	Asciminib						Investigator Selected TKI						Safety Pool	
	Imatinib Stratum		2G TKI Stratum		All Asciminib		Imatinib		2G TKI		All Comparators		All Asciminib	
	N=100		N=100		N=200		N=99		N=102		N=201		N=556	
	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 (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Blood and lymphatic system disorders	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)	0	0	2 (2.0)	2 (2.0)	2 (1.0)	2 (1.0)	8 (1.4)	8 (1.4)
Endocrine disorders	1 (1.0)	0	0	0	1 (0.5)	0	0	0	0	0	0	0	1 (0.2)	0
Eye disorders	0	0	1 (1.0)	0	1 (0.5)	0	0	0	0	0	0	0	8 (1.4)	4 (0.7)
General disorders and administration site conditions	0	0	1 (1.0)	0	1 (0.5)	0	0	0	0	0	0	0	18 (3.2)	13 (2.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)	4 (4.0)	2 (2.0)	3 (2.9)	2 (2.0)	7 (3.5)	4 (2.0)	12 (2.2)	9 (1.6)
Product issues	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	0	0	0	0	0	0	2 (0.4)	2 (0.4)
Respiratory, thoracic and mediastinal disorders	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	1 (1.0)	1 (1.0)	3 (2.9)	2 (2.0)	4 (2.0)	3 (1.5)	15 (2.7)	11 (2.0)
Cardiac disorders	0	0	0	0	0	0	1 (1.0)	1 (1.0)	2 (2.0)	2 (2.0)	3 (1.5)	3 (1.5)	25 (4.5)	22 (4.0)
Ear and labyrinth disorders	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.2)	0
Immune system disorders	0	0	0	0	0	0	0	0	0	0	0	0	2 (0.4)	1 (0.2)
Metabolism and nutrition disorders	0	0	0	0	0	0	0	0	0	0	0	0	5 (0.9)	5 (0.9)
Renal and urinary disorders	0	0	0	0	0	0	1 (1.0)	0	0	0	1 (0.5)	0	5 (0.9)	4 (0.7)

Scemblix (asciminib)

Primary system organ class	Study J12301													
	Asciminib						Investigator Selected TKI						Safety Pool	
	Imatinib Stratum		2G TKI Stratum		All Asciminib		Imatinib		2G TKI		All Comparators		All Asciminib	
	N=100		N=100		N=200		N=99		N=102		N=201		N=556	
	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 (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Reproductive system and breast disorders	0	0	0	0	0	0	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	0	0	0	0	0	0	0	0	2 (0.4)	0
Vascular disorders	0	0	0	0	0	0	0	0	0	0	0	0	12 (2.2)	12 (2.2)

Numbers (n) represent counts of subjects.

AEs occurring during treatment or within 30 days of the last study medication are summarized. A subject with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 26.1, CTCAE version 5.0

Source: [SCS Appendix 1-Table 2-6]

Scemblix (asciminib)

The Applicant's Position:

In **Study J12301**, there were no cases of fatal outcome due to an SAE in any of the treatment groups (**Table 20**). Overall, the incidence of individual SAEs was low for both treatment groups. The incidence of SAEs was lower in the asciminib treatment group compared to the IS-TKI treatment group (11.0% vs. 15.9%, grade ≥ 3 8.5% vs. 11.9%), including 2G TKI (19.6%, grade ≥ 3 13.7%), and comparable to the imatinib (12.1%, grade ≥ 3 10.1%) group (**Table 16**).

Most of the SAEs were reported as single cases, except, in the: asciminib treatment group, large intestine perforation (2 participants, 1.0%); no grade ≥ 3 SAEs occurred in more than 1 participant; IS-TKI treatment group: pneumonia (4 participants, 2.0%), COVID-19, pleural effusion and prostate cancer (2 participants, 1.0% each), and pneumonia was the only grade ≥ 3 SAE that occurred in more than 1 participant (3 participants, 1.5%) [SCS-Section 2.4.1]. As most of the SAEs were reported as single cases, SAEs by system organ class is presented in Table 15 above. SAEs by preferred term are provided in [SCS Appendix 1-Table 2-9].

The incidence of SAEs suspected to be study treatment related (per Investigator determination) was comparable between both asciminib and IS-TKI treatment groups (4.0% vs. 5.0%), including imatinib (4.0% vs. 4.0%) and 2G TKIs (4.0% vs. 5.9%). Except for pleural effusion (2 participants) in the 2G TKI group (none in the asciminib group), other suspected SAEs in both treatment groups were reported as single cases and no clinically meaningful comparisons could thus be derived [SCS-Section 2.4.3] [SCS Appendix 1-Table 2-8].

The FDA's Assessment:

FDA agrees with the Applicant about the frequency of SAEs according to System Organ Class (SOC) in the asciminib and IS-TKI arms of study CABL001J12301. FDA performed an analysis of all-grade treatment-emergent SAEs and events occurring in $\geq 1\%$ in both arms of the study which are presented in Table 17. The Applicant used SOC terms, and the FDA groups preferred terms that describe the same concept. The overall rate of SAEs was lower in the asciminib arm than in the IS-TKI arm and there was not any SAE which occurred at a significantly higher frequency in the asciminib arm. SAEs in study CABL001J12301 are acceptable because they are infrequent, and the differences between the groups are not thought to affect the safety profile of asciminib.

Table 17 Serious AEs ($\geq 1\%$) in study CABL001J12301

	Asciminib N=200 (%)	Investigator-Selected TKI N=201 (%)
Any SAE	11	15.9
Musculoskeletal Pain*	1	0.5
Pancreatitis*	1	0.5
Large Intestine Perforation	1	0
Pneumonia*	0	2.5

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Upper respiratory tract infection*	0	1
COVID-19	0	1
Prostate cancer	0	1

Source: FDA analysis using adae.xpt, adsl.xpt

*Grouped term (see Appendix 19.5)

SAEs which were seen in 1.4% of patients treated with asciminib as 2L treatment in study CABL001AUS08 are seen in Table 18. Similar to study CABL001J12301, SAEs were infrequent in study CABL001AUS08.

Table 18 Serious AEs (1.4%) in study CABL001AUS08

	Asciminib (N=71) (%)
Cardiovascular toxicity*	1.4
Gastrointestinal toxicity*	1.4
Vomiting*	1.4
Aortic valve disease	1.4
Catheter site pain	1.4
Source: FDA analysis using adae.xpt, adsl.xpt	
*Grouped term (see Appendix 19.5)	

Dropouts and/or Discontinuations Due to Adverse EffectsData

Scemblix (asciminib)

Table 19 Adverse Events Leading to Discontinuation, by Preferred Term (Safety Set)

Preferred term	Study J12301													
	Asciminib						Investigator Selected TKI						Safety Pool	
	Imatinib		2G TKI		All		Imatinib		2G TKI		All		All	
	Stratum		Stratum		Asciminib		Stratum		Stratum		Comparators		Asciminib	
	N=100		N=100		N=200		N=99		N=102		N=201		N=556	
	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 (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of subjects with at least one event	6 (6.0)	3 (3.0)	3 (3.0)	3 (3.0)	9 (4.5)	6 (3.0)	11 (11.1)	6 (6.1)	10 (9.8)	5 (4.9)	21 (10.4)	11 (5.5)	47 (8.5)	38 (6.8)
Lipase increased	3 (3.0)	1 (1.0)	0	0	3 (1.5)	1 (0.5)	0	0	0	0	0	0	11 (2.0)	9 (1.6)
Thrombocytopenia	1 (1.0)	1 (1.0)	1 (1.0)	0	2 (1.0)	1 (0.5)	0	0	0	0	0	0	7 (1.3)	6 (1.1)
Pancreatitis acute	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	0	0	0	0	0	0	2 (0.4)	1 (0.2)
Hepatotoxicity	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)	1 (1.0)	0	0	0	1 (0.5)	0	1 (0.2)	1 (0.2)
Neutrophil count decreased	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)	0	0	0	0	0	0	4 (0.7)	4 (0.7)
Cerebrovascular accident	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	0	0	0	0	0	0	1 (0.2)	1 (0.2)
Neuralgia	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)	0	0	0	0	0	0	1 (0.2)	1 (0.2)
Delirium	1 (1.0)	0	0	0	1 (0.5)	0	0	0	0	0	0	0	1 (0.2)	0
Neutropenia	0	0	0	0	0	0	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	3 (0.5)	3 (0.5)
Lymphopenia	0	0	0	0	0	0	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	0	0
Cardiac failure	0	0	0	0	0	0	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)	0	0
Pancreatitis	0	0	0	0	0	0	1 (1.0)	0	0	0	1 (0.5)	0	1 (0.2)	1 (0.2)

Scemblix (asciminib)

Preferred term	Study J12301													
	Asciminib						Investigator Selected TKI						Safety Pool	
	Imatinib		2G TKI		All		Imatinib		2G TKI		All		All	
	Stratum		Stratum		Asciminib		Stratum		Stratum		Comparators		Asciminib	
	N=100		N=100		N=200		N=99		N=102		N=201		N=556	
	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 (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Colitis	0	0	0	0	0	0	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)	0	0
Diarrhoea	0	0	0	0	0	0	2 (2.0)	0	0	0	2 (1.0)	0	0	0
Nausea	0	0	0	0	0	0	1 (1.0)	0	0	0	1 (0.5)	0	0	0
Asthenia	0	0	0	0	0	0	1 (1.0)	0	0	0	1 (0.5)	0	0	0
Face oedema	0	0	0	0	0	0	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	0	0
Generalised oedema	0	0	0	0	0	0	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)	0	0
Pyrexia	0	0	0	0	0	0	1 (1.0)	0	0	0	1 (0.5)	0	0	0
Hypersensitivity	0	0	0	0	0	0	0	0	1 (1.0)	0	1 (0.5)	0	1 (0.2)	0
Platelet count decreased	0	0	0	0	0	0	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)	4 (0.7)	4 (0.7)
ALT increased	0	0	0	0	0	0	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	0	0
AST increased	0	0	0	0	0	0	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	0	0
Electrocardiogram QT prolonged	0	0	0	0	0	0	0	0	1 (1.0)	0	1 (0.5)	0	0	0
Lymphocyte count decreased	0	0	0	0	0	0	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	0	0
Decreased appetite	0	0	0	0	0	0	1 (1.0)	0	0	0	1 (0.5)	0	0	0
Myalgia	0	0	0	0	0	0	1 (1.0)	0	0	0	1 (0.5)	0	1 (0.2)	1 (0.2)

Scemblix (asciminib)

Preferred term	Study J12301													
	Asciminib						Investigator Selected TKI						Safety Pool	
	Imatinib		2G TKI		All		Imatinib		2G TKI		All		All	
	Stratum		Stratum		Asciminib		Stratum		Stratum		Comparators		Asciminib	
	N=100		N=100		N=200		N=99		N=102		N=201		N=556	
	All	Grade	All	Grade	All	Grade	All	Grade	All	Grade	All	Grade	All	Grade
	grades	>=3	grades	>=3	grades	>=3	grades	>=3	grades	>=3	grades	>=3	grades	>=3
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Muscular weakness	0	0	0	0	0	0	0	0	1 (1.0)	1 (1.0)	1 (0.5)	1 (0.5)	0	0
Metastatic gastric cancer	0	0	0	0	0	0	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	0	0
Prostate cancer	0	0	0	0	0	0	1 (1.0)	0	0	0	1 (0.5)	0	0	0
Pleural effusion	0	0	0	0	0	0	0	0	2 (2.0)	1 (1.0)	2 (1.0)	1 (0.5)	0	0
Rash	0	0	0	0	0	0	0	0	1 (1.0)	0	1 (0.5)	0	1 (0.2)	0
Rash maculo-papular	0	0	0	0	0	0	0	0	1 (1.0)	0	1 (0.5)	0	0	0

Numbers (n) represent counts of subjects.

AEs occurring during treatment or within 30 days of the last study medication are summarized.

A subject with multiple severity grades for an AE is only counted under the maximum grade.

MedDRA version 26.1, CTCAE version 5.0

Source: [SCS Appendix 1-Table 2-19]

Scemblix (asciminib)

The Applicant's Position:

In **Study J12301**, the incidence of AEs (all grades) leading to treatment discontinuation was lower with asciminib (4.5%) compared to IS-TKIs (10.4%; imatinib: 11.1%; 2G TKI: 9.8%) and the majority of the events (except for diarrhea in 1 participant) were assessed by the Investigator as being related to study treatment. Most of the AEs leading to discontinuation were reported as single cases in both the asciminib and IS-TKI treatment group except for lipase increased (1.5% vs. 0%) and thrombocytopenia (1.0% vs. 0%); diarrhea (0% vs. 2.0%) in the imatinib group; and pleural effusion (0% vs. 2.0%) in the 2G TKI group. The incidence of grade ≥ 3 AEs leading to treatment discontinuation was lower with asciminib (3.0%) compared to IS-TKI (5.5%; imatinib: 6.1%; 2G TKI: 4.9%). All grade ≥ 3 AEs leading to treatment discontinuation were reported as single cases ([Table 19](#)) [SCS-Section 2.5.1].

The FDA's Assessment:

FDA agrees with the Applicant's assessment about discontinuations in study CABL001J12301. The percentage of patients who discontinued treatment for all grade adverse events was lower in the asciminib arm compared to the IS-TKI arm (4.5% vs. 10.4%). FDA also considered GTs which led to discontinuation. Particular adverse events leading to discontinuation did not occur in more than 1.5% of patients in the asciminib arm. AEs which led to discontinuation in the asciminib arm were lipase increased (1.5%), thrombocytopenia (GT) (1%), cardiovascular toxicity (GT) (0.5%), neuropathy peripheral (GT) (0.5%), neutropenia (GT) (0.5%), pancreatitis (GT) (0.5%), and delirium (0.5%). We agree that none of the grade 3 or 4 discontinuations in the asciminib arm occurred in more than 0.5% of the patients.

In study CABL001AUS08, one patient (1.4%) discontinued asciminib due to gastrointestinal toxicity (GT).

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

In **Study J12301**, the proportion of participants with treatment-related AEs leading to dose reduction was markedly lower with asciminib compared to the IS-TKIs (5.5% vs. 18.4%) as well as imatinib (14.1%) and 2G TKI (22.5%). There were no events by PT reported with a $\geq 5\%$ difference between asciminib and IS-TKI treatment groups ([Table 20](#)) [SCS-Section 2.5.3].

The proportion of participants with treatment-related AEs requiring dose interruption was lower with asciminib compared to the IS-TKIs (21.5% vs. 35.8%) as well as imatinib (31.3%) and 2G TKI (40.2%). There were no treatment-related AEs leading to dose interruption reported more frequently in the asciminib treatment group with a $\geq 5\%$ difference compared to the IS-TKI treatment group including imatinib. Compared to the 2G TKI group, ALT increased (1.0% vs. 7.8%) and anemia (0% vs. 4.9%) occurred with $\geq 5\%$ difference ([Table 20](#)) [SCS-Section 2.5.2].

Scemblix (asciminib)

The FDA's Assessment:

In study CABL001J12301, the majority of dose modifications (dose interruptions and dose reductions) were dose interruptions. FDA analysis showed that dose interruption occurred in 30% of patients in asciminib arm and 39.8% of patients in the IS-TKI arm. The most frequent causes for dose interruption in >5% of patients in the asciminib arm were thrombocytopenia (GT) (13%), and neutropenia (GT) (9.5%). FDA analysis also showed that adverse events leading to dose reduction occurred in 5.5% of patients in asciminib arm compared to 18.9% of patients in IS-TKI arm. The most frequent causes for dose reduction in the asciminib arm were thrombocytopenia (GT) (2.5%), and neutropenia (GT) (1.5%).

In study CABL001AUS08, dose interruptions due to adverse events occurred in 18.3% of patients and dose reductions due to adverse events occurred in 2.8% of patients. Adverse events which led to dose modifications in >1.4% of patients were thrombocytopenia (GT) (5.6%), fatigue (GT) (2.8%), and gastrointestinal toxicity (GT) (2.8%).

Significant Adverse Events

The Applicant's Position: The significant AEs reported are described above: SAEs, AEs leading to treatment discontinuation/dose interruption/reduction. Laboratory abnormalities are described below.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Scemblix (asciminib)

Table 20 Overview of Adverse Events (Safety Set)

Category	Study J12301													
	Asciminib						Investigator Selected TKI						Safety Pool	
	Imatinib Stratum		2G TKI Stratum		All Asciminib		Imatinib		2G TKI		All Comparators		All Asciminib	
	N=100		N=100		N=200		N=99		N=102		N=201		N=556	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse events	94 (94.0)	41 (41.0)	93 (93.0)	35 (35.0)	187 (93.5)	76 (38.0)	93 (93.9)	44 (44.4)	102 (100)	56 (54.9)	195 (97.0)	100 (49.8)	529 (95.1)	311 (55.9)
Treatment-related	72 (72.0)	25 (25.0)	78 (78.0)	26 (26.0)	150 (75.0)	51 (25.5)	83 (83.8)	33 (33.3)	97 (95.1)	43 (42.2)	180 (89.6)	76 (37.8)	434 (78.1)	202 (36.3)
SAEs	13 (13.0)	10 (10.0)	9 (9.0)	7 (7.0)	22 (11.0)	17 (8.5)	12 (12.1)	10 (10.1)	20 (19.6)	14 (13.7)	32 (15.9)	24 (11.9)	152 (27.3)	119 (21.4)
Treatment-related	4 (4.0)	3 (3.0)	4 (4.0)	4 (4.0)	8 (4.0)	7 (3.5)	4 (4.0)	3 (3.0)	6 (5.9)	5 (4.9)	10 (5.0)	8 (4.0)	37 (6.7)	30 (5.4)
Fatal SAEs	0	0	0	0	0	0	0	0	0	0	0	0	11 (2.0)	11 (2.0)
Treatment-related	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.2)	1 (0.2)
AEs leading to discontinuation	6 (6.0)	3 (3.0)	3 (3.0)	3 (3.0)	9 (4.5)	6 (3.0)	11 (11.1)	6 (6.1)	10 (9.8)	5 (4.9)	21 (10.4)	11 (5.5)	47 (8.5)	38 (6.8)
Treatment-related	5 (5.0)	3 (3.0)	2 (2.0)	2 (2.0)	7 (3.5)	5 (2.5)	9 (9.1)	5 (5.1)	10 (9.8)	5 (4.9)	19 (9.5)	10 (5.0)	31 (5.6)	26 (4.7)
AEs leading to dose adjustment/interruption	28 (28.0)	24 (24.0)	32 (32.0)	26 (26.0)	60 (30.0)	50 (25.0)	39 (39.4)	24 (24.2)	54 (52.9)	35 (34.3)	93 (46.3)	59 (29.4)	235 (42.3)	193 (34.7)

Numbers (n) represent counts of participants.

A participant with multiple severity grades for an AE is only counted under the maximum grade.

MedDRA version 26.1, CTCAE version 5.0.

Source: [SCS Appendix 1-Table 2-1]

Scemblix (asciminib)

Table 21 Adverse Events by Preferred Term (≥10% in Asciminib Treatment Group of Study J12301) (Safety set)

Preferred Term	Study J12301													
	Asciminib						Investigator Selected TKI						Safety Pool	
	Imatinib Stratum		2G TKI Stratum		All Asciminib		Imatinib		2G TKI		All Comparators		All Asciminib	
	N=100		N=100		N=200		N=99		N=102		N=201		N=556	
	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 (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
No of participants with at least 1 event	94 (94.0)	41 (41.0)	93 (93.0)	35 (35.0)	187 (93.5)	76 (38.0)	93 (93.9)	44 (44.4)	102 (100)	56 (54.9)	195 (97.0)	100 (49.8)	529 (95.1)	311 (55.9)
COVID-19	12 (12.0)	0	23 (23.0)	0	35 (17.5)	0	18 (18.2)	0	21 (20.6)	1 (1.0)	39 (19.4)	1 (0.5)	95 (17.1)	5 (0.9)
Diarrhoea	11 (11.0)	0	20 (20.0)	0	31 (15.5)	0	26 (26.3)	0	26 (25.5)	1 (1.0)	52 (25.9)	1 (0.5)	111 (20.0)	2 (0.4)
Neutrophil count decreased	12 (12.0)	2 (2.0)	17 (17.0)	9 (9.0)	29 (14.5)	11 (5.5)	16 (16.2)	8 (8.1)	21 (20.6)	8 (7.8)	37 (18.4)	16 (8.0)	48 (8.6)	28 (5.0)
Platelet count decreased	11 (11.0)	3 (3.0)	18 (18.0)	7 (7.0)	29 (14.5)	10 (5.0)	14 (14.1)	2 (2.0)	18 (17.6)	7 (6.9)	32 (15.9)	9 (4.5)	52 (9.4)	26 (4.7)
Fatigue	13 (13.0)	0	15 (15.0)	1 (1.0)	28 (14.0)	1 (0.5)	14 (14.1)	1 (1.0)	18 (17.6)	0	32 (15.9)	1 (0.5)	114 (20.5)	6 (1.1)
Headache	15 (15.0)	1 (1.0)	12 (12.0)	0	27 (13.5)	1 (0.5)	8 (8.1)	0	22 (21.6)	0	30 (14.9)	0	121 (21.8)	8 (1.4)
Thrombocytopenia	15 (15.0)	9 (9.0)	12 (12.0)	7 (7.0)	27 (13.5)	16 (8.0)	14 (14.1)	4 (4.0)	17 (16.7)	7 (6.9)	31 (15.4)	11 (5.5)	109 (19.6)	70 (12.6)
Myalgia	12 (12.0)	0	14 (14.0)	1 (1.0)	26 (13.0)	1 (0.5)	17 (17.2)	0	15 (14.7)	0	32 (15.9)	0	70 (12.6)	5 (0.9)

Scemblix (asciminib)

Preferred Term	Study J12301													
	Asciminib						Investigator Selected TKI						Safety Pool	
	Imatinib Stratum		2G TKI Stratum		All Asciminib		Imatinib		2G TKI		All Comparators		All Asciminib	
	N=100		N=100		N=200		N=99		N=102		N=201		N=556	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Rash	7 (7.0)	0	19 (19.0)	0	26 (13.0)	0	10 (10.1)	2 (2.0)	22 (21.6)	1 (1.0)	32 (15.9)	3 (1.5)	85 (15.3)	0
Anaemia	10 (10.0)	1 (1.0)	13 (13.0)	2 (2.0)	23 (11.5)	3 (1.5)	26 (26.3)	5 (5.1)	23 (22.5)	6 (5.9)	49 (24.4)	11 (5.5)	68 (12.2)	22 (4.0)
Lipase increased	19 (19.0)	6 (6.0)	4 (4.0)	0	23 (11.5)	6 (3.0)	14 (14.1)	1 (1.0)	11 (10.8)	4 (3.9)	25 (12.4)	5 (2.5)	92 (16.5)	48 (8.6)
White blood cell count decreased	10 (10.0)	1 (1.0)	12 (12.0)	2 (2.0)	22 (11.0)	3 (1.5)	17 (17.2)	5 (5.1)	13 (12.7)	2 (2.0)	30 (14.9)	7 (3.5)	34 (6.1)	10 (1.8)
Neutropenia	12 (12.0)	5 (5.0)	9 (9.0)	4 (4.0)	21 (10.5)	9 (4.5)	15 (15.2)	9 (9.1)	16 (15.7)	10 (9.8)	31 (15.4)	19 (9.5)	77 (13.8)	51 (9.2)

Numbers (n) represent counts of subjects.

