16 October 2025
EMADOC-1700519818-2475374
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Scemblix

International non-proprietary name: Asciminib

Procedure No. EMA/VR/0000265010

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

2G	Second generation
1L	First line
2L	Second line
ABL1/ABL1	Abelson oncogene; non-italicized: Abelson protein
ABL2/ABL2	Abelson related oncogene; non-italicized: Abelson related protein
ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
aGFR	Adjusted glomerular filtration rate
ALL	Acute lymphoblastic leukemia
ALLG	Australian Leukemia Lymphoma Group
Allo-SCT	Allogeneic stem cell transplantation
ALT	Alanine aminotransferase
AOEs	Arterial occlusive events
AP	Accelerated phase
AST	Aspartate aminotransferase
AUC	Area under curve
AUCinf	AUC from time zero to infinity
AUClast	AUC from time zero to the time of the last quantifiable concentration
AUCtau	AUC from time zero to the end of the dosing interval tau
BC	Blast crisis
BCR	Breakpoint Cluster Region
BCR::ABL1	Chimeric *BCR::ABL1* oncogene
BCR::ABL1	BCR::ABL1 oncoprotein with dysregulated ABL1 kinase activity
BID	*bis in diem*/twice a day
BMA	Bone marrow aspirate
BP	Blast phase
BP	Systolic blood pressure/diastolic blood pressure
CBC	Complete blood count
CCI	Charlson Comorbidity Index
CCyR	Complete Cytogenetic Response
CHMP	Committee for Medicinal Products for Human Use
CHR	Complete hematological response
CI	Confidence Interval
Cmax	Observed maximum plasma (or serum or blood) concentration following drug administration
CMH	Cochran–Mantel–Haenszel
Cmin	Trough concentration
CL	Systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration
CL/F	Apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration
CLr	Renal clearance from plasma (or serum or blood) [volume / time]
CML	Chronic Myeloid Leukemia
CML-AP	Chronic myeloid leukemia in accelerated 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
Ctrough/Cmin	Plasma concentration (measured concentration at the end of a dosing interval at steady state [taken directly before next administration])
CV	Coefficient of variation
CVD	Cardiovascular disease
CYP	Cytochromes P450
DDI	Drug-drug interaction

DMR	Deep molecular response
EAIR	Exposure-adjusted incidence rate
ECOG	Eastern Cooperative Oncology Group
EFS	Event Free Survival
ELN	European Leukemia Net
ELTS	EUTOS Long-Term Survival
EMA	European Medicines Agency
EORTC QLQC30	European organization for research and treatment of cancer - quality of life questionnaire
EORTC QLQCML24	European organization for research and treatment of cancer CML module
EOT	End of treatment
EQ VAS	EuroQol Visual Analogue Scale
EUTOS	European Treatment Outcome Study
EWOC	Escalation with overdose control
FAS	Full Analysis Set
FCT	Film-coated tablet
FDA	Food and Drug Administration
FFS	Failure Free Survival
FIH	First in human
FMI	Final market image
GGT	Gamma-glutamyltransferase
HRQoL	Health-related quality of life
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IS	International scale
IS-TKI	Investigator selected-TKI
KM	Kaplan-Meier
LPLV	Last patient last visit
MCyR	Major cytogenetic response
mCyR	Minor Cytogenetic Response
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Major molecular response
MoA	Mechanism of action
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not estimable
OS	Overall survival
PA	Primary analysis
Ph+ CML	Philadelphia chromosome-positive chronic myelogenous leukemia
Papp	Apparent permeability coefficient
PBPK	Physiologically based pharmacokinetic
PCR	Polymerase Chain Reaction
PCyR	Partial Cytogenetic response
PD	Pharmacodynamic(s)
PFS	Progression-free survival
Ph+	Philadelphia chromosome positive
PK	Pharmacokinetics
PopPK	Population PK
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient-reported outcomes
PRS-TKI	Pre-randomization selected-TKI
QD	Once daily
RDE	Recommended dose for expansion
RQ-PCR	Real time quantitative polymerase chain reaction
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SBP	Summary of biopharmaceutics
SCP	Summary of clinical pharmacology
SD	Standard deviation

SOC	System organ class
SOP	Standard operating procedure
sNDA	Supplementary New Drug Application
TEAE	Treatment-emergent adverse event
T1/2	Terminal elimination half-life
TFR	Treatment-free remission
TKI	Tyrosine kinase inhibitors
Tmax	Time to reach the maximum concentration after drug administration
TTF	Time to treatment failure
ULN	Upper limit of normal