AEs occurring during treatment or within 30 days of the last study medication are summarized. A subject with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 26.1, CTCAE version 5.0

Source: [SCS Appendix 1-Table 2-2.2]

Scemblix (asciminib)

The Applicant's Position:

The results from registration **Study J12301** show that the safety data are consistent with the known safety profile of asciminib. Overall, the AEs observed with asciminib treatment were as expected and could be attributed to the mechanism of action of asciminib and is in line with the current pre-clinical and clinical knowledge of asciminib. No unknown or unexpected safety concerns were observed. Adverse events reported with asciminib treatment appear to be manageable with appropriate monitoring and are reversible upon dose interruption and/or dose reduction of asciminib, and/or the use of supportive care [CO-Section 5.1.2].

AEs occurred in 93.5% of participants treated with asciminib compared to 93.9% of participants treated with imatinib and 100% of participants treated with 2G TKIs (97.0% for IS-TKIs overall). Grade ≥ 3 events were reported less frequently with asciminib (38.0%) compared to IS-TKIs (49.8%; imatinib: 44.4%; 2G TKI: 54.9%). AEs suspected to be study treatment related were reported less frequently in the asciminib treatment group (75.0%) compared to the IS-TKI treatment group (89.6%; imatinib: 83.8%; 2G TKI: 95.1%) ([Table 218](#)) [CO-Section 5.1.2.2.1].

The FDA's Assessment:

FDA analysis of treatment-emergent adverse events (TEAEs) aligns with that of the Applicant's except that FDA used GTs; however, the Applicant used PTs. Table 22 shows TEAEs $\geq 10\%$, all grades and grades 3-4, in study CABL001J12301. This table includes laboratory investigations which are generally underreported as adverse events and will be reported separately in labeling and are reviewed in the laboratory section below. Most TEAEs were less frequent in the asciminib arm. Only abdominal pain (GT) was more frequent in the asciminib arm compared to the IS-TKI arm (14% vs. 10%), upper respiratory tract infection (GT) (15%) and lipase increased (12%) were similar in both arms. Grade 3 or 4 adverse events which were $>5\%$ in the asciminib arm were thrombocytopenia (GT) (13%) and neutropenia (GT) (10%).

Table 22 TEAEs $\geq 10\%$ in CABL001J12301

	Asciminib N=200 (%)		Investigator-Selected TKI N=201 (%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any TEAE	94	38	97	50
Thrombocytopenia*	28	13	31	10
Neutropenia*	25	10	33	17
Musculoskeletal pain*	25	1.5	32	0.5
Rash*	19	0	25	2
Fatigue*	18	1	20	0.5
COVID-19	18	0	19	0.5
Diarrhea*	16	0	26	1

Scemblix (asciminib)

Upper respiratory tract infection*	15	0	15	0.5
Abdominal pain*	14	0.5	10	0
Headache*	14	0.5	15	0
Anemia*	12	1.5	24	6
Lipase increased	12	3	12	2.5
Source: FDA analysis using adae.xpt, adsl.xpt *indicates grouped terms, see Appendix 19.5.				

TEAEs seen in $\geq 10\%$ of patients treated with asciminib as 2L treatment in study CABL001AUS08 are seen in Table 23. The most frequent TEAEs were musculoskeletal pain (GT), vomiting (GT), and fatigue (GT). Grade 3-4 TEAEs were infrequent. The most frequent TEAEs ($\geq 10\%$) were similar in study CABL001J12301 and study CABL001AUS08.

Table 23 TEAEs $\geq 10\%$ in CABL001AUS08

	Asciminib N=71 (%)	
	Any Grade	Grade 3-4
Any TEAE	89	38
Musculoskeletal pain*	27	0
Vomiting*	17	1.4
Fatigue*	16	1.4
Headache*	14	0
Diarrhea*	13	1.4
Cough*	12	0
Upper Respiratory Tract Infection*	12	0
Source: FDA analysis using adae.xpt, adsl.xpt *indicates grouped terms, see Appendix 19.5.		

Adverse drug reactions**Data**

Scemblix (asciminib)

Table 24 Frequency and Frequency Category of ADR (≥10% in Asciminib Treatment Group of Study J12301) for Core Data Sheet (Safety set)

Adverse Drug Reactions	Study J12301														Frequency category
	Asciminib						Investigator Selected TKI						Safety Pool		
	Imatinib Stratum		2G TKI Stratum		All Asciminib		Imatinib		2G TKI		All Comparators		All Asciminib		
	N=100		N=100		N=200		N=99		N=102		N=201		N=556		
	All Grad es n (%)	Grad e ≥3 n (%)	All Grad es n (%)	Grad e ≥3 n (%)	All Grad es n (%)	Grad e ≥3 n (%)	All Grad es n (%)	Grad e ≥3 n (%)	All Grad es n (%)	Grad e ≥3 n (%)	All Grad es n (%)	Grad e ≥3 n (%)	All Grad es n (%)	Grad e ≥3 n (%)	
No of patients with at least one ADR	85 (85.0)	31 (31.0)	86 (86.0)	26 (26.0)	171 (85.5)	57 (28.5)	89 (89.9)	33 (33.3)	99 (97.1)	48 (47.1)	188 (93.5)	81 (40.3)	500 (89.9)	254 (45.7)	
Thrombocytopenia_ADR	26 (26.0)	12 (12.0)	30 (30.0)	14 (14.0)	56 (28.0)	26 (13.0)	28 (28.3)	6 (6.1)	35 (34.3)	14 (13.7)	63 (31.3)	20 (10.0)	156 (28.1)	92 (16.5)	Very common
Neutropenia	24 (24.0)	7 (7.0)	26 (26.0)	13 (13.0)	50 (25.0)	20 (10.0)	31 (31.3)	17 (17.2)	35 (34.3)	18 (17.6)	66 (32.8)	35 (17.4)	120 (21.6)	76 (13.7)	Very common
Musculoskeletal pain	23 (23.0)	1 (1.0)	23 (23.0)	1 (1.0)	46 (23.0)	2 (1.0)	30 (30.3)	1 (1.0)	31 (30.4)	0 (0.0)	61 (30.3)	1 (0.5)	183 (32.9)	15 (2.7)	Very common
Fatigue	18 (18.0)	1 (1.0)	18 (18.0)	1 (1.0)	36 (18.0)	2 (1.0)	22 (22.2)	1 (1.0)	19 (18.6)	0 (0.0)	41 (20.4)	1 (0.5)	139 (25.0)	8 (1.4)	Very common
Diarrhoea	11 (11.0)	0 (0.0)	20 (20.0)	0 (0.0)	31 (15.5)	0 (0.0)	26 (26.3)	0 (0.0)	26 (25.5)	1 (1.0)	52 (25.9)	1 (0.5)	111 (20.0)	2 (0.4)	Very common
Rash	9 (9.0)	0 (0.0)	21 (21.0)	0 (0.0)	30 (15.0)	0 (0.0)	12 (12.1)	2 (2.0)	25 (24.5)	2 (2.0)	37 (18.4)	4 (2.0)	107 (19.2)	0 (0.0)	Very common
Dyslipidaemia	15 (15.0)	1 (1.0)	13 (13.0)	1 (1.0)	28 (14.0)	2 (1.0)	6 (6.1)	1 (1.0)	12 (11.8)	0 (0.0)	18 (9.0)	1 (0.5)	69 (12.4)	11 (2.0)	Very common
Headache	15 (15.0)	1 (1.0)	12 (12.0)	0 (0.0)	27 (13.5)	1 (0.5)	8 (8.1)	0 (0.0)	22 (21.6)	0 (0.0)	30 (14.9)	0 (0.0)	121 (21.8)	8 (1.4)	Very common

Scemblix (asciminib)

	Study J12301															Frequency category
	Asciminib						Investigator Selected TKI						Safety Pool			
	Imatinib Stratum		2G TKI Stratum		All Asciminib		Imatinib		2G TKI		All Comparators		All Asciminib			
	N=100		N=100		N=200		N=99		N=102		N=201		N=556			
	All	Grad es	All	Grad es	All	Grad es	All	Grad es	All	Grad es	All	Grad es	All	Grad es		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	All Grades	
Adverse Drug Reactions	16 (16.0)	0	11 (11.0)	0	27 (13.5)	0	16 (16.2)	1 (1.0)	13 (12.7)	0	29 (14.4)	1 (0.5)	132 (23.7)	2 (0.4)	Very common	
Upper respiratory tract infection	21 (21.0)	6 (6.0)	4 (4.0)	0	25 (12.5)	6 (3.0)	14 (14.1)	1 (1.0)	14 (13.7)	5 (4.9)	28 (13.9)	6 (3.0)	107 (19.2)	52 (9.4)	Very common	
Pancreatic enzymes increased	9 (9.0)	0	16 (16.0)	1 (1.0)	25 (12.5)	1 (0.5)	6 (6.1)	0	12 (11.8)	0	18 (9.0)	0	104 (18.7)	6 (1.1)	Very common	
Abdominal pain	10 (10.0)	1 (1.0)	13 (13.0)	2 (2.0)	23 (11.5)	3 (1.5)	26 (26.3)	5 (5.1)	23 (22.5)	6 (5.9)	49 (24.4)	11 (5.5)	70 (12.6)	22 (4.0)	Very common	
Anaemia																

A subject with multiple occurrences of an ADR under one treatment is counted only once in the ADR category for that treatment. A subject 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 26.1, CTCAE version 5.0, Case Retrieval Strategy version released 2024-02-19.

Frequency category is based on the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Source: [SCS Appendix 1-Table 4-3a]

Scemblix (asciminib)

The Applicant's Position:

Adverse drug reaction candidate screening was based primarily on the randomized period of Study J12301, whereas all available data from Studies J12301, A2301, and X2101 were considered for causality assessment and ADR frequency estimation.

In Study J12301, the proportion of participants with at least one ADR was lower in the asciminib treatment group (85.5%) compared to the IS-TKI treatment group (93.5%) including 2G TKIs (97.1%) and comparable to imatinib (89.9%). The number of participants with at least one grade ≥ 3 ADR was lower with asciminib (28.5%) compared to IS-TKIs (40.3%) including imatinib (33.3%) and 2G TKIs (47.1%) [CO-Section 5.1.7] ([Table 249](#)).

The FDA's Assessment:

Most of the TEAEs which are listed in Table 24 as adverse drug reactions (ADRs) are not considered as ADRs by the FDA. The Agency will consider any TEAEs with $\geq 10\%$ incidence and occurring $\geq 2\%$ more frequent on the treatment arm an ADR. Causality is difficult to assess in a trial with an active control arm. FDA used custom queries and PTs to test for ADRs in study CABL001J12301. The only TEAE which should be listed as an ADR is abdominal pain (GT) (14% in asciminib arm and 10% in IS-TKI arm). The differences in the evaluation of ADRs are not thought to influence the safety profile of asciminib.

Laboratory Findings

Data:

Scemblix (asciminib)

Table 25 Hematology Worst Post-baseline Abnormality based on CTC grades (Safety Set)

	Study J12301													
	Asciminib						Investigator Selected TKI						Safety Pool	
	Imatinib		2G TKI		All		Imatinib		2G TKI		All		All Asciminib	
	Stratum	N=100	Stratum	N=100	Asciminib	N=200	Stratum	N=99	Stratum	N=102	Comparators	N=201	All Asciminib	N=556
	All	Grade	All	Grade	All	Grade	All	Grade	All	Grade	All	Grade	All	Grade
	grades	3/4	grades	3/4	grades	3/4	grades	3/4	grades	3/4	grades	3/4	grades	3/4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Lymphocytes, Blood decrease	84 (84.0)	3 (3.0)	83 (83.0)	3 (3.0)	167 (83.5)	6(3.0)	92 (92.9)	16 (16.2)	89 (87.3)	6 (5.9)	181 (90.0)	22 (10.9)	467 (84.0)	41 (7.4)
Hemoglobin, Blood decrease	68 (68.0)	2 (2.0)	76 (76.0)	4 (4.0)	144 (72.0)	6 (3.0)	82 (82.8)	5 (5.1)	93 (91.2)	8 (7.8)	175 (87.1)	13 (6.5)	381 (68.5)	25 (4.5)
Leukocytes, Blood decrease	57 (57.0)	4 (4.0)	58 (58.0)	6 (6.0)	115 (57.5)	10(5.0)	69 (69.7)	14 (14.1)	68 (66.7)	12 (11.8)	137 (68.2)	26 (12.9)	292 (52.5)	46 (8.3)
Platelets, Blood decrease	46 (46.0)	10 (10.0)	53 (53.0)	15 (15.0)	99 (49.5)	25 (12.5)	45 (45.5)	7 (7.1)	67 (65.7)	15 (14.7)	112 (55.7)	22 (10.9)	295 (53.1)	93 (16.7)
Neutrophils, Blood decrease	43 (43.0)	11 (11.0)	54 (54.0)	14 (14.0)	97 (48.5)	25 (12.5)	58 (58.6)	19 (19.2)	70 (68.6)	20 (19.6)	128 (63.7)	39 (19.4)	267 (48.0)	98 (17.6)
Prothrombin Intl. Normalized Ratio (RATIO), Plasma-increase	1 (1.0)	0	2 (2.0)	0	3 (1.5)	0	0	0	1 (1.0)	0	1 (0.5)	0	24 (4.3)	3 (0.5)

Numbers (n) represent counts of participants. 'All grades' represents participants with any grade 1, 2, 3 or 4 post-baseline.

Grades based on CTCAE version 5.0.

Source: [SCS Appendix 1-Table 3.3-3]

Scemblix (asciminib)

Table 26 Biochemistry Worst Post-baseline Abnormality (≥10% in Asciminib Treatment Group of Study J12301) based on CTC Grades (Safety set)

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib		2G TKI		All		Imatinib		2G TKI		All		All Asciminib	
	Stratum N=100		Stratum N=100		Asciminib N=200		Stratum N=99		Stratum N=102		Comparators N=201		All Asciminib N=556	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Triglycerides, Plasma or Serum-increase	53 (53.0)	2 (2.0)	53 (53.0)	2 (2.0)	106 (53.0)	4 (2.0)	51 (51.5)	1 (1.0)	56 (54.9)	2 (2.0)	107 (53.2)	3 (1.5)	366 (65.8)	30 (5.4)
Cholesterol, Serum-increase	54 (54.0)	0	48 (48.0)	0	102 (51.0)	0	28 (28.3)	0	66 (64.7)	0	94 (46.8)	0	217 (39.0)	1 (0.2)
Calcium Corrected, Plasma or Serum-decrease	46 (46.0)	1 (1.0)	48 (48.0)	0	94 (47.0)	1 (0.5)	72 (72.7)	1 (1.0)	80 (78.4)	3 (2.9)	152 (75.6)	4 (2.0)	218 (39.2)	4 (0.7)
Lipase, Serum-increase	46 (46.0)	12 (12.0)	33 (33.0)	7 (7.0)	79 (39.5)	19 (9.5)	49 (49.5)	8 (8.1)	45 (44.1)	11 (10.8)	94 (46.8)	19 (9.5)	210 (37.8)	71 (12.8)
Alkaline Phosphatase, Serum-increase	39 (39.0)	0	31 (31.0)	1 (1.0)	70 (35.0)	1 (0.5)	48 (48.5)	0	42 (41.2)	0	90 (44.8)	0	154 (27.7)	1 (0.2)
Alanine Aminotransferase, Serum-increase	34 (34.0)	2 (2.0)	34 (34.0)	1 (1.0)	68 (34.0)	3 (1.5)	28 (28.3)	3 (3.0)	62 (60.8)	8 (7.8)	90 (44.8)	11 (5.5)	242 (43.5)	13 (2.3)
Amylase, Serum-increase	31 (31.0)	1 (1.0)	15 (15.0)	0	46 (23.0)	1 (0.5)	25 (25.3)	2 (2.0)	33 (32.4)	5 (4.9)	58 (28.9)	7 (3.5)	142 (25.5)	19 (3.4)
Aspartate Aminotransferase, Serum-increase	20 (20.0)	1 (1.0)	17 (17.0)	1 (1.0)	37 (18.5)	2 (1.0)	21 (21.2)	1 (1.0)	45 (44.1)	2 (2.0)	66 (32.8)	3 (1.5)	180 (32.4)	10 (1.8)
Creatinine, Plasma or Serum-increase	23 (23.0)	0	12 (12.0)	0	35 (17.5)	0	36 (36.4)	0	27 (26.5)	0	63 (31.3)	0	137 (24.6)	0

Scemblix (asciminib)

	Study J12301														Safety Pool	
	Asciminib						Investigator Selected TKI									
	Imatinib		2G TKI		All		Imatinib		2G TKI		All		All Asciminib			
	Stratum		Stratum		Asciminib		Stratum		Stratum		Comparators		All Asciminib			
	N=100		N=100		N=200		N=99		N=102		N=201		N=556			
All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	
Bilirubin, Serum-increase	11 (11.0)	0	21 (21.0)	0	32 (16.0)	0	8 (8.1)	1 (1.0)	29 (28.4)	0	37 (18.4)	1 (0.5)	99 (17.8)	1 (0.2)		
Potassium, Plasma or Serum-increase	14 (14.0)	1 (1.0)	8 (8.0)	0	22 (11.0)	1 (0.5)	4 (4.0)	0	8 (7.8)	0	12 (6.0)	0	125 (22.5)	7 (1.3)		

Numbers (n)=counts of participants. 'All grades' represents participants with any grade 1, 2, 3 or 4 post-baseline. Grades based on CTCAE version 5.0.

Source: [SCS Appendix 1-Table 3.4-3]

Scemblix (asciminib)

The Applicant's Position:

Hematology laboratory abnormalities

In **Study J12301**, worst post-baseline hematological laboratory abnormalities occurred in lower proportions of participants with asciminib compared to IS-TKIs including imatinib and 2G TKIs. Most of these hematologic abnormalities were mild-to-moderate (grade 1 or 2) in all treatment groups (asciminib, IS-TKI, imatinib and 2G TKI). These hematology results are consistent with the observed hematologic AE profile for the study drugs ([Table 2520](#)) [SCS-Section 3.1].

There were no new or worsened post-baseline hematological laboratory abnormalities that were reported more frequently (and with a $\geq 5\%$ difference) with asciminib compared to IS-TKIs including imatinib and 2G TKIs [CO-Section 5.1.4].

Biochemistry laboratory abnormalities

Most of the biochemistry abnormalities were mild-to-moderate (grade 1 or 2) in all treatment groups. Few notable differences in the post-baseline biochemistry laboratory abnormalities were observed in the asciminib group vs. IS-TKI group including imatinib and 2G TKIs ([Table 261](#)).

Shifts from baseline normal to post-baseline high levels for serum glucose were observed in a lower proportion of participants in the asciminib treatment group (26.5%) compared to the IS-TKI treatment group (39.5%), including imatinib (36.7%) and 2G TKI (42.3%) groups. Of note, shifts from baseline normal to post-baseline high levels for serum HbA1C was observed in a fewer proportion of participants (2.9% in asciminib group, 1.7 % in IS-TKI group including 0% in imatinib group, and 3.1% in 2G TKI group). There was no permanent discontinuation due to either blood glucose increases or hyperglycemia AEs [SCS-Section 3.2.1].

Liver enzymes

In Study J12301, increases in ALT or AST $>3\times$ ULN were noted in a comparatively lower number of participants in the asciminib treatment group compared to the IS-TKI treatment group. In the asciminib treatment group, a lower proportion of participants had total bilirubin increase of $>2\times$ ULN compared to the IS-TKI treatment group (1.5% vs. 4.5%), and particularly when compared to the 2G TKI group (7.8%). 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 $>3\times$ ULN and total bilirubin $>2\times$ ULN and ALP $<2\times$ ULN meeting Hy's law biochemical criteria were observed in either treatment group [SCS-Section 3.2.2].

The FDA's Assessment:

FDA agrees with the Applicant's assessment of hematology parameters in study CABL001J12301. Myelosuppression resulting in anemia, leukopenia, and thrombocytopenia are known direct effects of tyrosine kinase inhibitors. Thrombocytopenia was the second most common cause for discontinuation of asciminib. Thrombocytopenia and neutropenia were the most common causes for dose reduction and dose interruption of asciminib. In study CABL001J12301, all grades and grades 3-4 anemia, leukopenia, neutropenia, lymphopenia, and

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thrombocytopenia were less frequent in the asciminib arm compared to the IS-TKI arm. Grades 3-4 thrombocytopenia was present in 12.5% of patients in the asciminib arm vs. 14.7% in the IS-TKI arm. Grade 3-4 neutropenia was seen in 12.5% of patients in the asciminib arm vs. 19.4% of those in the IS-TKI arm.

FDA agrees with the Applicant's assessment of biochemistry parameters in study CABL001J12301. All grades biochemical abnormalities, except cholesterol increase and potassium increase, were less frequent with asciminib compared to the IS-TKIs. Grades 3-4 biochemical abnormalities were not frequent in both arms. The most frequent grade 3-4 biochemical abnormality in the asciminib arm was lipase increase (9.5%) which was present at the same percentage in the IS-TKI arm. Other biochemical abnormalities which are not included in Table 26 include glucose increase (26% vs. 34%) (calculated by change of baseline low or normal values to post-baseline high values), GGT increase (29% vs. 37%), and creatine kinase increase (17% vs. 33%). There were no grade 3-4 glucose increases. Grade 3-4 GGT increase and creatine kinase increase were infrequent.

FDA agrees with the Applicant's assessment of hematology parameters in study CABL001AUS08 as presented in the CSR at IA2. The most frequent hematology abnormality was lymphocyte decrease (64.8%) followed by hemoglobin decrease (38%). The most frequent grade 3-4 hematology abnormality was neutrophil decrease (5.6%).

FDA agrees with the Applicant's assessment of biochemistry parameters in study CABL001AUS01 as presented in the CSR at IA2. The most frequent biochemistry abnormality was triglycerides increase (61%), followed by ALP increase (21%), amylase increase (16%), ALT increase (13%), and creatine kinase increase (13%).

In general, hematology and biochemistry abnormalities in study CABL001J12301 and study CABL001AUS08 were similar.

Vital Signs

The Applicant's Position:

In **Study J12301**, a higher proportion of participants in the asciminib treatment group reported increased systolic blood pressure (SBP) compared to IS-TKIs; ≥ 140 mmHg (27.5% vs. 20.9%), ≥ 160 mmHg (13.5% vs. 5.5%), and ≥ 180 mmHg (1.5% vs. 0%) in line with a higher incidence of vascular disorders, particularly hypertension, previously reported with asciminib compared to IS-TKI treated participants. There were no meaningful differences between the two treatment groups for other vital signs assessed [SCS-Section 4.1].

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

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Electrocardiograms (ECGs) and QT

The Applicant's Position:

In Study J12301, the proportion of participants with notable ECG intervals (including QTcF, QT, QRS, and PR) was low in all treatment groups, with a few notable differences observed when comparing the asciminib treatment group to the IS-TKI treatment group including imatinib and 2G TKIs. QTcF increase from baseline > 30 to ≤ 60 ms occurred in a lower proportion of participants treated with asciminib (2.0%) compared to IS-TKIs (4.5%; imatinib 4.0%, and 2G TKIs 4.9%). Post-baseline QTcF > 450 to ≤ 480 ms also occurred in a lower proportion of participants treated with asciminib (2.5%) compared to IS-TKIs (7.1%), as well as imatinib (5.1%) and 2G TKIs (9.2%). None of the participants in the asciminib and 2G TKI treatment groups as compared to 2 participants (2.0%) treated with imatinib experienced a QTcF > 480 to ≤ 500 ms.

Similarly, post-baseline uncorrected QT interval increase from baseline > 30 to ≤ 60 ms occurred in a lower proportion of participants with asciminib (24.5%) compared to IS-TKIs (36.8%), including as compared to imatinib (35.4%) and 2G TKIs (38.2%) [SCS-Section 4.2].

QTc prolongation is further discussed in [Section 8.2.5](#).

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Immunogenicity

The Applicant's Position: Not applicable as this was not assessed nor expected.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.5. Analysis of Submission-Specific Safety Issues

Data:

Scemblix (asciminib)

Table 27 Overview of Key Adverse Events of Special Interest (Safety set)

Safety topic	Study J12301													
	Asciminib						Investigator Selected TKI						Safety Pool	
	Imatinib Stratum		2G TKI Stratum		All Asciminib		Imatinib		2G TKI		All Comparators		All Asciminib	
	N=100		N=100		N=200		N=99		N=102		N=201		N=556	
	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 (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
GI toxicity	29 (29.0)	0	40 (40.0)	1 (1.0)	69 (34.5)	1 (0.5)	42 (42.4)	0	49 (48.0)	3 (2.9)	91 (45.3)	3 (1.5)	250 (45.0)	19 (3.4)
Myelosuppression*	41 (41.0)	18 (18.0)	45 (45.0)	20 (20.0)	86 (43.0)	38 (19.0)	51 (51.5)	23 (23.2)	64 (62.7)	33 (32.4)	115 (57.2)	56 (27.9)	219 (39.4)	125 (22.5)
Myelosuppression (Erythropenia)	10 (10.0)	1 (1.0)	13 (13.0)	2 (2.0)	23 (11.5)	3 (1.5)	26 (26.3)	5 (5.1)	23 (22.5)	6 (5.9)	49 (24.4)	11 (5.5)	70 (12.6)	22 (4.0)
Myelosuppression (Leukopenia)	30 (30.0)	10 (10.0)	32 (32.0)	15 (15.0)	62 (31.0)	25 (12.5)	38 (38.4)	22 (22.2)	41 (40.2)	19 (18.6)	79 (39.3)	41 (20.4)	135 (24.3)	83 (14.9)
Myelosuppression (Neutropenia)	24 (24.0)	7 (7.0)	26 (26.0)	13 (13.0)	50 (25.0)	20 (10.0)	31 (31.3)	17 (17.2)	35 (34.3)	18 (17.6)	66 (32.8)	35 (17.4)	120 (21.6)	76 (13.7)
Myelosuppression (Thrombocytopenia)	26 (26.0)	12 (12.0)	30 (30.0)	14 (14.0)	56 (28.0)	26 (13.0)	28 (28.3)	6 (6.1)	35 (34.3)	14 (13.7)	63 (31.3)	20 (10.0)	156 (28.1)	92 (16.5)
Myelosuppression (cytopenias ¹)	0	0	0	0	0	0	0	0	0	0	0	0	2 (0.4)	10 (2)
Hypersensitivity	20 (20.0)	0	28 (28.0)	1 (1.0)	48 (24.0)	1 (0.5)	41 (41.4)	3 (3.0)	42 (41.2)	2 (2.0)	83 (41.3)	5 (2.5)	169 (30.4)	8 (1.4)
Hepatotoxicity (including laboratory terms)	17 (17.0)	3 (3.0)	16 (16.0)	2 (2.0)	33 (16.5)	5 (2.5)	19 (19.2)	4 (4.0)	35 (34.3)	8 (7.8)	54 (26.9)	12 (6.0)	113 (20.3)	23 (4.1)

Scemblix (asciminib)

Safety topic	Study J12301													
	Asciminib						Investigator Selected TKI						Safety Pool	
	Imatinib Stratum		2G TKI Stratum		All Asciminib		Imatinib		2G TKI		All Comparators		All Asciminib	
	N=100		N=100		N=200		N=99		N=102		N=201		N=556	
	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 (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Hepatotoxicity ²	0	0	3 (3.0)	1 (1.0)	3 (1.5)	1 (0.5)	1 (1.0)	1 (1.0)	3 (2.9)	0	4 (2.0)	1 (0.5)	8 (1.4)	2 (0.4)
Acute pancreatitis (including isolated pancreatic enzyme elevations)	21 (21.0)	6 (6.0)	5 (5.0)	1 (1.0)	26 (13.0)	7 (3.5)	16 (16.2)	2 (2.0)	15 (14.7)	5 (4.9)	31 (15.4)	7 (3.5)	111 (20.0)	57 (10.3)
Pancreatic toxicity ²	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	2 (1.0)	2 (1.0)	2 (2.0)	1 (1.0)	0	0	2 (1.0)	1 (0.5)	11 (2.0)	6 (1.1)
Hemorrhage	6 (6.0)	0	6 (6.0)	0	12 (6.0)	0	7 (7.1)	1 (1.0)	10 (9.8)	2 (2.0)	17 (8.5)	3 (1.5)	75 (13.5)	10 (1.8)
Ischemic heart and CNS conditions	6 (6.0)	2 (2.0)	6 (6.0)	3 (3.0)	12 (6.0)	5 (2.5)	5 (5.1)	0	8 (7.8)	3 (2.9)	13 (6.5)	3 (1.5)	55 (9.9)	25 (4.5)
Ischemic heart conditions	5 (5.0)	1 (1.0)	6 (6.0)	3 (3.0)	11 (5.5)	4 (2.0)	5 (5.1)	0	8 (7.8)	3 (2.9)	13 (6.5)	3 (1.5)	43 (7.7)	17 (3.1)
Ischemic CNS conditions	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	0	0	1 (1.0)	0	1 (0.5)	0	16 (2.9)	9 (1.6)
Edema and fluid retention	3 (3.0)	0	4 (4.0)	0	7 (3.5)	0	13 (13.1)	0	12 (11.8)	3 (2.9)	25 (12.4)	3 (1.5)	72 (12.9)	9 (1.6)
QTc prolongation	1 (1.0)	1 (1.0)	2 (2.0)	1 (1.0)	3 (1.5)	2 (1.0)	0	0	4 (3.9)	0	4 (2.0)	0	22 (4.0)	11 (2.0)
Arterial-occlusive events (AOEs)	1 (1.0)	1 (1.0)	1 (1.0)	0	2 (1.0)	1 (0.5)	0	0	2 (2.0)	1 (1.0)	2 (1.0)	1 (0.5)	37 (6.7)	18 (3.2)
Phototoxicity	0	0	2 (2.0)	0	2 (1.0)	0	0	0	2 (2.0)	0	2 (1.0)	0	15 (2.7)	0

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Safety topic	Study J12301													
	Asciminib						Investigator Selected TKI						Safety Pool	
	Imatinib Stratum		2G TKI Stratum		All Asciminib		Imatinib		2G TKI		All Comparators		All Asciminib	
	N=100		N=100		N=200		N=99		N=102		N=201		N=556	
	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 (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Cardiac failure (clinical events)	0	0	0	0	0	0	0	0	2 (2.0)	2 (2.0)	2 (1.0)	2 (1.0)	14 (2.5)	11 (2.0)
Reproductive toxicity	0	0	1 (1.0)	0	1 (0.5)	0	1 (1.0)	0	1 (1.0)	0	2 (1.0)	0	7 (1.3)	3 (0.5)
Hepatitis B virus reactivation	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.2)	0

¹ Cytopenias affecting more than one lineage

² Clinical events

Numbers (n) represent counts of participants.

A participant with multiple severity grades for an AE is only counted under the maximum grade.

MedDRA version 26.1, CTCAE version 5.0, Case Retrieval Strategy version released 2023-11-04.

*Myelosuppression includes Erythropenia, Leukopenia, Neutropenia, Thrombocytopenia, cytopenias affecting more than one lineage.

Source: [SCS Appendix 1-Table 2-13]

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The Applicant's Position:

The AESIs were defined based on the class effects of other TKIs in the same class, mechanism of action and the current pre-clinical and clinical knowledge of the study drug. Compared to the original submission in Ph+ CML-CP, arterial-occlusive events (AOEs) have been added as an AESI for asciminib, (b) (4)

An overview of AESIs is presented in [Table 27](#). The overall pattern of AESIs associated with asciminib was consistent with its currently known safety profile and with that of the All Asciminib Safety Pool (Studies J12301, A2301, X2101). No new or worsening safety concerns were observed with asciminib in Study J12301 and in the All Asciminib Safety Pool.

Key categories of events related to myelosuppression, hypersensitivity, hepatotoxicity (including laboratory terms), hepatotoxicity (clinical events), acute pancreatitis (including isolated pancreatic enzyme elevations), pancreatic toxicity (clinical events), arterial-occlusive events (AOEs), and QTc prolongation, are discussed below, other AESI are discussed and summarized in [SCS-Section 2.6]. In Study J12301, there were no cases of hepatitis B virus reactivation [SCS-Section 2.6].

Overall, fewer AESIs, including TKI-class effects or other safety risks, were observed in participants treated with asciminib, in contrast to participants treated with IS-TKIs, including imatinib and 2G TKIs. The cumulative incidence of AESI events for most of the topics was lower with asciminib compared to IS-TKIs. For the AESI topics of acute pancreatitis and myelosuppression (thrombocytopenia), the cumulative incidence of events was comparable between the two treatment groups as expected [SCS-Section 2.6] [SCS Appendix 1-Figure 2.1-1].

8.2.5.1 Myelosuppression

In Study J12301, myelosuppression events (all grades and grade ≥ 3) occurred less frequently with asciminib (all grades: 43.0%; grade ≥ 3 : 19.0%) compared to IS-TKIs (all grades: 57.2%; grade ≥ 3 : 27.9%) including as compared to imatinib (all grades: 51.5%; grade ≥ 3 : 23.2%) and 2G TKI (all grades: 62.7%; grade ≥ 3 : 32.4%) ([Table 2722](#)). Grade 4 events occurred in similar proportions across all treatment groups. In most participants, these events were suspected to be related to study treatment, as assessed by the Investigator. SAEs occurred in a few participants across the treatment groups [CO-Section 5.1.3.1].

In all treatment groups, these events were successfully managed by dose interruptions, dose reductions, and additional medications/therapies; treatment discontinuation due to myelosuppression events was low.

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8.2.5.2 Hypersensitivity

Hypersensitivity events (all grades) occurred markedly less frequently with asciminib (24.0%) as compared to IS-TKIs (41.3%) including as compared to imatinib (41.4%) and 2G TKIs (41.2%) (Table 2722).

The proportion of participants with grade ≥ 3 events was low in all treatment groups and no SAEs were reported in either treatment group. Treatment interruption (asciminib: 1.0%, IS-TKIs: 3.5%, imatinib: 3.0%, 2G TKI: 3.9%), dose adjustment (asciminib: 0%, IS-TKIs: 3.0%, imatinib: 2.0%, 2G TKI: 3.9%), and discontinuation (asciminib: 0%, IS-TKIs: 2.0%, imatinib: 1.0%, 2G TKI: 2.9%) due to hypersensitivity events was less frequent with asciminib compared to IS-TKIs including as compared to imatinib and 2G TKIs [CO-Section 5.1.3.2].

8.2.5.3 Hepatotoxicity (including laboratory terms and clinical events)

Hepatotoxicity events (including laboratory values) (all grades and grade ≥ 3 events) occurred less frequently with asciminib (all grades: 16.5%; grade ≥ 3 : 2.5%) as compared to IS-TKIs (all grades: 26.9%; grade ≥ 3 : 6.0%) including as compared to 2G TKI (all grades: 34.3%; grade ≥ 3 : 7.8%) and was marginally lower to imatinib group (all grades: 19.2%; grade ≥ 3 : 4.0%) (Table 2722).

In most participants, these events were suspected to be related to study treatment, as assessed by the Investigator and were reversible, and not considered to be clinically relevant. Hepatotoxicity events leading to study treatment dose adjustment occurred less frequently across all treatment groups. The proportion of participants with hepatotoxicity (including laboratory terms) SAEs were low in all treatment groups [CO-Section 5.1.3.3].

Hepatotoxicity clinical events (all grades and grade ≥ 3 events) were comparable between the asciminib (all grades: 1.5%, grade ≥ 3 : 0.5%) and IS-TKI treatment group (all grades: 2.0%, grade ≥ 3 : 0.5%), including the imatinib (1% for both all grades and grade ≥ 3) and 2G TKI treatment groups (all grades: 2.9%, grade ≥ 3 : 0%) (Table 2722).

The incidence of PTs related to hepatotoxicity clinical events was low across the treatment groups. Hepatotoxicity clinical events leading to study treatment dose adjustment and dose interruption occurred in 1.0% of participants each in IS-TKI treatment group compared to none in the asciminib treatment group. The proportion of participants with hepatotoxicity (clinical events) SAEs were low in all treatment groups. Grade 4 hepatotoxicity event (not treatment-related, resolved) occurred in one participant in the asciminib treatment group and none in IS-TKI group [CO-Section 5.1.3.3].

8.2.5.4 Acute pancreatitis and pancreatic toxicity

Acute pancreatitis events, including isolated pancreatic enzyme elevations, (all grades and grade ≥ 3) occurred at a similar frequency with asciminib and IS-TKIs (all grades: 13.0% vs. 15.4%; grade ≥ 3 : 3.5% vs. 3.5%), as well as imatinib (all grades: 16.2%, grade ≥ 3 : 2.0%) and 2G TKIs (all grades:

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14.7%; grade ≥ 3 : 4.9%) (Table 2722). The majority of events were enzyme elevations without clinical manifestations.

Lipase increased and amylase increased were the most frequently reported acute pancreatitis/pancreatic toxicity events. The occurrences of all individual acute pancreatitis events were comparable across all treatment groups. Grade 4 events occurred in 2 participants (lipase increase) with asciminib and in 1 participant (amylase increased) with IS-TKIs (2G TKI).

The proportion of participants with grade ≥ 3 events, events leading to study treatment dose adjustment, interruption or withdrawal, and SAEs were low in all treatment groups and comparable. There were 3 treatment discontinuations reported with asciminib compared to 1 with IS-TKIs, specifically in imatinib group [CO-Section 5.1.3.4].

The incidence of pancreatic toxicity clinical events was low and comparable in both the treatment groups (1%) (asciminib and IS-TKI). In asciminib treatment group, these events were reported in 1 participant each, pancreatitis (serious, grade 3, suspected to be treatment-related, was resolved with drug interruption) and pancreatitis acute (serious, grade 3, suspected to be treatment-related, resolved). In the IS-TKI group, pancreatic toxicity clinical events were reported in 2 participants, pancreatitis acute (nonserious, grade 2, not treatment-related, resolved) in 1 participant, and pancreatitis acute (serious, grade 3, not treatment-related, resolved) and pancreatitis (serious, grade 3, suspected to be treatment-related, improved to grade 2, ongoing at data cut-off, drug was eventually discontinued) in the other participant [CO-Section 5.1.3.4].

8.2.5.5 QTc prolongation

The incidence of QTc prolongation events were comparable between asciminib and IS-TKI treatment groups (1.5% vs. 2.0%). The frequency of these events was lower in asciminib compared to 2G TKI treated participants (1.5% vs. 3.9%). None of the imatinib treated participants had QTc prolongation events (Table 2722).

None of the electrocardiogram QTc prolonged events were considered to be SAEs in both the treatment groups except for one 2G TKI treated participant in IS-TKI treatment group, and none were of grade 4 or grade 5 in intensity in either of the treatment groups. The grade 3 events were syncope and ECG QT prolonged in 1 participant each in the asciminib treatment group [CO-Section 5.1.3.6].

8.2.5.6 Arterial-occlusive events

Arterial-occlusive events occurred in 2 (1.0%) participants treated with asciminib and 2 (2.0%) participants treated with 2G TKIs. None of the imatinib treated participants had an AOE (Table 2722). In the asciminib treatment group, one participant had an SAE of cerebrovascular accident (grade 4, suspected to be treatment-related, resolved in one day). In the 2G TKI treatment group, one participant had an SAE of myocardial infarction (grade 4, suspected to be treatment-related by the Investigator, resolved) [CO-Section 5.1.3.5].

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The FDA's Assessment:

FDA performed analysis of all GTs including AESI in study CABL001J12301 and in the Asciminib Safety Pool of 556 patients. The Warnings and Precautions of the label includes myelosuppression, pancreatic toxicity, hypertension, hypersensitivity, and cardiovascular toxicity in 556 patients. Myelosuppression is the most frequent AESI in the CABL001J12301 study. Pancreatic toxicity manifests itself as pancreatic enzyme (amylase, lipase) elevations and pancreatitis. Hypertension is a known adverse event with asciminib and the USPI recommends monitoring for hypertension and using standard antihypertensive therapy, if needed. Hypersensitivity is another common risk factor with the TKIs. Cardiovascular toxicity section of the USPI consists of three main ADRs which are cardiovascular toxicity (including ischemic cardiac and CNS conditions, arterial thrombotic and embolic conditions), cardiac failure, and arrhythmia (including QTc prolongation).

FDA agrees with the Applicant's general assessment of submission-specific issues. In study CABL001J12301, AESI which were $\geq 10\%$ less frequent with asciminib compared to IS-TKIs were myelosuppression (GT) (43% vs. 56%) and hypersensitivity (GT) (23% vs. 41%).

FDA agrees with the Applicant's assessment of myelosuppression (GT). The most frequent form of myelosuppression is thrombocytopenia (28%), followed by neutropenia (25%), and anemia (12%). Myelosuppression (GT), thrombocytopenia (GT), neutropenia (GT), and anemia (GT) were less frequent with asciminib compared to IS-TKIs.

FDA agrees with the Applicant's assessment of pancreatic toxicity (GT). Pancreatic toxicity (GT) was observed in similar frequencies in the asciminib arm vs the IS-TKI arm (13% vs. 15%). The proposed USPI was referring to elevation of serum lipase and amylase as "asymptomatic" and the Applicant was requested to remove the word "asymptomatic" because these were reported as an elevation not relating to symptoms, and it was thought that the word "asymptomatic" understated the clinical significance of these elevations.

FDA agrees with the Applicant's assessment of hypersensitivity (GT). The most frequent hypersensitivity event in the asciminib arm of CABL001J12301 was rash (13% vs. 16%).