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 07 April 2025 an application for group of variations.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

A grouped application consisting of:

C.I.6.a: Extension of indication to include treatment of adult patients with newly diagnosed or previously treated Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase (CP) for SCEMBLIX, based on primary and key secondary analysis results from study CABL001J12301 (ASC4FIRST, J12301); this is an ongoing Phase III, multi-center, open-label, randomized study of oral asciminib (80 mg once daily, QD) versus Investigator selected tyrosine kinase inhibitor (TKI) in patients with newly diagnosed Ph+ CML-CP, with the primary and key secondary objectives to compare the major molecular response (MMR) rates at Week 48 and Week 96, respectively. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. RMP version 4.0 was also submitted. As part of the application the MAH is requesting a 1-year extension of the market protection.

C.I.4: Update of sections 4.2, 4.5, 5.1, 5.2 and 5.3 of the SmPC in order to introduce a new posology regimen based on results from studies CABL001J12301 and CABL001A2302 (ASC4OPT, A2302). CABL001A2302 is an ongoing Phase IIIb, multi-center, open-label, treatment optimization study of oral asciminib (80 mg daily, randomized to 40 mg BID or 80 mg QD) in patients with Ph+ CML-CP previously treated with two or more TKIs, with the primary objective to estimate the MMR rate at Week 48 of all the patients (40 mg BID and 80 mg QD) with no evidence of MMR at baseline. The Package Leaflet is updated accordingly. RMP version 4.0 has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Scemblix was designated as an orphan medicinal product EU/3/20/2261 on 24 March 2020. Scemblix was designated as an orphan medicinal product in the following indication: Treatment of chronic myeloid leukaemia.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation for the treatment of chronic myeloid leukaemia as

an orphan medicinal product in the approved indication. The outcome of the COMP review can be found here https://www.ema.europa.eu/en/medicines/human/Scemblix

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA-002347-PIP01-18 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-002347-PIP01-18 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Scemblix as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/en/medicines/human/EPAR/scemblix

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 25 March 2021 (EMA/SA/0000047632), on 19 September 2025 (EMA/SA/0000181795). The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martin Mengel Co-Rapporteur:n/a

Timetable	Actual dates
Submission date	7 April 2025
Start of procedure:	26 April 2025
CHMP Rapporteur's preliminary assessment report circulated on	26 June 2025
PRAC RMP advice and assessment overview adopted by PRAC on	10 July 2025
CHMP Rapporteur's updated assessment report circulated on	18 July 2025

Timetable	Actual dates
Request for supplementary information and extension of timetable adopted by the CHMP on	24 July 2025
MAH's responses submitted to the CHMP on	13 August 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	19 September 2025
PRAC RMP advice and assessment overview adopted by PRAC on	2 October 2025
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	10 October 2025
CHMP opinion:	16 October 2025
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Scemblix in comparison with existing therapies	16 October 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The newly claimed indication is:

*Scemblix is indicated for the treatment of adult patients with **newly diagnosed or previously treated** Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+CML-CP)*

Epidemiology

The disease has an annual incidence of one to two cases per 100000, with a median age of 66 years at presentation. Prevalence is steadily increasing due to improved survival.

Aetiology and pathogenesis

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm and is characterised by uncontrolled proliferation of mature and maturing granulocytes in blood and bone marrow. CML is caused by a reciprocal translocation of chromosomes 9 and 22 (t(9;22)(q34;q11)), generating a BCR::ABL1 fusion gene, which is translated into a constitutively active kinase protein, promoting cell growth and replication via downstream signalling pathways such as RAS, RAF; MYC and STAT.

Clinical presentation, diagnosis and prognosis

The natural history of CML is characterized by a triphasic course. In most of the patients, the disease is diagnosed in the chronic phase (CP), which is characterized by overproduction and accumulation of immature myelogenous cells and mature granulocytes in the spleen, bone marrow, and peripheral blood. If CML-CP remains untreated, or it is not controlled with available therapies, patients will progress to an intermediate phase known as accelerated phase (AP), marked by the presence of primitive blast cells in the bone marrow and peripheral blood.

Most patients with CML-AP eventually progress to a blastic phase (BP), a condition resembling acute leukaemia in which myeloid or lymphoid blasts proliferate in an uncontrolled manner (Apperley 2015). Based on the experience with TKIs, the best approach to avoid advanced CML (CML-AP/-BP) is preventing progression and keeping patients in the well-controlled chronic phase.

The prognosis of CML has changed during the past two decades from a disease with an overall survival of only 5-7 years to one in which patients responding to TKI treatment can expect a near to normal life expectancy (Apperley 2015) with 1% CML associated mortality. However, some patients do not respond to the treatment (primary resistance), lose their response (secondary resistance), or experience tolerability issues. Also, the detection of BCR-ABL1 mutations in CML-CP, in particular T315I mutation, are associated with a greater likelihood of resistance to TKI treatment and consequent disease progression (Soverini 2005).

Management

Since the approval of imatinib in 2001, the 10-year survival rates for patients with CML have improved from approximately 20% to around 80-90%, and targeted therapy with TKIs has become the gold standard of treatment (Jabbour and Kantarjian 2018). There are four TKIs approved in the EU for the treatment of newly diagnosed CML in the chronic phase (1st generation: imatinib; 2nd generation: nilotinib, dasatinib, bosutinib).

The two main goals of CML treatment are to normalise survival and to achieve durable deep molecular responses (DMR, including MR4 and MR4.5 lasting for 2-5+ years) allowing for a treatment free remission (TFR). The choice of the TKI depends on 1) the patient's age and comorbidities 2) the CML risk profile 3) the cost and affordability of the TKI 4) the treatment goal, as imatinib is considered to be equally effective for prolongation of survival to 2nd generation TKI. Achievement of deep molecular remissions is potentially faster with 2nd generation TKI, possibly reaching the criteria for a discontinuation attempt in a TFR faster.

Achievement of major molecular response (MMR, MR3.0, BCR-ABL1 $\leq$ 0.1%) is, following clinical guidelines, predictive for CML-specific survival, as disease progression is uncommon, once this level of cytoreduction has been achieved (European Leukemia Net GL, 2020).

Clinical decision making in 1st and 2nd line treatment is guided by monitoring milestones of BCR-ABL1 transcript levels on the international scale (IS). Here, optimal response implies treatment continuation, failure implies a change in treatment and warranting careful consideration, considering treatment goals, tolerance and comorbidities.

Table 1 Milestones for treating CML

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%, resistance mutations, high-risk ACA

For patients aiming at TFR, the optimal response (at any time) is BCR-ABL1 ≤ 0.01% (MR_4). A change of treatment may be considered if MMR is not reached by 36–48 months. NA not applicable, ACA additional chromosome abnormalities in Ph+ cells, ELTS EUTOS long term survival score. [a]Loss of MMR (BCR-ABL1 > 0.1%) indicates failure after TFR

A respectable number of patients fail to reach or maintain deep remissions due to primary or secondary resistance or have difficulties in the tolerability of the drug. The optimal sequence of TKI therapy remains controversial in respect to safety of a long-term treatment, especially in patients with comorbidities. Ponatinib is approved after treatment with dasatinib or nilotinib or in the presence of a T315I mutation.

Asciminib is currently approved in the EU for adults after treatment with two or more TKIs and recommended by the National Comprehensive Cancer Network (NCCN) 2025 guideline and 2025 European LeukemiaNet.

2.1.2. About the product

Asciminib (ABL001), administered orally, is a potent allosteric inhibitor of ABL/BCR-ABL1 tyrosine kinase by specifically targeting the ABL myristoyl pocket (STAMP).BCR-ABL1 is a chimeric oncoprotein with the constitutively active ABL1 tyrosine kinase domain. Asciminib inhibits the ABL1 kinase activity of the BCR-ABL1 fusion protein, by specifically targeting the ABL myristoyl pocket. Asciminib (ABL001) is an inhibitor that targets the myristoyl pocket of BCR-ABL1, in contrast to the currently available TKIs that target the BCR-ABL1 ATP binding site. By virtue of asciminib not interacting with the ATP-binding site, asciminib maintains activity against cells expressing clinically observed ATP-binding TKI resistant mutations. Asciminib was approved in the EU for adults with Ph+ CML-CP after treatment with two or more TKIs on 25 August 2022.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Advice for the development of asciminib monotherapy as 1L treatment was received from CHMP on 25 March 2021 and included the following aspects:

- Population: Including patients with moderate renal – and hepatic impairment was endorsed. Excluding patients with a history of acute pancreatitis within one year prior to randomisation or with chronic pancreatitis or chronic liver disease was considered acceptable.