In study CABL001J12301, cardiovascular toxicity (GT) was seen in 4.5% of patients in the asciminib arm and 5.5% of patients in the IS-TKI arm. In the Asciminib Safety Pool of 556 patients in the USPI, cardiovascular toxicity (GT) was reported in 11% patients. Cardiac failure was not present in any patients in study CABL001J12301, and it was reported in 2.3% patients in the Asciminib Safety Pool. Arrhythmia (GT) occurred in 2% of patients in CABL001J12301 and in 6% in the Asciminib Safety Pool. The higher frequencies of cardiovascular toxicity (GT), cardiac failure (GT), arrhythmia (GT) in the Asciminib Safety Pool compared to study

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CABL001J12301 might be because of the previous TKIs used in study CABL001A2301 and in study CABL001X2101.

The Applicant proposed

(b) (4)

. Their proposal was not found acceptable as the proposed sentences did not provide additional information and

(b) (4)

FDA agrees with the Applicant's assessment of hepatotoxicity (GT). As stated above, hepatotoxicity (GT) was less frequent with asciminib and the most frequent hepatotoxicity event in the asciminib arm was alanine aminotransferase increased (7% vs. 12%).

Other AESI which were $\geq 10\%$ less frequent with asciminib but not included in the USPI are gastrointestinal toxicity (GT) (34% vs. 45%), hepatotoxicity (GT) (16% vs. 26%), and edema (3.5% vs. 20%). These are not included as W&P in the USPI because they are generally of lower grades and can be mitigated with dose modification measures.

FDA also conducted analysis of AESI in study CABL001AUS08. Table 28 shows AESI $\geq 10\%$ in CABL001AUS08. The most frequent AESI was hypertension (GT), and it was grade 3-4 in 12% of patients. Warnings and Precautions section of the USPI includes hypertension and mentions mitigation measures.

Table 28 Adverse events of special interest $\geq 10\%$ in study CABL001AUS08

	Asciminib N=71 (%)	
	Any Grade	Grade 3-4
Hypertension*	17	12
Hypersensitivity*	16	0
Pancreatic Toxicity*	13	0
Rash*	10	0
Source: FDA analysis using adae.xpt, adsl.xpt *indicates grouped terms, see Appendix 19.5.		

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing

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Safety/Tolerability

The Applicant's Position:

Patient-related outcomes data were collected in Study J12301. However, no formal statistical analysis was performed and only descriptive summaries are provided in the CSR [Study J12301 PA CSR-Section 11.5]

The FDA's Assessment:

Patient-reported outcomes data were collected and included in the submission. However, the Applicant did not perform any formal statistical analysis and they were not evaluated by the FDA.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Subgroup analyses were conducted to identify potential safety issues that might have been limited to a subgroup of participants, or safety issues that were more commonly observed in a subgroup of participants [CO-Section 5.1.5.1].

The following subgroup analyses were performed for Study J12301 and the All Asciminib Safety Pool:

- Age group (18-< 65, ≥65, ≥75 years)
- Gender (male vs. female)
- Race (Caucasian, Asian, Other)
- Renal impairment at baseline (moderate, mild, normal)
- Hepatic impairment at baseline (moderate, mild, normal)

In Study J12301, exposure (measured in PTY) across all age groups (18 to < 65 years, ≥65 years, and ≥75 years) irrespective of gender and race was comparable between both asciminib and IS-TKI treatment groups.

Overview of AEs by age, gender, and race (Study J12301)

Age: Overall, no meaningful differences in the safety of asciminib were observed between participants 65 years of age or older compared to younger participants. AEs and treatment-related AEs were comparable between all age categories across all treatment groups other than as expected, a higher incidence of AEs was observed in participants ≥75 years compared to those <75 years. However, no imbalance in the type of events or age-related events was observed, with asciminib showing a consistent safety profile across all age groups [SCS-Section 5.1.1.2].

Most of the AESIs were consistent across all age groups in both the treatment groups except for: Acute pancreatitis events occurred at a higher incidence in participants aged ≥65 years across

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the treatment groups compared to 18 to <65 years however, in participants ≥ 75 years, these events occurred at a lower incidence with asciminib compared to the IS-TKI treatment group (10.0% vs. 21.4%); edema and fluid retention events in asciminib treatment group occurred at a higher incidence in ≥ 75 years age group (20.0%) compared to the 18 to <65 years (2.6%) and ≥ 65 years (6.5%) age groups; these events however were less frequent with asciminib compared to IS-TKIs in ≥ 65 years age group (6.5% vs. 29.2%). Most of the AESIs in asciminib treatment group occurred at lower incidence compared to the IS-TKI treatment group across all age group categories except for hemorrhage events which occurred at a higher incidence in participants ≥ 75 years in asciminib treatment group compared to the IS-TKI treatment group (20.0% vs. 0%) [SCS-Section 5.1.1.2].

Gender: Overall, no clinically meaningful differences in safety profile of asciminib were observed by gender [SCS-Section 5.1.1.3].

Race: In the asciminib treatment group, the incidence of most of the AE categories was similar in White and Asian subgroups. In the IS-TKI treatment group, the incidence of AEs leading to dose adjustment/interruption (40.7% vs. 52.8%) and AEs requiring additional therapy (78.7% vs. 89.9%) was higher in Asian participants compared to White/Caucasian participants [SCS-Section 5.1.1.4].

Overview of AEs based on renal and hepatic impairment status at baseline

In **Study J12301**, based on the eGFR at baseline, the number of participants in the asciminib and IS-TKI treatment group, respectively, with normal renal function were 119 vs. 123 participants and 68 vs. 67 participants with mild renal impairment. As the number of participants with moderate renal impairment is small in both the treatment groups (13 and 11 participants), this group has not been considered for comparison.

In both the treatment groups, the incidence of most of the AEs across all the AE categories was similar in the mild renal impairment and normal renal function group and was comparable to the incidence of AEs observed in the overall patient population in Study J12301.

Most of the AESIs were consistent in participants with mild renal impairment and participants with normal renal function except for: Gastrointestinal toxicity (asciminib treatment group) higher incidence in mild renal impairment vs. normal renal function subgroup (41.2 % vs. 28.6%); myelosuppression (asciminib treatment group) lower incidence in mild renal impairment vs. normal renal function subgroup (36.8% vs. 47.1%); hypersensitivity (imatinib treated participants) higher incidence in mild renal impairment vs. normal renal function subgroup (50.0% vs. 34.5%); acute pancreatitis events higher incidence in mild renal impairment vs. normal renal function subgroup in the asciminib treatment group (19.1% vs. 8.4%) and vice-versa for imatinib treated participants (13.2% vs. 20.0%); edema and fluid retention higher incidence in mild renal impairment vs. normal renal function subgroup in IS TKI treatment group (17.9% vs. 9.8%), including for imatinib (18.4% vs. 9.1%).

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Except for myelosuppression events, none of the grade ≥ 3 AEs occurred at a higher incidence ($\geq 10\%$) across all subgroups in both the treatment groups. The incidence of most of the grade ≥ 3 AEs in both the asciminib and IS-TKI treatment groups was comparable between the mild renal impairment and normal subgroups [SCS-Section 5.1.1.5].

In **Study J12301**, as most participants in this subgroup analysis had normal hepatic function at baseline (357 participants) with a small number of participants with mild hepatic impairment (43 participants), a meaningful comparison cannot be made across various AEs categories and the results were comparable to the overall analysis of AEs in Study J12301 [SCS-Section 5.1.1.6].

Subgroup analysis in All Asciminib Safety Pool is presented in the [SCS-Section 5.1.1]

The FDA's Assessment:

FDA agrees with the Applicant's assessment. In the Asciminib Safety Pool of 556 patients, TEAEs $\geq 10\%$ were similar in patients < 65 vs. ≥ 65 years of age, and in patients < 75 vs. ≥ 75 years of age. Two TEAEs which were higher in patients ≥ 75 years compared to patients < 75 years were musculoskeletal pain (GT) (52% vs. 35%) and fatigue (GT) (32% vs. 25%). The higher frequency of these two TEAEs may be related to older age and concomitant diseases. In study CABL001J12301, TEAEs in patients < 65 and ≥ 65 years of age were similar except neutropenia (28% vs. 15%), hypersensitivity (25% vs. 13%), and rash (21% vs. 9%) which were $\geq 10\%$ higher in patients < 65 years of age. In study CABL001J12301, musculoskeletal pain (GT) (22% vs. 70%) was much higher in patients ≥ 75 years of age compared to those aged < 75 years.

Female and male patients compared similarly in terms of TEAEs. When White patients were compared to Asian patients, it was seen that there was $\geq 10\%$ difference in the TEAEs of musculoskeletal pain (GT) (31% vs. 18%), myelosuppression (GT) (31% vs. 59%), fatigue (GT) (28% vs. 7%), and headache (GT) (18% vs. 8%) between the groups. The number of Black or African American patients was not sufficient to include in racial comparisons.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Study AUS08 showed a consistent and favorable safety profile in 43 participants with Ph+ CML-CP in the 2L cohort in the Safety Set at 6 months. There were no major safety concerns observed. The median duration of exposure to study treatment was 11.4 weeks (range: 0-66). One participant had SAEs (chest pain, catheter site pain, and intractable nausea and vomiting), all were grade 3 events, and while nausea was reported as related to asciminib, vomiting, catheter site pain and chest pain were reported as not related to asciminib. All SAEs were reported to have been resolved. One participant had AEs leading to treatment discontinuation (nausea, grade 3, treatment-related). There were no deaths [CO-Section 5.2].

The FDA's Assessment:

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The Applicant submitted an interim analysis for the 2L cohort of study CABL001AUS08 on 30 August 2024 which included “Applicant’s 6-Month Efficacy Key Outputs for 2L Cohort (IA2) Document.”

Twenty-eight patients completed the 6-month efficacy assessment or discontinued treatment prior in the 2L cohort. Seventy-one patients were enrolled in the 2L cohort between 11 November 2022 and 28 June 2024 and were included in the Full Analysis Set. Safety results of 71 patients in the 2L Asciminib cohort related to study CABL001AUS08 are included in relevant sections of the Assessment Aid.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant’s Position:

Based on the currently available nonclinical data from the 2-year rat carcinogenicity study, the relevance of these findings to humans is unknown. Based on routine pharmacovigilance activities to date and the evaluation of cumulative data available in the Clinical Database and Novartis Safety Database, there is no evidence of a potential safety signal of any ovarian malignant or benign tumors in asciminib-treated patients.

The FDA’s Assessment:

FDA agrees with the Applicant’s position. On 6 February 2024 the Applicant submitted Supplement 007 which included the results of a 2-year carcinogenicity study of asciminib in Wistar Han rats and it was based on data from a 26-week repeat-dose toxicology. There was a statistically significant increase in the incidence of benign Sertoli cell tumors in the ovaries of high-dose female rats. Currently, the clinical significance of these findings in humans is unknown. Relevant changes were incorporated into section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility of the USPI. Supplement 007 was approved on 6 August 2024. Refer to the nonclinical pharmacology toxicology review.

Human Reproduction and Pregnancy

The Applicant’s Position:

No new information is provided in support of the current application, recommendations are described in the approved prescribing information.

The FDA’s Assessment:

FDA confirms the Applicant’s position.

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Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Not applicable (b) (4).

The FDA's Assessment:

FDA confirms the Applicant's position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

No new information about overdose has been generated in support of this application; recommendations are described in the approved prescribing information.

There is no known potential for abuse of asciminib. Given the pattern of side effects and the absence of effects that could lead to dependence, no abuse potential is expected and hence, no abuse studies have been performed [SCS-Section 5.5]

No studies have been conducted to assess withdrawal and rebound effects and withdrawal and rebound effects were not reported in clinical studies [SCS-Section 5.6].

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:

Up to 15-Jan-2024, no new safety signals were identified based on regular reviews by qualified medical personnel of worldwide literature searches and frequency analyses in external databases or registries containing safety data as part of routine signal detection activities. No new safety signals and no substantial changes to the safety profile of the drug were identified for the reviews conducted for SAEs and deaths from ongoing studies whose data were included in the pooled analyses, for events reported between the latest cut-off date for the pooled data (28-Nov-2023 for Study J12301) and 15-Jan-2024. Furthermore, no new or changing safety signal was identified for the reporting interval from 29-Apr-2023 to 28-Oct-2023 of the most recent PSUR presenting postmarketing analyses with an estimated cumulative post-marketing exposure of (b) (4) patient-treatment years [SCS-Section 6].

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The FDA's Assessment:

FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Toxicities appear to have been adequately represented in Studies J12301, A2301, and X2101. Potential safety concerns beyond the risks conveyed in the proposed prescribing information are considered not expected. Routine pharmacovigilance will be conducted to monitor for unexpected AEs.

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 study CABL001J12301 and also in the Asciminib Safety Pool of 556 patients. A PMR for 5-year follow-up about safety and efficacy of study CABL001J12301 will be requested.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The results from the registration study J12301 in participants with newly diagnosed Ph+ CML-CP shows that the safety data is consistent with the known safety profile of asciminib. These results were further strengthened by the results from the All Asciminib Safety Pool where longer-term treatment continued to be consistent with the previously established safety profile. An unmet need related to safety for treatment of 1L Ph+ CML-CP is a specific targeted therapy with improved safety/tolerability profile. Asciminib shows favorable safety and tolerability vs. Investigator selected-TKIs overall, including vs. 2G TKIs and vs. imatinib, fulfilling this unmet need in the newly diagnosed patient population.

Key conclusions

- No new or worsening safety concerns were identified from the data from Study J12301, further reinforcing the safety profile of asciminib.
- In Study J12301, overall, AEs occurred in 93.5% of participants treated with asciminib compared to 93.9% participants treated with imatinib and 100% participants treated with 2G TKIs (97.0% for IS-TKIs overall).
- All other key categories of AEs were less frequently observed in asciminib-treated participants compared to participants treated with IS-TKI (imatinib or 2G TKIs), irrespective of whether considered related to study treatment as assessed by the Investigator, including: severe AEs (grade ≥ 3 AEs), serious AEs (SAEs), AEs leading to discontinuation, AEs leading to dose interruption/dose adjustment, and AEs requiring additional therapy.

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- Asciminib has a better safety profile for most of the safety topics including those which are considered as class effects for TKIs. In Study J12301 overall, AEs were reported in a lower proportion of participants treated with asciminib. The proportion of participants experiencing treatment-emergent AEs of myelosuppression, gastrointestinal toxicity, hepatotoxicity (including laboratory terms), hypersensitivity, and fluid retention/edema were lower in the asciminib treatment group compared to the IS-TKI treatment group, including imatinib and 2G TKI treated participants (both all grades and grade ≥ 3). There was no cardiac failure reported in asciminib and imatinib-treated participants; 2 dasatinib-treated participants had severe cardiac failure (grade ≥ 3).
- The safety profile for age, race, gender, and renal and hepatic impairment subgroups was consistent with the overall safety profile observed in participants with newly-diagnosed Ph+ CML-CP treated with asciminib in Study J12301.
- Size of the safety database and duration of exposure were considered robust and adequate for safety assessment of asciminib in clinical studies (n=556 All Asciminib Safety Pool), with additional postmarketing data of (b) (4) patient-treatment years as of 28-Oct-2023, and with a maximum treatment duration of 8 years and median duration of treatment of 6 years from Study X2101.
- The data from the All Asciminib Safety Pool further strengthen the safety of asciminib with longer exposure and demonstrate consistency with the known safety profile of asciminib.

Overall Summary

Asciminib 80 mg QD in Study J12301 demonstrated a markedly favorable safety and tolerability profile with fewer all grade and severe (grade ≥ 3) AEs, SAEs, and AEs requiring dose interruption/dose adjustments or treatment discontinuations, all grades and severe (grade ≥ 3) AEs, compared to IS-TKI overall as well as compared to participants treated with imatinib and 2G TKIs. In particular, asciminib demonstrated a more favorable safety profile across all key safety parameters, including TKI class risks, vs. 2G TKIs.

Thus, the safety of asciminib can be established by extrapolation to the 2L setting based on the existing safety profile in 3L+, the absence of any new safety concerns in 1L, and the fact that this 2L setting does not have any unique disease characteristics that would impact the safety profile. Emerging safety data from Study AUS08 showed that the safety data is consistent with the previously established safety profile of asciminib as of the data cut-off of 22-March-2024 with a median duration of exposure of 11.4 weeks in 43 participants. Only 1 participant had discontinued due to AE, and SAE was reported in 1 participant. Moreover, with asciminib also showing a better safety and tolerability profile in the 1L and 3L+ setting, compared to all IS-TKIs, including 2G TKIs which are most commonly used in the 2L setting, it can be expected that asciminib also shows better safety than 2G TKIs in the 2L setting.

Scemblix (asciminib)

The FDA's Assessment:

FDA agrees with the Applicant's overall safety summary. In study CABL001J12301, the most frequent TEAEs in the asciminib arm were thrombocytopenia (GT) (28%), neutropenia (GT) (25%), and musculoskeletal pain (GT) (25%). The most frequent grade 3-4 TEAEs were thrombocytopenia (GT) (13%) and neutropenia (GT) (10%). The most frequent TEAEs in the IS-TKI arm were similar to the asciminib arm, albeit at a higher frequency, neutropenia (GT) (33%), musculoskeletal pain (GT) (32%), and thrombocytopenia (GT) (31%). Most TEAEs $\geq 10\%$ were less frequent in the asciminib arm than in the IS-TKI arm. The only TEAE which was more frequent with asciminib was abdominal pain (GT) (14% vs. 10%). Upper respiratory tract infection (GT) and lipase increased were similar in both arms (15% and 12%).

Safety data from study CABL001AUS08 was evaluated to investigate safety in the 2L indication. In the safety set of 71 patients, musculoskeletal pain (GT) (27%) was the most frequent TEAE followed by vomiting (GT) (17%) and fatigue (16%). Grade 3-4 TEAEs in study CABL001AUS08 were infrequent. AESI $\geq 10\%$ were hypertension (GT) (17%), hypersensitivity (GT) (16%), pancreatic toxicity (GT) (13%), and rash (GT) (10%).

The Applicant proposed

(b) (4)

. The Applicant was requested to remove this information
(b) (4) from the USPI.

(b) (4)

In addition, Pancreatic Toxicity section of Warnings & Precautions included the word "asymptomatic" to define "elevation of serum lipase and amylase." The Applicant agreed to removing the word "asymptomatic" in two places in this section because adverse events were reported as an elevation not relating to symptoms, and "asymptomatic" understated the clinical significance of these elevations.

The Applicant's proposed tables for adverse reactions ($\geq 10\%$) (Table 3 in the USPI) and select laboratory abnormalities ($\geq 20\%$) that worsened from baseline (Table 4 in the USPI) in study CABL001J12301 included (b) (4) groups of patients: asciminib, IS-TKIs, (b) (4)

(b) (4)

. The Applicant was requested to remove

(b) (4)

and they

made the tables difficult to interpret.

Safety overview in study CABL001J12301 is seen in Table 29.

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Table 29 Safety overview in study CABL001J12301

	Asciminib N=200 N (%)	Investigator-Selected TKI N=201 N (%)
All Grade TEAEs	187 (94)	195 (97)
Grade $\geq$ 3 TEAEs	76 (38)	100 (50)
Grade 3 TEAEs	55 (28)	82 (41)
Grade 4 TEAEs	21 (11)	18 (9)
Grade 5 (On -treatment deaths due to TEAEs)	0	0
Serious TEAEs (SAEs)	22 (11)	32 (16)
Drug Withdrawn – due to AEs	9 (5)	21 (10)
Drug Interrupted – due to AEs	60 (30)	80 (40)
Drug Reduced – due to AEs	11 (6)	38 (19)
Source: FDA analysis using adae.xpt, adsl.xpt.		

The safety overview of study CABL001AUS08 is seen in Table 30.

Table 30 Safety overview in study CABL001AUS08

	Asciminib (N=71) N (%)
All Grade TEAEs	63 (89)
Grade $\geq$ 3 TEAEs	18 (25)
Grade 3 TEAEs	15 (21)
Grade 4 TEAEs	3 (4)
Grade 5 (On-treatment deaths due to TEAEs)	0
Serious TEAEs (SAEs)	2 (3)
Drug Withdrawn – due to AEs	1 (1.4)
Drug Interrupted – due to AEs	13 (18)
Drug Reduced – due to AEs	2 (3)
Source: FDA analysis using adae.xpt, adsl.xpt.	

In the FDA assessment, the submitted evidence has provided substantial evidence for the safe use of asciminib for both indications of newly diagnosed and previously treated Ph+ CP-CML. Overall, single-agent asciminib was well tolerated in patients with newly diagnosed disease and also in the 2L setting. Asciminib is approved for 3L+ indication, therefore, the safety and efficacy data from study CABL001AUS08 was evaluated to extend the indication to “previously

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treated Ph+ CP-CML.” The level of toxicity described for asciminib was thought to be acceptable for the clinical benefit observed.

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SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The statistical review team agrees with the Applicant that statistical aspects of study CABL001J12301 provide evidence for the effectiveness of the asciminib in newly-diagnosed Ph+ CP-CML. Asciminib demonstrated an improvement of 18.88% in MMR rate at Week 48 vs. the control arm. This endpoint is appropriate for this setting.

The statistical review team notes that the overall treatment effect on MMR at Week 48 is not representative of the relative efficacy of asciminib versus all treatments used in the control arm. For instance, this difference was 8.17% for the 2nd generation TKI stratum. This heterogeneity was expected a priori, as all of the 2nd generation TKIs included were approved based on an improvement in response rates as compared to imatinib in randomized trials. Given this heterogeneity of treatment effect, the associated subgroup estimates should be considered more reliable for understanding the benefit of asciminib over imatinib or 2nd generation TKIs. This heterogeneity has no impact on the approvability of asciminib in the first-line setting.