- Endpoints: 1) in this context, it was accepted that only activity to measure positive effects, supported by endpoints that reflect changes in clinical management (loss of or not obtaining activity), and favourable safety are acceptable to support an extension of the indication. 2) The endpoint 'MMR at 48 weeks' was considered early but was in line with other recently approved TKI (nilotinib, bosutinib), although EMA Anticancer guideline recommends MMR at 18 months. 3) EFS as a secondary endpoint, including treatment change could further justify the clinical relevance of the primary endpoint 4) 'Region' should be noted in the randomisation or analysis to provide information about regional differences.
- Statistical design: 1) The proposed global comparison of activity (MRR) in an 'overall population' against a multi-comparator-control was considered less useful due to heterogeneous populations, heterogeneous activity/tolerability profiles and that the comparison might be driven by the effect of imatinib rather than 2G TKIs. 2) The difficulty to define a non-inferiority margin in case the applicant favours a comparison with 2G TKI in terms of favourable safety.

2.2. Non-clinical aspects

2.2.1. Toxicology

No new non-clinical data were submitted other than for the new posology, 80 mg QD additional safety margins were calculated and section 5.3. of the SmPC was updated accordingly.

2.2.2. Ecotoxicity/environmental risk assessment

In a parallel submission for the indication CML-CP with T315I mutation (EMA/X/0000256688) for which the assessment is ongoing, a phase II ERA for the active substance asciminib was provided. As this revised ERA is based on prevalence data for CML, the applicant claimed that the already approved ERA (provided with the initial MAA) also covers the patient population applied for in the current authorisation application. Furthermore, the maximum daily dose of 400 mg/day used in the respective ERA is higher than in the current submission (80 mg/day). Therefore, the MAH stated that the conclusions from the recently submitted assessment remain conservative and valid and the ERA does not warrant an update.

2.2.3. Discussion on non-clinical aspects

No new nonclinical data were submitted which is considered acceptable as this extension of indication relates to the same condition and is therefore covered by previously submitted data.

As for this type II variation, the recommended daily dose of 80 mg/day is less than the maximum daily dose of 400 mg/day used in the already provided ERA and therefore an increase in the environmental exposure is not anticipated. Consequently, the MAH's conclusion can be followed and an update of the existing ERA is deemed not required. Furthermore, for this type II variation the calculation of PECSW (under consideration of a maximum daily dose of 80 mg/day and the refined Fpen of 0.00013) results in a value of 0.0052 µg/l and does not exceed the trigger value of 0.01 µg/l.

2.2.4. Conclusion on the non-clinical aspects

The new/extended indication does not lead to a significant increase in environmental exposure further to the use of asciminib hydrochloride.

Considering the above, asciminib hydrochloride is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2 Overview of key clinical studies

Studies/ Population/ No. of participants (N) No. of participants included in the All Asciminib Safety Pool (n)	**Study description**	**Dose schedule**	**Data cut-off date**	**Completion status**
Phase III registration study				
CABL001J12301 Adult participants with newly diagnosed Ph+ CML-CP N=405 n=200	A phase III, multi-center, open-label, randomised study of oral asciminib versus Investigator selected TKI in patients with newly diagnosed Ph+ CML-CP	80 mg QD	28-Nov-2023 (Week 48 Primary CSR) 22-Oct-2024 (Week 96 Secondary CSR)	Ongoing
Supportive studies in the All Asciminib Safety pool				
CABL001A2301 Adult participants with Ph+ CML-CP previously treated with ≥2 TKIs N=233 n=156	A phase III, multi-center, open-label, randomised study of oral ABL001 (asciminib) versus bosutinib in patients with CML-CP, previously treated with two or more TKIs	40 mg BID	22-Mar-2023 (EOT CSR)	Ongoing
CABL001X2101 Adult participants with Ph+ CML or ALL,	A phase I, multicenter, open-label study of oral ABL001 in	10, 20, 40, 80, 150, 160, 200, 280 mg BID and 40, 60 80, 120, 160, 200 mg	14-Mar-2023 (final CSR)	Completed

relapsed, refractory to or intolerant of TKIs N=326 n=200	patients with Ph+ CML or Ph+ALL[a]	QD as single agent or in combination with imatinib, nilotinib or dasatinib		
Additional study in 2L				
CABL001AUS08 N=101 (2L cohort)	A Phase II multicenter, open-label, single-arm dose escalation study of Asciminib monotherapy in 2nd and 1st Line Chronic Phase–Chronic Myelogenous Leukemia	80 mg QD	15-Nov-2024 (IA 4 including efficacy set=63 safety set=101)	Ongoing

2.3.2. Pharmacokinetics

For the requested extension of indication, PK data from the pivotal ongoing Phase III study J12301 in newly diagnosed Ph+ CML-CP patients (1L) were submitted.
In addition, new PopPK analyses based on study X2101 (completed FIH study (N=326) including adult patients with cytogenetically confirmed, previously diagnosed CML or Ph+ ALL), J12301 (N=405; n=201 in asciminib arm), A2103 (hepatic impairment study), and A2105 (renal impairment study) were presented.
Exposure-response analyses based on studies J12301, A2301 (pivotal phase III study in 3L+ CML for initial MAA), and X2101, as well as PK-pharmacogenomics analyses for UGT2B7 and UGT2B17 based on J12301 were also included.

In addition, the current variation also concerned the addition of the 80 mg QD regimen as alternative dosing for the previously approved 3L+ CML population. In this respect, the new PopPK model was also used for an updated PK profile comparison of the asciminib 40 mg BID and 80 mg QD dosing regimens and by exposure-efficacy analyses.

An intrapolation to second-line treatment with a total-daily dose regimen of 80 mg (either 40 mg BID or 80 mg QD) based on ER modelling was also included.

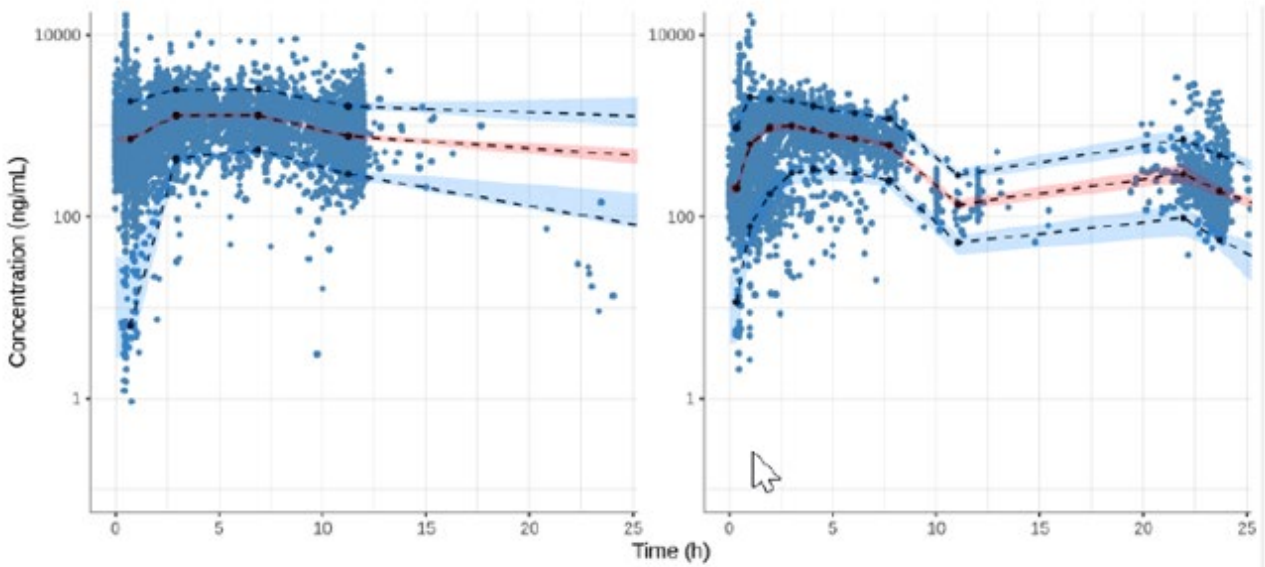
2.3.1. Methods

PopPK modelling

The newly submitted revised popPK model comprised the following studies: A2103 (renal impairment in HV), A2105 (hepatic impairment in HV), X2101 (FIH), A2301, and J12301. The starting model was a combination of the original popPK model and the model developed by the FDA, incorporating all interaction terms and all covariates retained in either one of those models. The total number of subjects in the updated popPK pool was 637. During model refinement, formulation on Tlag and the correlation between ka and Tlag was deleted. Thus, the final model was a 2-compartment model with first order absorption, lag time for absorption, clearance from central compartment and total daily dose as a structural covariate on clearance. The final covariate model included race on Tlag (Asian or non-Asian), formulation on Ka (capsule versus table), total daily dose, baseline age, sex, baseline weight, and baseline aGFR on CL, and formulation, sex and baseline weight on V1. Inter-individual variabilities

were applied following a log-normal distribution on the parameters Tlag, Ka, CL, V1 and V2, with correlation terms between CL and V1, CL and V2, and between V1 and V2. The residual error model selected combined both additive and proportional residual error model.