The MMR rates observed in study CABL001J12301 are higher than those reported historically. This speaks to the importance of randomization, as historical rates may not be representative of the efficacy of any one product. While not an issue for study CABL001J12301, study CABL001AUS08 was a single-arm trial whose interpretation is limited by the absence of a control arm as well as a limited sample size.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The review team was able to verify or clarify the safety and efficacy endpoints as provided by the Applicant. The review team recommends approval of the NDA.

The FDA approach toward approval in newly diagnosed CP-CML is to grant accelerated approval when there is at least 48 weeks (one year) of safety and efficacy data. For conversion to regular approval, the FDA requires 60 months (5 years) of safety and efficacy information. Follow up to the later time point is required only from the study-drug treatment arm in the case of an active-controlled study to demonstrate benefit with the use of the study drug. In this submission, the Applicant provided safety and efficacy information from study CABL001J12301 to 48 weeks. Therefore, the data from CABL001J12301 supports accelerated approval in patients with newly diagnosed Ph+ CP-CML. A PMR will be issued to obtain safety and efficacy information at 60 months (5 years).

Asciminib has regular approval for the treatment of patients with Ph+ CP-CML, previously

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treated with two or more TKIs. They have provided 6-month efficacy data from study CABL001AUS08 when a minimum of 28 patients in the 2L cohort had completed their week 24 (6 months) visit or discontinued prior. The safety set includes 71 patients enrolled in the 2L cohort. As the safety and efficacy data from study CABL001AUS08 was found acceptable and adequate safety and efficacy information was provided from studies A2301 and J12301, the “previously treated with two or more TKIs” indication was updated to “previously treated” indication, and the review team recommends for this indication to be approved under regular approval.

8.4.1. Approach to Substantial Evidence of Effectiveness

The FDA’s Assessment:

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (*enter approved indication if the application was approved and the Applicant’s proposed indication if the application received a complete response*):

Asciminib for the treatment of adult patients with newly diagnosed Philadelphia chromosome-positive (Ph+ CML) in chronic phase (CP).

2. SEE was established with (*check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE*)

- a. Adequate and well-controlled clinical investigation(s):

- i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**

- ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

- b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence^{1,2,3}

OR

- c. ☐ Evidence that supported SEE from a prior approval (*e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch*)²

3. Complete response, if applicable

- a. ☐ SEE was established

- b. ☐ SEE was not established (*if checked, omit item 2*)

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Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (*enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response*):

Asciminib for the treatment of adult patients with previously treated Ph+ CML in CP.

2. SEE was established with (*check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE*)

d. Adequate and well-controlled clinical investigation(s):

- i. ☒ Two or more adequate and well-controlled clinical investigations, **OR**
- ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

e. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence^{1,2,3}

OR

f. ☐ Evidence that supported SEE from a prior approval (*e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch*)²

3. Complete response, if applicable

a. ☐ SEE was established

b. ☐ SEE was not established (*if checked, omit item 2*)

¹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)

² FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)

³ Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

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X

X

Primary Statistical Reviewer

Statistical Team Leader

X

X

Primary Clinical Reviewer

Clinical Team Leader

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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.

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10 Pediatrics

The Applicant's Position:

Not applicable, as the applicant has not proposed any changes to the pediatric sections of the Scemblix label.

The FDA's Assessment:

FDA agrees with the Applicant's position. The sNDA is exempt from PREA requirements as asciminib has orphan drug exclusivity that includes the proposed indications.

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11 Labeling Recommendations

Data:

Table 31 Summary of Significant Labeling Changes (High level changes and not direct quotations)

<u>Section</u>	<u>Applicant's Proposed Labeling</u>	<u>FDA's proposed Labeling</u>
1	Proposed line extension of the currently-approved indication	FDA added the accelerated approval statement. As the accelerated approval language only applies to patients with newly diagnosed Ph+ CML in CP, FDA split the indication as follows: • newly diagnosed Ph+ CML in CP • previously treated Ph+ CML in CP
5	Update of the Warnings and Precautions section based on data pooled across clinical studies (J12301, A2301 and X2101)	FDA removed (b) (4) (b) (4) FDA removed (b) (4)

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		(b) (4)
6.1	Inclusion of an introductory paragraph regarding the most common Adverse Reactions pooled across clinical studies	FDA agreed.
6.1	Inclusion of the Adverse Reactions section relevant to J12301 study results	FDA removed (b) (4)
8.5	Update of geriatric use based on data a) pooled across clinical studies and b) from J12301 study	FDA agreed.
14.1	Inclusion of clinical efficacy data relevant to J12301 study	FDA revised this section to remove proposed (b) (4) FDA agreed with including the MMR, and associated confidence intervals, at 48 weeks in patients receiving SCEMBLIX and investigator-selected-TKIs within the second generation TKI stratum.

The Applicant's Position:

Details provided in [Table 31](#).

The FDA's Assessment:

FDA modified sections of the USPI as described in Table 31; see the approval letter for final labeling.

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12 Risk Evaluation and Mitigation Strategies (REMS)

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.

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13 Postmarketing Requirements and Commitment

The FDA's Assessment:

FDA will request a PMR for 60 months (5 years) of follow-up data from the CABL001J12301 trial. The findings will be used to determine whether asciminib will receive regular approval for the newly diagnosed Ph+ CP-CML indication.

Current trials have not enrolled patients that are reflective of the ethnic diversity of patients with CML in the US. Black or African American and Hispanic / Latino patients with CML are underrepresented in study CABL001J12301. However, differential response and tolerance may exist among different racial and ethnic minorities. Therefore, FDA will request a PMC to determine whether asciminib shows a similar safety and efficacy profile in these underrepresented racial and ethnic groups.

Refer to FDA action letter for final PMR/PMC wording.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
x	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	☐ Yes ☒ No
x	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	☒ Yes ☐ No
x	Other considerations (e.g.: PK/PD), if applicable:	☐ Yes ☒ No

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14 Division Director (DHOT) (NME ONLY)

X

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15 Division Director (OCP)

X

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16 Division Director (OB)

X

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17 Division Director (Clinical)

X

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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:

- [Bosulif SmPC (2023)] Bosulif (bosutinib) Film coated tablets. Summary of Product Characteristics. Pfizer, Bruxelles (Belgium). Last updated: 06/2023.
- [Bosulif USPI (2023)] Bosulif (bosutinib) Tablets, capsules. US Prescribing Information. Pfizer, New York (USA). Revised: 09/2023.
- [Branford S (2016)] Molecular monitoring in chronic myeloid leukemia-how low can you go? Hematology Am Soc Hematol Educ Program; 2016(1):156-163.
- [Campbell D, Blazer M, Bloudek L, et al (2019)] Realized and Projected Cost-Savings from the Introduction of Generic Imatinib Through Formulary Management in Patients with Chronic Myelogenous Leukemia. Am Health Drug Benefits; 12(7):333-42.
- [Cross NC, White HE, Müller MC, et al (2012)] Standardized definitions of molecular response in chronic myeloid leukemia. Leukemia; 26(10):2172-5.
- [Cortes J, Kantarjian H (2016)] Chronic myeloid leukemia: sequencing of TKI therapies. Hematology Am Soc Hematol Educ Program; 2016(1):164-9.
- [Cortes JE (2018)] A second-generation TKI should always be used as initial therapy for CML. Blood Adv; 2(24):3653-5.
- [Cortes JE, Lang F (2021)] Third-line therapy for chronic myeloid leukemia: current status and future directions. J Hematol Oncol (2021); 14(1):44
- [Dulucq S, Mahon FX (2016)] Deep molecular responses for treatment-free remission in chronic myeloid leukemia. Cancer Med;5(9):2398-2411.
- [European Medicines Agency (2015)] Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man. Anticancer guideline. EMA/CHMP/703715/2012 Rev 2.
- [Faderl S, Talpaz M, Estrov Z, et al (1999)] Chronic Myelogenous Leukemia: Biology and Therapy. N. Engl. J. Med; 131(3):207-19.
- [Gambacorti-Passerini C, Brümmendorf TH, Kim DW, et al (2014)] Bosutinib efficacy and safety in chronic phase chronic myeloid leukemia after imatinib resistance or intolerance: Minimum 24-month follow-up. Am J Hematol; 89(7):732-42.
- [García-Gutiérrez V, Hernández-Boluda JC (2019)] Tyrosine kinase inhibitors available for chronic myeloid leukemia: efficacy and safety. Front Oncol; 9(603):1-10.
- [Greiner G, Ratzinger F, Gurbisz M, et al (2020)] Comparison of BCR-ABL1 quantification in peripheral blood and bone marrow using an International Scale-standardized assay for

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assessment of deep molecular response in chronic myeloid leukemia. Clin Chem Lab Med; 58(8):1214–22.

[Gleevec USPI (2022)] Gleevec (imatinib) Tablets. US Prescribing Information. Novartis, New Jersey (USA). Revised: 08/2022.

[Glivec SmPC (2023)] Glivec (imatinib) Hard capsule. Summary of Product Characteristics. Novartis, Dublin (Ireland). Last updated: 11/2023.

[Hochhaus A, Saglio G, Hughes TP, et al (2016)] Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia;30(5):1044–54.

[Hochhaus A, Saussele S, Rosti G, et al (2017)] Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology; 28 (Supplement 4): iv41–iv51.

[Hochhaus A, Baccarani M, Silver RT, et al (2020)] European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia; 34(4):966-84.

[Hochhaus A, Rea D, Boquimpani C, et al (2023)] Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. Leukemia; 37(3):617-26.

[Hughes TP, Hochhaus A, Branford S, et al (2010)] Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). Blood; 116(19):3758-65.

[Jabbour E, Kantarjian H (2022)] Chronic myeloid leukemia: 2022 update on diagnosis, therapy, and monitoring. Am J Hematol; 97(9):1236-56.

[Kantarjian H, Shah NP, Hochhaus A, et al (2010)] Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med; 362(24):2260-70.

[Kantarjian HM, Giles FJ, Bhatta KN, et al (2011)] Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood; 117(4):1141-5.

[National Comprehensive Cancer Network (2024)] NCCN Clinical Practice Guidelines in Oncology:Chronic Myeloid Leukemia. NCCN guidelines Version 1.2024. (Online) National Comprehensive Cancer Network, Washington, PA.

[National Cancer Institute (2024)] Surveillance, epidemiology, and end result program (SEER). Cancer Stat Facts: Leukemia-Chronic Myeloid Leukemia.

[NCT00123474] Chronic Myelogenous Leukemia (CML) - Follow on: Study of BMS-354825 in Subjects With CML (Internet) Available from:
<<https://clinicaltrials.gov/ct2/show/NCT00123474>> (Accessed on 26 Apr 2021).

[Press RD (2010)] Major molecular response in CML patients treated with tyrosine kinase inhibitors: the paradigm for monitoring targeted cancer therapy. Oncologist; 15(7):744-9.

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[Réa D, Mauro MJ, Boquimpani C, et al (2021)] A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood ;138(21):2031-41.

[Saglio G, Kim DW, Issaragrisil S, et al (2010)] Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med; 362(24): 2251-59.

[Saglio G, Jabbour E (2018)] First-line therapy for chronic phase CML: selecting the optimal BCR-ABL1-targeted TKI. Leuk Lymphoma; 59(7):1523-38.

[Scemblix USPI (2021)] Scemblix (asciminib) for Tablets. US Prescribing Information. Novartis, New Jersey (USA). Revised 10/2021.

[Senapati, J, Sasaki K, Issa GC, et al (2023)] Management of chronic myeloid leukemia in 2023 – common ground and common sense. Blood Cancer J. 13:58.

[Seong D, Kantarjian HM, Albitar M, et al (1999)] Analysis of Philadelphia chromosome-negative BCR-ABL-positive chronic myelogenous leukemia by hypermetaphase fluorescence in situ hybridization. Ann Oncol; 10(8):955-9.

[Shah NP, Kim DW, Kantarjian H, et al (2010)] Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. Haematologica;95(2):232-40.

[Sweet KL, Cortes JE, Apperley JF, et al (2023)] Project Confirm: accelerated drug approvals for chronic myeloid leukemia. Clin Cancer Res; 29(12):2179-83.

[Sprycel USPI (2023)] Sprycel (dasatinib) for Tablets. US Prescribing Information. Bristol-Myers Squibb, New Jersey (USA). Revised 02/2023.

[Sprycel SmPC (2022)] Sprycel (dasatinib) Film coated tablets. Summary of Product Characteristics. Bristol-Myers Squibb, Dublin, Ireland. Last updated: 06/2022.

[Tasigna SmPC (2023)] Tasigna (nilotinib) Hard capsules. Summary of Product Characteristics. Novartis, Dublin (Ireland). Last updated: 11/2023.

[Tasigna USPI (2021)] Tasigna (nilotinib) for capsules. US Prescribing Information. Novartis, New Jersey (USA) Revised 09/2021.

The FDA's References:

Sobieski CE, Vardell VA, Tantravahi SK. Racial and ethnic disparities in survival outcomes in chronic myeloid leukemia. Blood 2022; 140 (Supplement 1): 1507–1508.

19.2. Financial Disclosure

The Applicant's Position:

No clinical Investigators are full or part-time employees of Novartis Pharmaceuticals Corporation. Disclosable financial arrangements and interests are identified on the spreadsheets by bolding

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the Investigators name and are detailed in the disclosure forms that follow FDA Form 3455. These arrangements and interests are provided in [Table 32](#). Any bias resulting from these arrangements is minimized by independent data monitoring by Novartis.

Table 32 Summary of disclosable financial arrangements and interests

Investigator	Study No.	Center No.	Amount Disclosed	Category of Disclosure
(b) (6)	CABL011J12301	(b) (6)	2,000,000 USD	Research grants Investigator initiated trials

Covered Clinical Study (Name and/or Number): * Study CABL001J12301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 896		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
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: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>0</u> Sponsor of covered study: <u>0</u>		
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)

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Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>NA</u>		
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.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of financial disclosure information. CABL001J12301 was a covered study.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

No new information is provided in the current submission for non-clinical pharmacology/toxicology.

The FDA's Assessment:

FDA confirms the Applicant's position.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

The Applicant's summary of the validation data supporting the bioanalytical methods used for determination of asciminib concentrations in human plasma samples from Study CABL001J12301 was provided in a response to information request and is provided below. FDA assessment is provided in the tables highlighted in gray.

Summary method DMPK R1701209 performance of a bioanalytical method to measure asciminib (ABL001) in Human plasma

Bioanalytical method validation report name, amendments, and hyperlinks	Method # 1 Report Name: Method Validation Report Report Title: Quantitative determination of ABL001 in human plasma by LC-MS/MS Amendments: 01, 02, 03 and 04 [DMPK R1701209] (original), [DMPK R1701209-01] (amendment 1), [DMPK R1701209-02] (amendment 2), [DMPK R1701209-03] (amendment 3), [DMPK R1701209-04] (amendment 4)
Method description	Quantitative determination of ABL001 in human plasma by LC-MS/MS 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 to each tube. 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±2°C. Supernatant was

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	transferred to pre-labeled autosampler vials. A 5 µL aliquot of the reconstituted extract was injected into the LC-MS/MS system.	
Materials used for calibration curve & concentration	Reference standard: Ref: Method Validation Report No. DMPK R1701209 Asciminib (ABL001-AAA.003), Lot No. 1010009610, Retest date Dec 2017, 2019, [M+5] ABL001 Chemical Isotope, Batch No. SSU6181-2013-8438-01, Retest date Jul 2020. Ref: Method Validation Report No. 03 DMPK R1701209-03 Asciminib (ABL001-AAA.005), Lot No. C0002.REF, Retest date APR 2023, [2H5]-ABL001 Chemical Isotope, Batch No. SSU6181-2013-8438-01, Retest date 04 Aug 2023. Ref: Method Validation Report No. 04 DMPK R1701209-04 Asciminib (ABL001-AAA.006), Lot No. C0030.REF, Retest date Oct 2027 [2H5]-ABL001 Chemical Isotope, Batch No. SVI-ALS-20-175/SSU6181-2013-8438-01, Retest 24 Aug 2027 Matrix: Pooled Human Plasma with K₂EDTA as anticoagulant Concentration: 1.00, 2.00, 15.0, 40.0, 100, 250, 500, 1000, 2500, 5000 ng/mL	
Validated assay range	1.00 - 5000 ng/mL	
Material used for QCs & concentration	Reference standard: Asciminib (ABL001-AAA.003), Lot No. 1010009610, Retest date Dec 2017, 2019, Asciminib (ABL001-AAA.005), Lot No. C0002.REF, Retest date APR 2023, Asciminib (ABL001-AAA.006), Lot No. C0030.REF, Retest date Oct 2027 Internal standard: [M+5] ABL001 Chemical Isotope, Batch No. SSU6181-2013-8438-01, Retest date Jul 2020. [2H5]-ABL001 Chemical Isotope, Batch No. SSU6181-2013-8438-01, Retest date 04 Aug 2023. [2H5]-ABL001 Chemical Isotope, Batch No. SVI-ALS-20-175/SSU6181-2013-8438-01, Retest 24 Aug 2027 Matrix: Pooled Plasma with K₂EDTA as anticoagulant Concentration: 1.00, 3.00, 200, 2000, 4000 ng/mL	
Minimum required dilutions (MRDs)	Not applicable	
Source & lot of reagents (LBA)	Not applicable	
Regression model & weighting	Linear Regression Weighting factor: 1/x²	
Validation parameters	Method validation summary (Sep 2017- Nov 2017)	Acceptability

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Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ (1.00, 2.00, 15.0, 40.0, 100, 250, 500, 1000, 2500 and 5000 ng/mL)	10	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.6 to 4.4 %	Yes
	<u>Cumulative precision (%CV) from LLOQ to ULOQ</u>	≤ 9.8%	Yes
<u>QCs performance during accuracy & precision</u>	<u>Cumulative accuracy (%bias) in 5 QCs</u> QCs: 1.00, 3.00, 200, 2000, 4000 ng/mL LLOQ QC (1.00 ng/mL) LQC (3.00 ng/mL) MQC2 (200 ng/mL) MQC1 (2000 ng/mL) HQC (4000 ng/mL)	-0.4 to 5.0 % -0.4% 2.0% 5.0% 4.0% 5.0%	Yes
	<u>Inter-batch %CV</u> QCs: LLOQ QC (1.00 ng/mL) LQC (3.00 ng/mL) MQC2 (200 ng/mL) MQC1 (2000 ng/mL) HQC (4000 ng/mL)	≤ 12.6% 12.6% 5.0% 7% 5.7% 4.4%	Yes
	<u>Total error</u> QCs:	≤ x%	Not applicable
Validation parameters	Method validation summary (Jan 2018- Sep 2018)	Source location	Acceptability
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ (1.00, 2.00, 15.0, 40.0, 100, 250, 500, 1000, 2500 and 5000 ng/mL)	10	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.5 to 3.6 %	Yes
	<u>Cumulative precision (%CV) from LLOQ to ULOQ</u>	≤ 6.4%	Yes
<u>QCs performance during accuracy & precision</u>	<u>Cumulative accuracy (%bias) in 5 QCs</u> QCs: 1.00, 3.00, 200, 2000, 4000 ng/mL LLOQ QC (1.00 ng/mL) LQC (3.00 ng/mL) MQC2 (200 ng/mL) MQC1 (2000 ng/mL) HQC (4000 ng/mL)	-5.0 to 8.0 % 8.0% -2.3% -5.0% -3.5% 1.0%	Yes

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	<u>Inter-batch %CV</u> QCs: 1.00, 3.00, 200, 2000, 4000 ng/mL LLOQ QC (1.00 ng/mL) LQC (3.00 ng/mL) MQC2 (200 ng/mL) MQC1 (2000 ng/mL) HQC (4000 ng/mL)	≤ 14.9% 14.9% 10.4% 7.4% 8.9% 2.5%	Yes
	<u>Total error</u> QCs:	≤ x%	Not applicable
Selectivity & matrix effect	Specificity and Selectivity were evaluated with six different lots of human plasma, one hemolyzed & one lipemic plasma and all passed with pre-determined criteria. % Bias range 0.7 to 12.0 % Mean Matrix Factor 01, evaluated by comparing response from six different lot of human plasma, one hemolyzed and one lipemic plasma at low, mid and high QCs: At LQC (3.00 ng/mL): 7.8 % CV At MQC1 (2000 ng/mL): 3.2 % CV At HQC (4000 ng/mL): 3.6 % CV Mean MF inter-concentration level: 1.10 CV (%) Inter-concentration level: 6.0 Mean Matrix Factor 02, evaluated by comparing response from six different lot of human plasma, one hemolyzed and one lipemic plasma at low, mid and high QCs: At LQC (3.00 ng/mL): 9.8 % CV At MQC1 (2000 ng/mL): 2.8 % CV At HQC (4000 ng/mL): 5.8 % CV Mean MF inter-concentration level: 1.09 CV (%) Inter-concentration level: 6.0 Selectivity from co-administered drugs: No interference or impact was detected in human plasma spiked with Imatinib, Nilotinib and Dasatinib		Yes
Interference & specificity	A total of six different lots of single human plasma, one lot of hemolyzed and one lot of hyperlipidemic human plasma were evaluated. Obtained result passed the predetermined acceptance criteria		Yes
Hemolysis effect	Evaluated and meeting acceptance criteria at low QC 3.00 ng/mL and high QC 4000 ng/mL in hemolyzed plasma		Yes
Lipemic effect	Evaluated and meeting acceptance criteria at low QC 3.00 ng/mL and high QC 4000 ng/mL in lipemic plasma		Yes
Dilution linearity & hook effect	Dilution factor: 10-fold % Bias: 6.7 % CV: 1.5 Hook effect: Not applicable		Yes

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Bench-top/process stability	Post-preparative stability in extract with the autosampler Stable up to 142 hours in human plasma at 5±3°C At LQC (3.00 ng/mL): % Bias at 4.3% At HQC (4000 ng/mL): % Bias at -3.3% Post-preparative stability in extract at ambient temperature Stable up to 4 hours in human plasma at ambient temperature At LQC (3.00 ng/mL): % Bias at 9.3% At HQC (4000 ng/mL): % Bias at -3.5% Stability in spiked human plasma samples stored at room temperature Stable up to 22 hours in human plasma samples stored at ambient temperature At LQC (3.00 ng/mL): % Bias at 11.7% At HQC (4000 ng/mL): % Bias at -4.8% Stability in fresh blood and plasma for human plasma Stable up to 2 hours in human blood at wet ice bath maintained at 5±5°C temperature At LQC (3.00 ng/mL): 6.3% change 3.0% CV At HQC (4000 ng/mL): 3.3% change 2.8% CV Stable up to 2 hours in human blood at ambient temperature At LQC (3.00 ng/mL): 3.1% change 2.8% CV At HQC (4000 ng/mL): 2.0% change 1.6% CV Autosampler reinjection reproducibility as per ICH M10 At LLOQC (1.00 ng/mL): % Bias at -7.1%, CV 5.6% At LQC (3.00 ng/mL): % Bias at -4.0%, CV 4.2% At MQC2 (200 ng/mL): % Bias at 2.0%, CV 1.8% At MQC1 (2000 ng/mL): % Bias at 0.5%, CV 2.0% At HQC (4000 ng/mL): % Bias at -1.0%, CV 1.6%	Yes
Freeze-Thaw stability	Freeze thaw stability: Five freeze thaw cycle at -20±5°C & -78±8°C. At -20±5°C At LQC (3.00 ng/mL): % Bias at 0.0 % At HQC (4000 ng/mL): % Bias at -3.5% At -78±8°C At LQC (3.00 ng/mL): % Bias at -8.0% At HQC (4000 ng/mL): % Bias at -8.0%	Yes
Long-term storage	Long term stability of analyte in plasma at -20±5°C & -78±8°C for 1733 days	Yes

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	At -20±5°C At LQC (3.00 ng/mL): % Bias at 8.0 % At HQC (4000 ng/mL): % Bias at 3.0% At -78±8°C At LQC (3.00 ng/mL): % Bias at 7.0 % At HQC (4000 ng/mL): % Bias at 3.0%	
Parallelism	Not applicable	Not applicable
Carry over	Asciminib (ABL001): 0 to 14.8 % Internal standard (² H ₅ ABL001): 0.0 %	Yes
<u>Method performance in study CABL001J12301</u> <u>Interim Bioanalytical report, DMPK RCABL001J1230-int</u>		
Materials used for calibration curve & QC	Ref: Interim Bioanalytical Data Report, DMPK RCABL001J12301-int Reference standard: Asciminib (ABL001-AAA.005), Lot No. C0002.REF, Retest date Apr 2023 Asciminib (ABL001-AAA.006), Lot No. C0030.REF, Retest date Oct 2027 Internal standard: [² H ₅]-ABL001 Chemical Isotope, Batch No. SVI-ALS-20-175/SSU6181-2013-8438-01, Retest date 04 Aug 2023. [² H ₅]-ABL001 Chemical Isotope, Batch No. SVI-ALS-20-175/SSU6181-2013-8438-01, Retest 24 Aug 2027 Matrix: Pooled Human Plasma with K ₂ EDTA as anticoagulant	
		Acceptability
Assay passing rate	The number of passed runs: 17 The number of failed runs: 0 ISR: Incurred sample analysis was performed and meeting acceptance criteria 96%	Yes
Standard curve performance	- Cumulative bias range: -2.2 to 1.9 % - Cumulative precision: ≤ 6.9 % CV	Yes
QC performance	- Cumulative bias range: -3.5 to -2.1% - Cumulative precision: ≤ 8.0 % CV - TE: ≤ x% (LBA only) Not Applicable	Yes
Method reproducibility	Incurred sample reanalysis was performed in 100 % of study samples and 96 % of samples met the pre-specified criteria	Yes

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Study sample analysis/ stability	Study date: From 19 Nov 2022 to 20 Dec 2023 Duration of sample analysis Longest storage duration (Collection to Analysis) for sample are 497 Days Stability of ABL001 in human plasma is demonstrated for 1733 days at -20±5°C and -78±8°C. The study samples were covered by the demonstrated stability.	Yes
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Summary of method DMPK R1701209 modification(s)

Bioanalytical method validation report name and hyperlink	Method Validation Report [DMPK R1701209]		
Changes in method	Changes in the method parameter i.e chromatographic parameter as well as extraction procedure		
New validated assay range if any	Not applicable (there has been no change in assay range, 1.00 - 5000 ng/mL)		
Validation parameters	Cross-validation performance (Based on Incurred samples)		Acceptability
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-6.8 to 4.6 %	Yes
	Cross check experiment was performed with run 20 but % bias was not mentioned for specific run 20 in method validation report however we calculated and represented here		
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 8.7 %	Yes
<u>QCs performance during accuracy & precision</u>	Cumulative accuracy (%bias) in 5 QCs	-11.0 to 1.5 %	Yes
	% CV	≤ 6.7 %	
	Inter-batch %CV	≤ x%	Not Applicable
	Percent total error (TE)	≤ x%	Not Applicable
Cross-validation	Cross Check between sites Numbers of incurred samples analyzed and result No. of incurred samples analyzed 30 No. of incurred samples meeting acceptance criteria 29	96.7%	Yes

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List other parameters	Not applicable		
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Summary method DMPK R1500058 performance of a bioanalytical method to measure asciminib (ABL001) in Human plasma

Bioanalytical method validation report name, amendments, and hyperlinks	Method # 1 Report Name: Method Validation Report Report Title: Quantitative determination of ABL001 in human plasma (K ₂ EDTA) by LC-MS/MS Amendments: 01 and 02 [DMPK R1500058] (original), [DMPK R1500058-01] (amendment 1), [DMPK R1500058-02] (amendment 2)
Method description	Quantitative determination of ABL001 in human plasma by LC-MS/MS
Materials used for calibration curve & concentration	Ref: Method Validation Report No. DMPK R1500058 Asciminib (ABL001-NXA.002), Lot No. 1010003530, Retest date 31 Mar 2015, [M+5] ABL001 Chemical Isotope, Batch No. SSU6181-2013-8438-01, Retest date 25 Jan 2016 Ref: Amendment 01 to Method Validation Report No. DMPK R1500058 01Asciminib (ABL001-AAA.003), Lot No. 1010009610, Retest date 31 Dec 2017, [M+5] ABL001 Chemical Isotope, Batch No. SSU6181-2013-8438-01, Retest Date 25 Jan 2016 Matrix: Pooled Human Plasma with K ₂ EDTA as anticoagulant Concentration: 1.00, 2.00, 10.0, 50.0, 100, 500, 2000, 4500, 5000 ng/mL
Validated assay range	1.00 - 5000 ng/mL
Material used for QCs & concentration	Ref: Method Validation Report No. DMPK R1500058 Asciminib (ABL001-NXA.002), Lot No. 1010003530, Retest date 31 Mar 2015, [M+5] ABL001 Chemical Isotope, Batch No. SSU6181-2013-8438-01, Retest date Jul 2020. Ref: Amendment 01 to Method Validation Report No. DMPK R1500058 01 Asciminib (ABL001-AAA.003), Lot No. 1010009610, Retest date 31 Dec 2017, Internal standard: Matrix: Pooled Human Plasma with K ₂ EDTA as anticoagulant Concentration: 1.00, 3.00, 200, 2500, 4000 ng/mL
Minimum required dilutions (MRDs)	NA
Source & lot of reagents (LBA)	NA
Regression model & weighting	Quadratic Regression Weighting factor: 1/x ²

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Validation parameters	Method validation summary		Acceptability
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ (1.00, 2.00, 10.0, 50.0, 100, 500, 2000, 4500, 5000 ng/mL)	9	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.0 to 1.4 %	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 4.4%	Yes
<u>QCs performance during accuracy & precision</u>	<u>Cumulative accuracy (%bias) in 5 QCs</u> QCs: 1.00, 3.00, 200, 2500, 4000 ng/mL	-1.9 to 2.0%	Yes
	LLOQ QC (1.00 ng/mL)	-1.9%	
	LQC (3.00 ng/mL)	1.3%	
	MQC2 (200 ng/mL)	1.5%	
	MQC1 (2500 ng/mL)	2.0%	
	HQC (4000 ng/mL)	1.3%	
	<u>Inter-batch %CV</u> QCs: 1.00, 3.00, 200, 2500, 4000 ng/mL	≤ 6.4%	Yes
	LLOQ QC (1.00 ng/mL)	6.4%	
	LQC (3.00 ng/mL)	6.1%	
	MQC2 (200 ng/mL)	2.9%	
	MQC1 (2500 ng/mL)	2.8%	
	HQC (4000 ng/mL)	2.4%	
	<u>Total error</u> QCs:	≤ x%	Not applicable
Selectivity & matrix effect	Specificity was evaluated with six different lots of human plasma and all passed with pre-determined criteria. % Interference: 1.6 to 4.3 % Contribution of [M+5] to the signal of ABL001 was evaluated and meeting all passed with predetermined criteria 6.4 % Contribution of ABL001 to the signal of [M=5] was evaluated and meeting all passed with predetermined criteria 0.0 % Mean Matrix Factor evaluated by comparing response from six different lot of human plasma, one hemolyzed and one lipemic plasma at low, mid and high QCs: At LQC (3.00 ng/mL): 2.0 % CV At MQC1 (2500 ng/mL): 3.2 % CV At HQC (4000 ng/mL): 1.2 % CV Mean MF inter-concentration level: 0.95		Yes

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	CV (%) Inter-concentration level: 2.1	
Interference & specificity	A total of six different lots of single human plasma were evaluated and result passed predetermined acceptance criteria	Yes
Hemolysis effect	Evaluated and meeting acceptance criteria at low QC 3.00 ng/mL and high QC 4000 ng/mL in hemolyzed plasma	Yes
Lipemic effect	Evaluated and meeting acceptance criteria at low QC 3.00 ng/mL and high QC 4000 ng/mL in lipemic plasma	Yes
Dilution linearity & hook effect	Dilution factor: 10-fold % Bias: 1.2 % CV: 2.7 Hook effect: Not applicable	Yes
Bench-top/process stability	Post-preparative stability in extract with the autosampler set at 4°C Stable up to 156 hours in human plasma at 4°C At LQC (3.00 ng/mL): % Bias at -8.2% At HQC (4000 ng/mL): % Bias at 1.0% Stability in spiked human plasma samples stored at room temperature Stable up to 24 hours in human plasma samples stored at ambient temperature At LQC (3.00 ng/mL): % Bias at -6.0% At HQC (4000 ng/mL): % Bias at -3.6% Stability in whole blood samples at RT Stable up to 2 hours in human blood at wet ice bath At LQC (3.00 ng/mL): 5.2 % change 5% CV At HQC (4000 ng/mL): 1.7% change 2.2% CV	Yes
Freeze-Thaw stability	Freeze thaw stability: Five freeze thaw cycle at -20°C and -70°C At -20°C At LQC (3.00 ng/mL): % Bias at 2.8 % At HQC (4000 ng/mL): % Bias at 0.1% At -70°C At LQC (3.00 ng/mL): % Bias at 2.6%	Yes

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	At HQC (4000 ng/mL): % Bias at 0.5%	
Long-term storage	Long term stability of analyte in plasma at -20±5°C for 188 days & -70±10°C for 1191 days At -20±5°C for 188 days At LQC (3.00 ng/mL): % Bias at -9.6% At HQC (4000 ng/mL): % Bias at -4.4% At -78±8°C for 1191 days At LQC (3.00 ng/mL): % Bias at -8.2% At HQC (4000 ng/mL): % Bias at 0.7%	Yes
Parallelism	Not applicable	Not applicable
Carry over	Asciminib (ABL001): Carry over was > 20% in first and second blank after ULOQ samples. 3rd double Blank injection carry over < 20% and injection sequence was arranged low to high concentration. The carry over was judged to have negative impact. Internal standard (²H₅ ABL001): 0.0%	Yes
<u>Method performance in study CABL001J12301</u> <u>Interim Bioanalytical report, DMPK RCABL001J12301a-int</u>		
		Acceptability
Materials used for calibration curve & QC	Ref: Interim Bioanalytical Report, DMPK RCABL001J12301a-int Reference standard: Asciminib (ABL001-AAA.005), Lot No. C0002.REF, Retest date 30 Apr 2023 Internal standard: [²H₅]-ABL001 Chemical Isotope, Batch No. SVI-ALS-20-175/SSU6181-2013-8438-01, Retest date 04 Aug 2023. Matrix: Pooled Plasma with K₂EDTA as anticoagulant	Yes
Assay passing rate	The number of passed runs: 6 The number of failed runs: None ISR: Incurred sample analysis was performed and meeting acceptance criteria 100%. Assay passing rate: 100%	Yes
Standard curve performance	- Cumulative bias range: -1.0 to 1.6 % - Cumulative precision: ≤ 9.0 % CV	Yes
QC performance	Cumulative bias range: 0.0 to -3.5%	

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	- Cumulative precision: $\leq 7.5\%$ CV - TE: $\leq x\%$ (LBA only) Not Applicable	Yes
Method reproducibility	Incurred sample reanalysis was performed in 24 samples and 100 % of ISR samples met the pre-specified criteria	Yes
Study sample analysis/ stability	Study date: From 28 April 2023 to 06 Nov 2023 Duration of sample analysis Longest storage duration for sample are 609 Days Stability of ABL001 in human plasma demonstrated for 188 days at $-20\pm 5^{\circ}\text{C}$ and 1191 days $-70\pm 10^{\circ}\text{C}$. The study samples were covered by the demonstrated stability.	

Summary of cross-validation results

Bioanalytical method validation report name and hyperlink	Method Validation Report [DMPK R1500058]		
Changes in method	Changes in the method parameter i.e. chromatographic parameter as well as extraction procedure		
New validated assay range if any	Not applicable (no change in assay range, 1 - 5000 ng/mL)		
Validation parameters	Cross-validation performance (Based on Incurred samples)		Acceptability
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	x to y%	Not applicable
	<u>Cumulative precision (%CV) from LLOQ to ULOQ</u>	$\leq x\%$	Not applicable
<u>QCs performance during accuracy & precision</u>	Cumulative accuracy (%bias) in 5 QCs	x to y%	Not applicable
	Inter-batch %CV	$\leq x\%$	Not applicable
	Percent total error (TE)	$\leq x\%$	Not applicable
Cross-validation	Numbers of incurred samples analyzed and result No. of incurred samples analyzed 26 No. of incurred samples meeting acceptance criteria 25	96.2%	Yes

19.4.2. Population PK Analysis

19.4.2.1. Executive Summary

The FDA's Assessment:

The Applicant updated the population PK (PPK) analysis using asciminib dose and concentration data from Studies J12301 (CML, prior treatment=0, n=197), A2301 (CML, prior treatments = 1, 2 or NA, n=154), X2101 (CML, prior treatments = 1,2,3,4,5, or NA, n=240), A2013 (HV HI study,

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n=32), and A2105 (HV RI study, n=14). The updated population PK modeling in the current submission did not identify any additional significant covariates on the PK of asciminib. The treatment line was not identified as a covariate of any PPK parameters in the Applicant's PPK analysis.

19.4.2.2. PPK Assessment Summary**The Applicant's Position:**

General Information	
Objectives of PPK Analysis	To revise the previously developed PopPK model for oral administration of asciminib in 3L CML participants with additional data and re-evaluate covariates that were previously assessed to impact the PK of asciminib, To determine whether asciminib PK differs between lines of therapy (1L vs. 3L+), To evaluate the clinical relevance of covariates of interest through comparison of simulated exposures using population estimates, To simulate individual daily exposure metrics (AUC_{0-24h}, C_{trough}, C_{max}) of asciminib using empirical Bayes estimates in participants from studies X2101, A2301, and J12301 using participants' actual dosing records, to support exposure-response analyses, To use simulated exposure metrics for an updated PK profile comparison of the asciminib 40 mg BID and 80 mg QD dosing regimens.
Study Included	Studies J12301, A2301, X2101, A2103, and A2105
Doses Included	Study J12301: 80 mg QD Study A2301: 40 mg BID Study X2101: (10 mg BID up to 200 mg QD) multiple doses including 80 mg QD Studies A2103 and A2105: 40 mg single dose
Population Included	The analysis was conducted on the following studies, referred to as the PKPD analysis set 1 (PKPDAS1, N=637): - Study J12301 (n=197): all 1L CML-CP participants in the asciminib arm - Study A2301 (n=154): all 3L CML-CP participants in the asciminib arm; participants who switched from bosutinib to asciminib were excluded - Study X2101 (n=240): all participants with CML who were treated with asciminib alone (including AP, CP, BP, Ph+ ALL, and participants with CML with the T315I mutation) - Study A2103 (n=32): all participants (healthy volunteers and participants with hepatic impairment)

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		Study A2105 (n=14): all participants (healthy volunteers and participants with renal impairment) <i>Note:</i> Three participants from Study J12301, 2 participants from Study A2301 and 3 participants from Study X2101 had missing PK samples and were not included in the PopPK pool.
Population Characteristics	General	Pooled set (Studies A2103, A2105, X2101, A2301, J12301) Age median (range): 54 (18-88) years Weight median (range): 75.8 (34.9-184.2) kg Male: 387 (60.8%) Race: Asian 167 (26.2%), non-Asian 470 (73.8%)
	Organ Impairment	<u>Renal function classification by aGFR:</u> Normal: 348 (54.6%), Mild: 233 (36.6%), Moderate: 48 (7.5%), Severe: 8 (1.3%) <u>Hepatic function classification (NCI liver function criteria)</u> Normal: 540 (84.8%), Mild: 88 (13.8%), Moderate: 4 (0.6%), Severe: 5 (0.8%)
	Pediatrics	<i>Not Applicable</i>
No. of Participants, PK Samples, and BLQ		N=637 participants and 10254 PK samples No. BLQ samples, N (% of total)=410 (4.0%)
Sampling Schedule	Rich Sampling	Table 33
	In ITT Population	Table 33
Covariates Evaluated	Static	Sex, baseline body weight, baseline age, race (Asian vs. non-Asian), asciminib nominal total daily dose, aGFR, formulation (capsule vs. FMI tablet), baseline renal function (normal vs. mild, moderate or severe), baseline hepatic function (normal vs. mild, moderate or severe), number of prior lines of TKI therapy (0-7), study effect, patients vs. healthy participants, patient population (CML-CP, CML-AP, CML-BP, Ph+ ALL, healthy participants).
	Time-varying	No time-varying covariate evaluated.
Final Model		Summary Acceptability [FDA's comments]
Software and Version		The analysis was performed using the Monolix software system, MONOLIX 2023 R2 (Lixoft, Paris, France) utilizing the DaVinci high performance computing environment accessed from GPSII. All model building was performed using Stochastic Approximation Expectation Maximization (SAEM) method. Acceptable

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	Data preparation, graphical exploration, goodness-of-fits plots and other model diagnostics were performed using R 4.3.1.	
Model Structure	A PopPK model is composed of (1) the structural model, which accounts for the systematic trends in the data and, to the extent possible, the mechanisms generating those trends; and (2) the random effects model, which accounts for the inter-individual variability about those trends. PK structural model was a two-compartment disposition model, with first order absorption (Ka) with time lag (Lag), clearance (CL), central and peripheral volume of distribution (V1 and V2), and inter-compartmental clearance (Q). With oral PK data, the V1, Q, V2 and CL here implicitly contain the 1/F term, wherein F refers to the relative bioavailability factor.	Acceptable
Model Parameter Estimates	Table 34	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Relative standard errors of parameter estimates were less than 40% for the fixed effects and less than 10% for the random effects. Interindividual variability (IIV) for apparent clearance and volume of central compartment was less than 0.4 (SD). Larger IIV reported for Tlag, Ka and apparent peripheral volume.	Acceptable
BLQ for Parameter Accuracy	Of the total number of PK samples, 4.0% of the sample concentrations were BLQ. M4 method, which maximized the log-likelihood for all the data by treating the BLQ observation as a censored endpoint, was implemented in the model.	Acceptable
GOF, VPC	There was good agreement between the observed data and the population fitted or individual fitted data for the final covariate model. The individual weighted residual (iwRes) versus time and population fit plots showed a horizontal line centered around 0 across time and increasing concentrations, respectively, indicating that there was no time-varying and concentration-dependent change in asciminib clearance. NPDE plots versus time and population fit also did not show any major trends [PopPK report-Figure 7-4. Figure 7-5, Figure 7-6].	Acceptable

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	Prediction-corrected visual predictive checks (pcVPC) showed that the model adequately captures the majority of the observed data, indicating that the final PK model described the observations reasonably well for the relevant doses and dosing regimens evaluated in the patient population [PopPK report-Figure 7-7].	
Significant Covariates and Clinical Relevance	The covariates retained in the final model have been previously investigated either in the [Asciminib original popPK report] or in the FDA independent review, and results of these evaluations suggested their effects were deemed to not be clinically significant. Simulations based on the updated popPK model confirmed this assessment.	Acceptable
Analysis Based on Simulation (optional)	Overall, the mean AUC _{0-24h} values were very similar between the two regimens (40 mg BID and 80 mg QD), while the mean C _{max} and C _{min} (concentration at the end of a dosing interval) of 80 mg QD were 1.55-fold and 0.69-fold of that of 40 mg BID, respectively (Table 35).	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	As described in the approved prescribing information. No new information has been added based on this application.	Acceptable
Source: [PopPK report-Section 5, Section 6.5, Section 7.6.2, Section 7.7, Section 7.8; PopPK report-Table 7-2, Table 7-5, Table 7-6; PopPK report-Figure 7-4, Figure 7-5, Figure 7-6, Figure 7-7].		

Table 33 Summary of PK Sampling Schedules of Studies Included in the PopPK Analysis

Study	PK collection schedule
A2301	All participants allocated to the asciminib treatment arm: Week 1 Day 1 (2 hr), Week 2 Day 1 (0, 2, 3, 4 hr), Week 4 any day (0 hr), Week 12 any day (0 hr), Week 24 any day (0 hr), Week 96 any day (0 hr) Full Profile (n=15): Week 1 Day 1 (2 hr), Week 2 Day 1 (0, 0.5, 1, 2, 3, 4, 6, 8, 12 (pre-dose) hr), Week 4 any day (0 hr), Week 12 any day (0 hr), Week 24 any day (0 hr), Week 96 any day (0 hr)
X2101	Dose escalation part: Cycle 1 Day 1 (8h, 12h), Cycle 1 Day 2 (24h/pre-dose), Cycle 1 Day 8 (0h), Cycle 1 Day 15 (0h, 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h), Cycle 1 Day 16 (0h), Cycle 1 Day 22 (0h), Cycle 2 Day 1 (0h, 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h), Cycle 2 Day 2 (24h/pre-dose), Cycle 3 Day 1 (pre-dose), Cycle 4 Day 1 (pre-dose), Cycle 5 Day 1 (pre-dose), Cycle 6 Day 1 (pre-dose) Dose expansion part (n=109 participants with CML-CP/-AP (including participants with disease harboring the T315I mutation, n=43 patients with CML-BP and Ph+ ALL): Cycle 1 Day 1 (0h, 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h),

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Study	PK collection schedule
J12301	Cycle 1 Day 2 (0h), Cycle 1 Day 8 (0h), Cycle 1 Day 15 (0h), Cycle 2 Day 1 (0h, 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h), Cycle 3 Day 1 (pre-dose), Cycle 4 Day 1 (pre-dose), Cycle 5 Day 1 (pre-dose) , Cycle 6 Day 1 (pre-dose) All participants allocated to the asciminib treatment arm: Week 2 Day 14 (0, 2, 3, 4 h), Week 4 Day 28 (0 h), Week 12 Day 84 (0 h), Week 24 Day 168 (0 h), Week 48 Day 336 (0 h) Full PK profiles (29 participants): Week 2 Day 14 (0, 1, 2, 3, 4, 6, 8, 12 h), Week 4 Day 28 (0 h), Week 12 Day 84 (0 h), Week 24 Day 168 (0 h), Week 48 Day 336 (0 h)
A2103	All participants: Day 1 at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72 hours post-dose
A2105	All participants: Day 1 at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72 hours post-dose

Table 34 Final Model – PK Parameter Estimates

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Parameter (unit)	Estimate	SE	RSE (%)
Fixed Effects			
Tlag (h)	0.487	0.0297	6.08
θ (Asian on Tlag)	0.816	0.106	12.9
Ka (1/h)	2	0.139	9.94
θ (Formulation on Ka)	-0.405	0.117	28.8
CL (L/h)	6.89	0.168	2.44
θ (Total daily dose on CL)	-0.293	0.0214	7.32
θ (Age on CL)	-0.15	0.0533	35.5
θ (Sex on CL)	-0.131	0.0357	27.2
θ (Weight on CL)	0.417	0.0794	19
θ (aGFR on CL)	0.192	0.0515	26.8
V1(L)	56.7	1.67	2.95
θ (Formulation on V1)	0.12	0.0396	33.1
θ (Sex on V1)	-0.232	0.0357	27.2
θ (Weight on V1)	0.586	0.0866	14.8
Q (L/h)	7.21	0.387	5.36
V2 (L)	51.9	3.18	6.13
Standard Deviation of the Random Effects			
sd _{Tlag}	1.06	0.0404	3.82
sd _{Ka}	0.826	0.0504	6.1
sd _{CL}	0.39	0.0123	3.15
sd _{V1}	0.308	0.0181	5.8
sd _{V2}	0.877	0.0512	5.84
Correlations			
Correlation V1~ CL	0.592	0.0586	9.9
Correlation V2~ CL	0.0459	0.0782	170
Correlation V1~ V2	0.464	0.101	21.7
Error Model Parameters			
Residual Error (additive)	2.51	0.171	6.81
Residual Error (proportional)	0.39	0.00351	0.899

Source: [PopPK Report-Table 7-5]

Table 35 Summary of Simulated PK Metrics of 40 mg BID and 80 mg QD

Regimen	Cmax (ng/mL)	AUC0-24h (ng*h/mL)	Cmin (ng/mL)
40 mg BID	829 (33%)	12564 (39%)	320 (53%)
80 mg QD	1289 (35%)	12558 (41%)	222 (71%)

Arithmetic mean and %CV are presented
Source: [PopPK Report-Table 7-6]

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The FDA’s Assessment:

Overall, the updated PPK model is consistent with the PPK from the original NDA submission. We noted that the PK data of healthy volunteers from Study A2103 and A2105 appear to be different than that of patients. If only PK data of CML patients are included in the PPK analysis, TLAG1 is not needed in the structure model.

19.4.2.3. PPK Review Issues (As mentioned in the last paragraph)

19.4.2.4. Reviewer’s Independent Analysis (No need to include for no impact on labeling)

19.4.3. Exposure-Response Analysis

19.4.3.1. ER (efficacy) Executive Summary

The FDA’s Assessment:

In the patients with newly diagnosed Ph+ CML-CP, the observed Week-48 MMR rate was 68% in Study J12301, and a positive ER relationship was observed as shown in Figure 7.

In addition, a 3-compartment model representing quiescent leukemic stem cells (q), proliferating bone marrow cells (p), and resistant cells (r) was developed using PKPD dataset from 430 participants with CML-CP to describe the time-course of BCR::ABL1 transcript. Drug kill of the p cells by asciminib was characterized by an Emax model. The potential influences of the number of previous TKI treatments (i.e. line of treatment) and patient's baseline and disease characteristics (including ELTS risk group) were investigated. The extrapolation of longitudinal BCR::ABL1 transcript response to asciminib in the 2L setting utilized the difference in the p, r and Emax parameters between nilotinib as first and second line treatments. As shown in Table 38, the predicted MMR rates were within those for both 1L and 3L+. For 2L, the prediction was also similar to the observation from Study AUS08. The PKPD model provided supportive evidence that asciminib is effective in patients with 2L Ph+ CML-CP.

19.4.3.2. ER (efficacy) Assessment Summary

The Applicant’s Position:

General Information	
Goal of ER analysis	To describe the results of exposure-response analyses for efficacy to support the use of asciminib as treatment for newly diagnosed participants (first line, 1L) with Ph+ CML-CP, to determine the relationship between the exposure of asciminib and the time course of BCR-ABL% (IS, International Standard), and to extrapolate longitudinal BCR::ABL1 response in Ph+ CML-CP participants previously treated with one tyrosine kinase inhibitor (TKI, second line).

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Study Included		Studies J12301, A2301, and X2101
Endpoint		Time course of BCR-ABL (%) (IS) for J12301, A2301 and X2101. Binary major molecular response (0 for >0.1% BCR-ABL (IS); 1 for ≤0.1% BCR-ABL (IS)) at Week 48 for Study J12301
No. of Participants (total, and with individual PK)		PKPD dataset=430 participants with CML-CP, treated with asciminib. Study X2101 (n=83): participants with CML-CP who were treated with asciminib alone. Study A2301 (n=150): 3L participants with CML-CP in the asciminib arm; participants who switched from bosutinib to asciminib were excluded. Study J12301 (n=197): all 1L participants with CML-CP in the asciminib arm.
Population Characteristics	General	Pooled set (Studies X2101, A2301, J12301) Age median (range): 52 (18-86) years Weight median (range): 76.2 (34.9-184.2) kg Male: 253 (58.8%) Race: Asian 126 (29.3%), White 271 (63.0%)
	Pediatrics	Not applicable
Dose(s) Included		Refer Section 19.4.2.2 for details
Exposure Metrics Explored (range)		Daily predicted AUC, C _{max} and C _{min} .
Covariates Evaluated		Study effect (reference group: J12301) Baseline BCR-ABL (%) (IS) as continuous covariate and as categorical covariate Baseline demographic covariates (age, race, weight and gender) Number of prior TKI treatment (i.e. line setting, first line as reference) Time since first diagnosis of disease EUTOS long-term survival (ELTS) risk group only included in the binary MMR analysis set.
Final Model Parameters		Summary
		Acceptability [FDA's comments]
Model Structure		A logistic regression analysis was used to analyze the exposure vs. binary MMR data at 48 week in J12301 study. The semi-mechanistic PKPD model is a three-compartment model representing three subpopulations of leukemic cells in the bone marrow: 1) quiescent leukemic stem cells (q), 2) proliferating leukemic bone marrow cells (p), and

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	3) proliferating resistant leukemic cells (r). Asciminib kills the p cells by an Emax term and reduces the net growth rate of p. The q cells are protected from drug effect in a peripheral compartment, whereas the r cells are impervious to asciminib.	
Model Parameter Estimates	Table 36	Acceptable
Model Evaluation	Model adequacy was assessed by visual inspection on the standard goodness-of-fit plots: - Individual fit plots of observations, individual predictions, and population predictions (including covariate effects, if applicable) versus time, - Plots of individual weighted residuals versus individual predictions and versus time, - Relationships between empirical Bayes estimates and covariate to assess relevance of inclusion/exclusion of covariates from the model, - Visual predictive check (VPC) for the final model.	Acceptable
Covariates and Clinical Relevance	The result of the logistic regression showed positive relationship between exposure metrics (average daily AUC₀₋₂₄ and C_{min}) and the probability of MMR at Week 48 for asciminib 80 mg QD regimen based on the Binary MMR analysis set of Study J12301. Clopper-Pearsons confidence intervals showed lower MMR rates for the first quartile of exposure metrics and no correlation for second through the fourth quartiles of AUC₀₋₂₄ and C_{min}. The response was constant around 70% to 80% from the second to the fourth quartiles of AUC₀₋₂₄ and C_{min}, suggesting the response has reached plateau by second quartile of AUC₀₋₂₄ and C_{min}. Logistic regression model predictions follow the empirical probability estimates well. The final PK-PD model retained number of treatment lines as covariate of p, r and Emax parameters; baseline log₁₀-transformed BCR::ABL1 (L10BA0) was a covariate of p and r cell populations. The key covariate was "the number of treatment lines" which revealed important characteristics of drug-resistance associated with higher lines. The extrapolation into the 2L setting took advantage of this covariate effect by borrowing the information on the difference	Acceptable

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	between 1L and 2L setting on model parameters of the nilotinib PKPD model; the same total daily asciminib dose of 80 mg is expected to achieve satisfactory MMR rates with some degree of uncertainty.	
Simulation for Specific Population	Simulation of BCR-ABL (%) (IS) in 1L, 2L and 3L settings and computation of MMR rates at 48-, 96-weeks.	Acceptable
Visualization of E-R relationships	The result of the logistic regression showed positive relationship between exposure metrics (average daily AUC_{0-24} and C_{min}) and the probability of MMR at Week 48 for asciminib 80 mg QD regimen based on the Binary MMR analysis set of Study J12301. The first quartile exposure metrics were associated with lower MMR rate (~45%), as represented by red squares with error bars. Relatively more participants in the first quartile exposure had a relative dose intensity (RDI) $\leq 75\%$ as represented by red dots, contributing to the low MMR rate (Figure 7). Clopper-Pearsons confidence intervals showed lower MMR rates for the first quartile of exposure metrics and no correlation for second through the fourth quartiles of AUC_{0-24} and C_{min}. The response was constant between 70% to 80% from the second to the fourth quartiles of AUC_{0-24} and C_{min}, suggesting the response has reached plateau by second quartile of AUC_{0-24} and C_{min}. Logistic regression model predictions follow the empirical probability estimates well. Two scenarios were used in the extrapolation based on the line effect on the model parameters to provide a range of likely MMR rates in the 2L. These two scenarios were used to simulate the time-course of BCR::ABL1 to determine an MMR rate at Week 48 and Week 96 (Table 37). In 200 <i>in silico</i> replicates of the original 430 participants using their recorded dosing schedule, a 48-week MMR rate of $70 \pm 3\%$ was predicted for the newly diagnosed CML-CP participants who were treated with asciminib 80 mg QD. In 200 <i>in silico</i> replicates of 500 virtual participants per trial per number of lines, no dropout, dose reduction or interruption was assumed in the simulations to determine the MMR rates at Week 48 and Week 96. The simulations were based on the	Acceptable

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	average daily AUC₀₋₂₄ generated from 80 mg QD and 40 mg BID. Assuming no dose interruption, the model predicted MMR rates at Weeks 48 and 96 were approximately 75% and 82%, respectively, in the 1L; the Week-48 MMR prediction is consistent with the results from the logistic regression analysis of binary MMR of the 2nd to 4th quartile exposure metrics. For the extrapolation into 2L setting, the predicted MMR rates, assuming a total daily dose of 80 mg (80 mg QD or 40 mg BID) without interruption, ranged from 54 to 63% at Week 48 and 66 to 74% at Week 96. The lower MMR values were resulted from model parameter differences from the second scenario, whereas the higher values were from the first scenario. The predicted MMR rate in the 2L setting is in between the 1L and 3L settings (Table 38).	
Overall Clinical Relevance for ER	Section 6.3.2.1	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
	As described in the approved prescribing information. No new information has been added based on this application.	Acceptable
Source: [Exposure-efficacy report-Section 2.1, Section 3.3.4, Section 3.3.5, Section 4.3.4, Section 5.3, Table 5-1, Section 5.6, Section 7.0.].		

Table 36 Parameter Estimates and Inter-Individual Variability of the Final Covariate Model using AUC₀₋₂₄, C_{max} and C_{min} as PK Metrics

Parameter (Description, unit)	Final covariate model (AUC)	Final covariate model (C _{max})	Final covariate model (C _{min})
Population mean			
q (Quiescent leukemic stem cells)	0.0212 (14.1%)	0.0241 (13.7%)	0.0215 (14.3%)
p (Proliferating leukemic bone marrow cells)	0.13 (11%)	0.12 (11.1%)	0.118 (10.5%)
r (Proliferating resistant leukemic cells)	4.88x10 ⁻⁷ (49.8%)	8.2 x10 ⁻⁷ (48.3%)	8.31x10 ⁻⁷ (43.3%)
K _{gr} (Growth rate constant, 1/yr)	28 (fixed)	28 (fixed)	28 (fixed)
K _{qp} (Quiescent to proliferating cells transformation rate constant, 1/yr)	0.893 (0.0225%)	0.872 (0.0242%)	0.894 (0.0555%)
K _{qr} (Quiescent to resistant cells transformation rate constant, 1/yr)	6.5	6.5	6.5

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Parameter (Description, unit)	Final covariate model (AUC)	Final covariate model (C _{max})	Final covariate model (C _{min})
E _{max} (Maximum response, 1/yr)	64.8 (1.65%)	63.3 (1.63%)	65.3 (1.63%)
EC ₅₀ (daily AUC, C _{max} and C _{min} at half maximal effect, mg.h/L, ng/mL, ng/mL)	0.15 (0.613%)	7.34 (3.43%)	3.44 (0.284%)
Gamma (sigmoidicity)	1	1	1
<i>Variance of random effects (IIV)</i>			
q	2.6 (4.21%)	2.49 (4.24%)	2.64 (4.21%)
p	0.427 (7.72%)	0.358 (8.55%)	0.358 (8.93%)
r	1.73 (7.54%)	1.64 (7.17%)	1.54 (6.63%)
E _{max}	0.213 (4.08%)	0.207 (3.9%)	0.21 (3.99%)
Covariate effect magnitude[‡]			
L10BA0~p (baseline log10-transformed BCR::ABL1 effect on proliferating bone marrow cells) [†]	2.46 (1.87%)	2.45 (1.83%)	2.43 (1.78%)
L10BA0~r (baseline log10-transformed BCR::ABL1 effect on proliferating resistant leukemic cells) [†]	1.36 (15.1%)	1.09 (18.2%)	1.24 (15.4%)
Linenum on p [2nd line]	-1.61 (14.9%)	-1.52 (14.3%)	-1.58 (14.2%)
Linenum on p [3rd+ line]	-1.6 (6.02%)	-1.54 (6.42%)	-1.5 (6.19%)
Linenum on r [2nd line]	4.6 (22.3%)	3.95 (27.2%)	3.77 (31.6%)
Linenum on r [3rd+ line]	3.98 (10.3%)	3.66 (11.2%)	3.52 (10.1%)
Linenum on E _{max} [2nd line]	-0.56 (15.7%)	-0.554 (15.2%)	-0.571 (15.0%)
Linenum on E _{max} [3rd+ line]	-0.478 (4.66%)	-0.66 (4.68%)	-0.48 (4.63%)
Correlations			
Correlation between p and E _{max}	0.223 (34%)	0.151 (54.9%)	0.121 (70%)
Correlation between q and E _{max}	-0.375 (15.1%)	-0.464 (10.8%)	-0.345 (15.9%)
Correlation between q and p	-0.0348 (246%)	-0.114 (89.5%)	0.013 (725%)
Residual error			
Additive error	0.225 (1.05%)	0.23 (1.06%)	0.225 (1.06%)
Fit statistics			
-2 log-likelihood (OFV)	3051.1	3101.24	3003.49
Corrected BIC (BICc)	3095.1	3252.64	3154.9
Source: [Exposure-efficacy report-Table 5-8]			

Table 37 Exposure-Response Analysis for Probability of MMR at Week 48 versus Asciminib Average daily AUC₀₋₂₄ / C_{min} in Participants Newly Diagnosed with CML-CP without T3151 Mutation – Study J12301

Parameter	Estimate	Standard error	95% CI	P-value
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AUC : Without dose adjustment				
Intercept (β_0)	-0.812	0.491	(-1.807, 0.12)	0.098
AUC	1.542×10^{-4}	4.667×10^{-5}	$(6.818 \times 10^{-5}, 2.511 \times 10^{-4})$	$9.501 \times 10^{-4}^{\dagger}$
C_{min} : Without dose adjustment				
Intercept (β_0)	Intercept (β_0)	Intercept (β_0)	Intercept (β_0)	Intercept (β_0)
C _{min}	C _{min}	C _{min}	C _{min}	C _{min}

[†] significance at 0.01

Source: [Exposure-efficacy report-Table 5-5] [Exposure-efficacy report-Table 5-6]

Table 38 Model-Predicted MMR rates for a Total Daily dose of 80 mg Asciminib at Week 48 and Week 96 by No. of Treatment Lines, Assuming, Maintenance of Uninterrupted Dosing

Line number	Time of readout	Predicted MMR rates (mean $\pm$ SD)	Observed MMR rates Estimate [95% CI]	Reference for observed data
First line	Week 48	75 $\pm$ 2%	67.66% [60.72, 74.07]	[Study J12301 PA CSR]
	Week 96	82 $\pm$ 2%	Not applicable	
Second line	Week 48	54 ^a or 63 ^b $\pm$ 2%	Not applicable	Not applicable
	Week 96	66 ^a or 74 ^b $\pm$ 2%	Not applicable	
Third+ line	Week 48	34 $\pm$ 2%	29.30% [22.32, 37.08]	[Study A2301 Week 96 CSR]
	Week 96	41 $\pm$ 3%	37.58% [29.99, 45.65]	

^a: Prediction with scenario 2 of a conservative assumption that the effect of number of treatment lines was implemented on the Emax, as well as the proliferating bone marrow (p) cells and the resistant LSC (r) cells

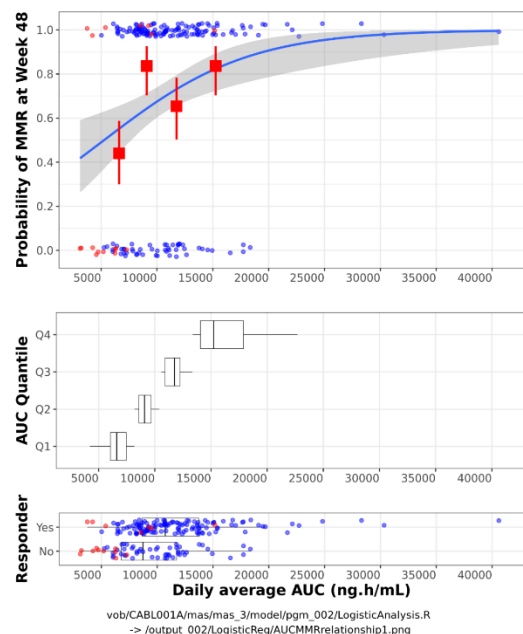
^b: Prediction with scenario 1 assuming that only the Emax parameter is affected by no. of treatment lines

Source: [Exposure-efficacy report-Table 5-9]

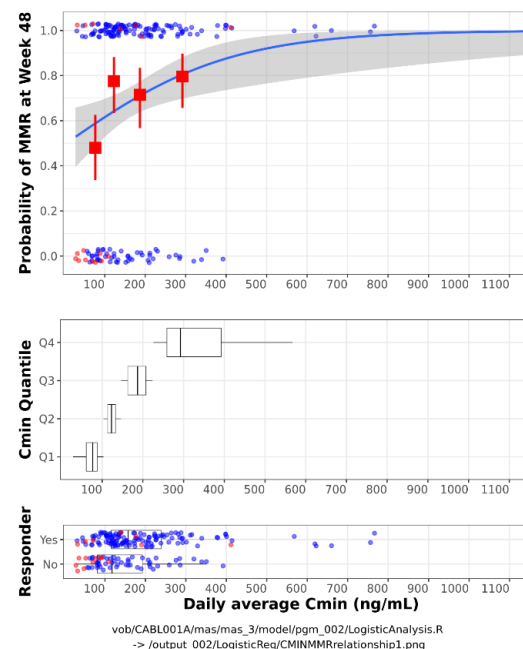
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Figure 7 Exposure-Efficacy Relationship Between the Probability of Achieving MMR at Week 48 and Daily Average AUC₀₋₂₄ and Average C_{min} from Prior 48 weeks (top) - Study J12301

Distribution of AUC₀₋₂₄ Quantiles (middle); AUC₀₋₂₄ Spread between Responders and Non-responders (bottom)



Distribution of C_{min} quartiles (middle); C_{min} Spread Between Responders and Non-responders (bottom)



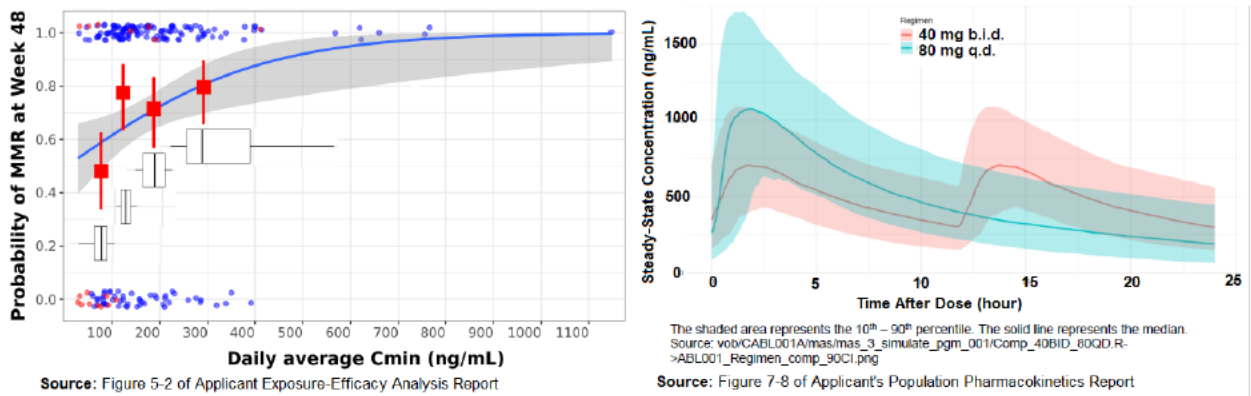
Source: [Exposure-efficacy report-Figure 5-1, Figure 5-2]

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The FDA’s Assessment:

The Applicant’s ER analysis for efficacy is acceptable in general. The asciminib 80 mg QD and 40 mg BID regimens were predicted to result in comparable MMR rates as shown in Figure 8.

Figure 8 MMR Relationship (left panel) Suggested That Asciminib 80 mg QD and 40 mg BID Result in Comparable MMR Rate



19.4.3.3. ER (safety) Assessment Summary

The Applicant’s Position:

General Information	
Goal of ER analysis	- To assess the association between asciminib exposure and the probability of occurrence of key safety events using the pooled data from the newly diagnosed (1L) and pretreated (3L+) participants with Ph+ CML. - To evaluate the effect of line of therapy on the probability of occurrence of key safety events.
Study Included	Studies J12301, A2301, and X2101
Population Included	- Study J12301 (n=197): all 1L participants with CML-CP in the asciminib arm. - Study A2301 (n=154): all 3L participants with CML-CP in the asciminib arm; participants who switched from bosutinib to asciminib were excluded. - Study X2101 (n= 199): all participants with CML who were treated with asciminib alone (including AP, CP, and participants with CML with the T315I mutation).
Endpoint	Laboratory parameters

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		- Based on maximum toxicity grade compared to baseline: grade ≥ 3 amylase increase, grade ≥ 3 lipase increase, grade ≥ 3 platelet count decrease, grade ≥ 3 neutrophil count decrease, grade ≥ 3 hemoglobin decrease, grade ≥ 2 AST increase, grade ≥ 2 ALT increase, grade ≥ 2 total bilirubin increase, grade ≥ 1 triglycerides. - Based on normal range (low/normal/high categorization): glucose increase, HBA1c. Hypertension based on vital sign SBP≥ 160 mmHg or DBP≥ 100 mmHg. Fatigue or asthenia: if maximum toxicity grade ≥ 2 for at least one of fatigue or asthenia.										
No. of Participants (total, and with individual PK)		PK-Safety Set=550 participants treated with single-agent asciminib who had at least one post-hoc exposure estimate from the PopPK model.										
Population Characteristics	General	Pooled set (Studies X2101, A2301, J12301) Age median (range): 53.0 (18-88) years Male: 330 (60.0%) Race: Asian 158 (28.7%), Caucasian 338 (61.5%)										
	Organ impairment	Hepatic impairment status at baseline: Normal 480 (87.3%) Renal impairment status at baseline: Normal 298 (54.2%)										
	Pediatrics	Not applicable										
	Geriatrics	≥ 65 years: 128 (23.3%)										
Dose(s) Included		Refer Section 19.4.2.2 for details										
Exposure Metrics Explored (range)		Average daily AUC up to the time of first flagged safety event and average daily Cmax up to the time of first flagged safety event.										
Covariates Evaluated		Exposure metric, baseline values of safety endpoint, number of lines of therapy, baseline demographics (age, age group, gender, race, hepatic impairment status at baseline, renal impairment status at baseline).										
Final Model Parameters		<table><tr><th>Summary</th><th>Acceptability [FDA's comments]</th></tr><tr><td>Model Structure</td><td>Acceptable</td></tr><tr><td>Model Parameter Estimates</td><td>Acceptable</td></tr><tr><td>Model Evaluation</td><td>Acceptable</td></tr><tr><td>Covariates and Clinical Relevance</td><td>Acceptable</td></tr></table>	Summary	Acceptability [FDA's comments]	Model Structure	Acceptable	Model Parameter Estimates	Acceptable	Model Evaluation	Acceptable	Covariates and Clinical Relevance	Acceptable
Summary	Acceptability [FDA's comments]											
Model Structure	Acceptable											
Model Parameter Estimates	Acceptable											
Model Evaluation	Acceptable											
Covariates and Clinical Relevance	Acceptable											
		A logistics regression model was used to describe the association between the probability of a safety event and asciminib exposure.										
		Table 39										
		Logistic regression model										
		Of all safety endpoints analyzed, the only statistically significant positive relationship was identified between exposure and the worsening event for grade ≥ 3 lipase increase. Though an increase in exposure was associated with an										

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	increased incidence of this safety event, event probabilities were low over the full range of exposure investigated for 1L participants, ranging from 5.8-11.2%. Line of therapy was investigated as a covariate, and the resulting coefficient estimates were positive for all safety endpoints, indicating a lower probability of all safety events occurring in newly diagnosed participants than in pretreated participants. The higher event probability in 3L participants is expected, considering their more advanced disease status and the evolution of their disease characteristics due to exposure to other TKIs.	
Simulation for Specific Population	Not applicable	Acceptable
Visualization of E-R relationships	Logistic regression of asciminib average AUC/Cmax vs. probability of worsening of key safety events are provided in [Exposure-Safety report-Figure 7-1 to 7-26]. Logistic regression of asciminib average AUC/Cmax vs. probability of worsening event for grade ≥ 3 lipase increase are illustrated in Figure 9 .	Acceptable
Overall Clinical Relevance for ER	Section 6.3.2.1	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	As described in the approved prescribing information. No new information has been added based on this application.	Acceptable
Source: [Exposure-safety-report-Section 4.0, Section 5.1, Section 5.4, Section 5.5, Section 7.1, Section 7.2, Section 8, Section 9, Table 7-3]		

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Table 39 Logistic Regression Model: Asciminib Exposure vs. Probability of Safety Event (PK Safety Set)

Safety event	Exposure metric	Log(exposure) coefficient estimate	Standard Error	Odds ratio	95% CI
Grade 3 or Higher Amylase Increase ¹	Average AUC	0.21	0.24	1.39	(0.65, 3.00)
	Average Cmax	0.28	0.27	1.57	(0.67, 3.67)
Grade 3 or Higher Lipase Increase ¹	Average AUC	0.31	0.15	1.65	(1.04, 2.62)
	Average Cmax	0.37	0.16	1.82	(1.10, 3.02)
Grade 3 or Higher Platelet Count Decrease ¹	Average AUC	-0.22	0.14	0.70	(0.46, 1.07)
	Average Cmax	-0.19	0.15	0.73	(0.46, 1.17)
Grade 3 or Higher Neutrophil Count Decrease ¹	Average AUC	-0.39	0.14	0.53	(0.34, 0.82)
	Average Cmax	-0.40	0.15	0.53	(0.33, 0.85)
Grade 3 or Higher Hemoglobin Decrease ¹	Average AUC	0.32	0.23	1.67	(0.80, 3.47)
	Average Cmax	0.32	0.26	1.68	(0.74, 3.81)
Grade 2 or Higher AST Increase ¹	Average AUC	0.43	0.24	1.99	(0.95, 4.19)
	Average Cmax	0.49	0.26	2.19	(0.96, 5.01)
Grade 2 or Higher ALT Increase ¹	Average AUC	0.34	0.19	1.72	(0.94, 3.12)
	Average Cmax	0.34	0.21	1.72	(0.89, 3.32)
Grade 2 or Higher Total Bilirubin Increase ¹	Average AUC	0.38	0.23	1.84	(0.89, 3.81)
	Average Cmax	0.45	0.26	2.07	(0.91, 4.69)
Grade 1 or Higher Triglycerides Increase ¹	Average AUC	0.06	0.10	1.10	(0.80, 1.51)
	Average Cmax	0.12	0.11	1.21	(0.85, 1.71)
Fasting Glucose Increase ¹	Average AUC	-0.21	0.48	0.71	(0.16, 3.22)

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Version date: February 9, 2024 (ALL NDA/ BLA reviews)

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

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Safety event	Exposure metric	Log(exposure) coefficient estimate	Standard Error	Odds ratio	95% CI
Hemoglobin A1c Increase ¹	Average Cmax	-0.59	0.58	0.39	(0.06, 2.39)
	Average AUC	0.56	1.16	2.46	(0.06, 96.96)
Hypertension (SBP ≥ 160 or DBP ≥ 100)	Average Cmax	0.50	1.53	2.23	(0.02, 276.46)
	Average AUC	0.15	0.12	1.28	(0.88, 1.87)
Grade 2 or Higher Fatigue or Asthenia	Average Cmax	0.15	0.13	1.28	(0.85, 1.93)
	Average AUC	0.10	0.15	1.18	(0.73, 1.91)
	Average Cmax	0.15	0.17	1.28	(0.76, 2.16)

¹ The safety events are worsening events from baseline.

The model is a logistic regression to estimate the probability of occurrence of an event and its association to the covariates log(exposure), line setting and other adjusted covariates.

AUC and Cmax are average daily AUC and Cmax up to the time of the event (or up to 3 days after last dose if no event or event after (last dose + 3) days).

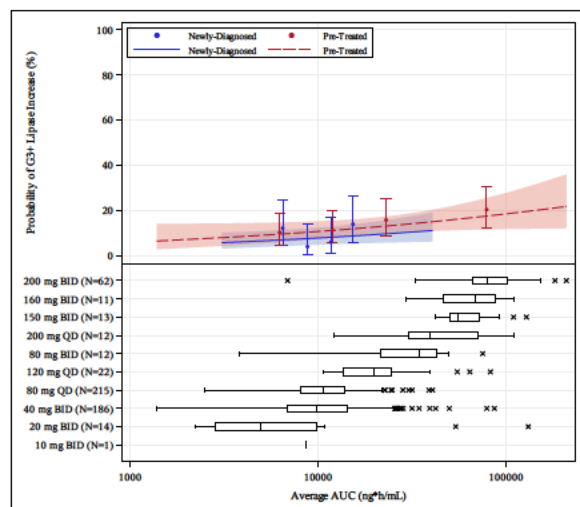
Odds ratio and its corresponding 95% CI calculated for 5-times increase in exposure at 80 mg QD.

Source: [Exposure-safety-report-Table 11-3]

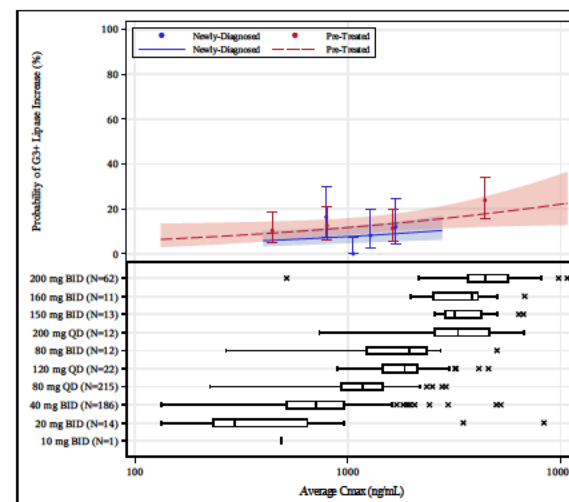
Scemblix (asciminib)

Figure 9 Logistic Regression of Asciminib

Average AUC/ vs. Probability of Worsening Event for Grade ≥ 3 Lipase Increase



Average Cmax vs. Probability of Worsening Event for Grade ≥ 3 Lipase Increase



N is the number of participants used in logistic regression model for each dose/regimen.

Upper panel: color dots and bars represent observed proportion and 95% CI probability of the event for each quartile of asciminib average daily exposure; the 95% CI is based on Clopper-Pearson method.

Color lines and boundaries represent predicted mean probability of the event and the 95% CI (based on median baseline lab values for labs and baseline status="No" for hypertension).

Lower Panel: boxes and whiskers represent distribution of predicted asciminib average daily exposure at each dosage level.

Source: [Exposure-Safety-Report-Figure 7-17] [Exposure-Safety-Report-Figure 7-18]

The FDA's Assessment:

The Applicant's ER analysis for safety is acceptable in general.

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19.4.3.4. Overall benefit-risk evaluation based on E-R analyses**The Applicant's Position:**

- The probability of occurrence of all safety events was lower for newly diagnosed than for pretreated participants with Ph+ CML. The higher event probability in pretreated participants is expected, given the persistent side effects of prior TKIs, increased incidence of cross-intolerance, and evolution of their disease characteristics due to prolonged exposure to other TKIs. Over the range of exposure for 1L participants, the probability of grade ≥ 3 lipase increase was low and ranged from 5.8-11.2%, indicating a slight positive relationship between asciminib exposure and probability of grade ≥ 3 lipase increase. The probability of occurrence of all other safety events is unlikely to increase with increased exposure of asciminib. Comparable exposure was reached with the 40 mg BID and 80 mg QD asciminib doses, and no association was observed between exposure and most safety events, indicating the interchangeability of these two dosing regimens with respect to their safety profile [Exposure-safety report-Section 9].
- In the newly diagnosed participants with Ph+ CML-CP, a predicted 70% 48-week MMR rate is achieved based on the participant's dosing history in Study J12301, and an enhanced MMR rate of 75% is predicted in uninterrupted dosing situation. Higher MMR rates is achieved when participants maintained uninterrupted dosing; dose interruptions were predicted to lead to lower MMR rates, highlighting the importance of treatment compliance. The asciminib 80 mg QD and 40 mg BID regimens were predicted to result in comparable MMR rates across treatment lines and timepoints. The model-based analysis that characterized the longitudinal BCR::ABL1 by treatment lines (1L, 2L or 3L+) is suitable for extrapolation across lines of asciminib treatment in CML-CP. In the 2L, the total daily dose of 80 mg administered either as once-daily (80 mg QD) or twice-daily (40 mg BID) is predicted to achieve a Week-48 MMR rate of 54-63% and a Week-96 MMR rate of 66-74% [ER-efficacy-report-Section 7].

The FDA's Assessment:

FDA agrees with the Applicant's position.

19.5. Additional Safety Analyses Conducted by FDA**The FDA's Assessment:**

Grouped preferred terms are displayed in Table 40.

Table 40 List of preferred terms for the grouped terms

Grouped term	Preferred terms
Abdominal Pain	Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort, Gastrointestinal pain, Hepatic pain

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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

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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 26.1 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

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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, Abnormal uterine bleeding, 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

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	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, 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,
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	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
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	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 enzyme increased, Hepatic lesion, Hepatic pain, Hepatocellular injury, Hepatomegaly, Hyperbilirubinaemia, Hypertransaminasaemia, 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 generalised, 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 maculopapular, Rash maculovesicular, Rash morbilliform, Rash papular, 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, Central hypothyroidism, Hypothyroidic goitre, Hypothyroidism, Primary 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,

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	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, Paraneoplastic pneumonia, Parasitic pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia acinetobacter, Pneumonia adenoviral, Pneumonia anthrax, Pneumonia aspiration, Pneumonia bacterial, 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 lipid, Pneumonia measles, Pneumonia moraxella, Pneumonia mycoplasmal, Pneumonia necrotising, 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, Pulmonary blastomycosis, Varicella zoster pneumonia
Pneumonitis	Acute interstitial pneumonitis, Immune-mediated lung disease, Interstitial lung disease, Organising pneumonia, Pneumonitis

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Pyrexia	Body temperature increased, Hyperpyrexia, Hyperthermia Pyrexia
Rash	Autoimmune dermatitis, Dermatitis, Dermatitis acneiform, Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, 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 dermatitis, Perineal rash, Rash, Rash erythematous, Rash follicular, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash morbilliform, Rash papular, Rash papulosquamous, Rash pruritic, Rash pustular, Rash vesicular, Scrotal dermatitis, Skin exfoliation, Stevens-Johnson syndrome, Superficial inflammatory dermatosis, 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

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/APPROVED	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.	Select one: ☒ Authored ☐ Approved
	Signature: Gulsum E. Pamuk -S Digitally signed by Gulsum E. Pamuk -S Date: 2024.10.28 14:48:27 -04'00'			
Clinical Team Leader	Lori Ehrlich, MD, PhD	Office of Oncologic Diseases (OOD)/ Division of Hematologic Malignancies I (DHM1)	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 19.	Select one: ☒ Authored ☒ Approved
	Signature: Lori Ehrlich -S Digitally signed by Lori Ehrlich -S Date: 2024.10.28 16:06:50 -04'00'			
Clinical Pharmacology Reviewer	Hongfei Zhang, PhD	Office of Clinical Pharmacology/ Division of Cancer Pharmacology I	Sections: 6, 19	Select one: ☒ Authored ☐ Approved
	Signature: Hongfei Zhang -S Digitally signed by Hongfei Zhang -S Date: 2024.10.23 12:31:15 -04'00'			
Clinical Pharmacology Team Leader	Ruby Leong, Pharm D	Office of Clinical Pharmacology/ Division of Cancer Pharmacology I	Sections: 6, 19	Select one: ☒ Authored ☒ Approved
	Signature: Ruby Leong -S Digitally signed by Ruby Leong -S Date: 2024.10.23 12:37:30 -04'00'			
Pharmacometrics Reviewer	Hongshan Li, PhD	Office of Clinical Pharmacology/ Division of Pharmacometrics	Sections: 19	Select one: ☒ Authored ☐ Approved
	Signature: Hongshan Li -S Digitally signed by Hongshan Li -S Date: 2024.10.23 14:57:49 -04'00'			

Pharmacometrics Team Leader	Jiang Liu, PhD	Office of Clinical Pharmacology/ Division of Pharmacometrics	Sections: 19	Select one: ☒ Authored ☒ Approved
	Signature: Hao Zhu -S Digitally signed by Hao Zhu -S Date: 2024.10.23 14:54:41 -04'00'			
Pharmacokinetics Reviewer	Javier Blanco, PhD	Office of Clinical Pharmacology/ Division of Translational & Precision Medicine	Sections: 6	Select one: ☒ Authored ☐ Approved
	Signature: Jeffrey B. Kraft Jr -S Digitally signed by Jeffrey B. Kraft Jr Date: 2024.10.23 15:05:18 -04'00'			
Pharmacokinetics Team Leader	Jeffrey Kraft, PhD	Office of Clinical Pharmacology/ Division of Translational & Precision Medicine	Sections: 6	Select one: ☒ Authored ☒ Approved
	Signature: Jeffrey B. Kraft Jr -S Digitally signed by Jeffrey B. Kraft Jr Date: 2024.10.23 15:05:48 -04'00'			
Clinical Pharmacology Division Director	Brian Booth, PhD	Office of Clinical Pharmacology/ Division of Cancer Pharmacology I	Sections: 6, 19	Select one: ☒ Approved
	Signature: Brian P. Booth -S Digitally signed by Brian P. Booth Date: 2024.10.23 14:52:23 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Pharmacology Toxicology Reviewer	Shwu Luan Lee, PhD	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☐ Approved
	Signature: Shwu-luan Lee -S Digitally signed by Shwu-luan Lee -S Date: 2024.10.23 16:00:56 -04'00'			
Pharmacology Toxicology Team Lead	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Brenda Gehrke -S Digitally signed by Brenda Gehrke -S Date: 2024.10.23 16:12:22 -04'00'			
Biostatistics Reviewer	Radhika Avadhani, PhD	Office of Biostatistics/ Division of Biometrics IX	Sections: 8	Select one: ☒ Authored ☐ Approved
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Biostatistics Team Lead	Jonathon Vallejo, PhD	Office of Biostatistics/ Division of Biometrics IX	Sections: 8	Select one: ☒ Authored ☒ Approved
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Biostatistics Division Director	Yuan Li Shen, PhD	Office of Biostatistics/ Division of Biometrics IX	Sections: 8	Select one: ☐ Authored ☒ Approved
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Cross- Disciplinary Team Leader (CDTL)	Lori Ehrlich, MD, PhD	OOD	Sections: All	Select one: ☒ Authored ☐ Approved
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Division Director (Clinical)	R. Angelo de Claro, MD	OOD/DHMI	Sections: All	Select one: ☒ Authored ☒ Approved
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