With the update of the dataset, also more data on the dosing regimen of 80 mg QD were available. The original popPK analysis included only n=18 patients receiving 80 mg QD in study X2101. The updated popPK dataset now includes n=197 patients from Study J12301 where the 80 mg QD dosing regimen was studied. In order to further compare the two-dosing regimen 40mg BID and 80 mg QD, the final popPK model was used to update the PK profile comparison of the two regimens simulating 500 subjects in each dosing regimen. PcVPCs for the different dosing regimens 80mg QD and 40 mg BID are depicted below.



Blue dots: observations. Black dashed lines: 5th, 50th, and 95th percentiles of the observations. Blue solid lines: 5th, 50th, and 95th percentiles of the predictions. Blue shades: 95% confidence interval of 5th and 95th percentiles of the predictions. Red shade: 95% confidence interval of 50th percentile of the predictions.
Source: vob/CABL001A/mas/mas_3/model/pgm_001/pcVPC.R->pcVPC.png
Model: vob/CABL001A//mas/mas_3/model/pgm_001/PopPK/Run_final0.mlxtran

Figure 1 Prediction-corrected visual predictive checks (pcVPC) on first dosing day of asciminib, stratified by dosing regimen- QD left panel, BID right panel

Results of the simulated PK metrics for the 40 mg BID and 80 mg QD dosing regimens are summarized below (see Table 3).

Table 3 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 b.i.d.	829 (33%)	12564 (39%)	320 (53%)
80 mg q.d.	1289 (35%)	12558 (41%)	222 (71%)

Arithmetic mean and %CV are presented
Source: vob/CABL001A/mas/mas_3/simulation/pgm_001/Comp_40BID_80QD.R

2.3.2. Pharmacokinetics in the target population

Newly diagnosed Ph+ CML-CP (1L)

Study J12301 in newly diagnosed Ph+ CML-CP (1L)

Study J12301 is the pivotal ongoing Phase III, multi-centre, open-label, randomised study of asciminib 80 mg QD vs. investigator selected TKI (imatinib, nilotinib, dasatinib, or bosutinib) in patients with newly diagnosed (ND) Ph+ CML-CP (1L). 405 patients were randomised, of which 201 received asciminib.

Full PK sampling was performed in 25 patients over 12 hours on week 2/day 14 at selected sites. All patients had sparse sampling pre-dose at weeks 2 /day 14 and at weeks 4, 12, 24 and 48 and analysed by a validated LC-MS/MS method with a LLOQ of 1.00 ng/ml. No PK samples were collected after Week 48 visit.

The primary Week 48 data cut-off was on 28-Nov-2023. The data cut-off date (30-Oct-2023) for the PK analysis (Week 2 / Day 14) was different from the primary analysis DCO date. There were 6 additional samples (Week 48 sparse samples) that were collected between 30-Oct-2023 and 28-Nov-2023. Therefore, these additional data were included in the Week 96 CSR. However, the MAH identified that at the time of the PK analysis DCO that dosing information were improperly merged with PK concentration data which led to errors in the PK data in the Week 48 primary analysis CSR. In total, data from 59 samples from 51 unique participants were impacted. All impacted data were for participants with sparse PK samples.

As a consequence of these corrected PK data outputs and additional 6 samples, there was a minor change in the trough concentration (Ctrough) geo-mean range to 161 - 192 ng/mL (from the previously reported 160 - 182 ng/mL) (Figure 3).

Plasma concentrations of asciminib increased rapidly after oral administration of asciminib 80 mg QD with a median Tmax of 2.0 hr. The steady-state geo-mean Cmax was 1470 ng/mL (geo-mean CV% 38.2%), geo-mean of AUClast was 8590 ng*hr/mL (geo-mean CV% 42.2%; note: Tlast was 12 hr post-dose).

Figure 2: Asciminib steady-state plasma concentration-time profiles in 1L Ph+ CML-CP, study J12301

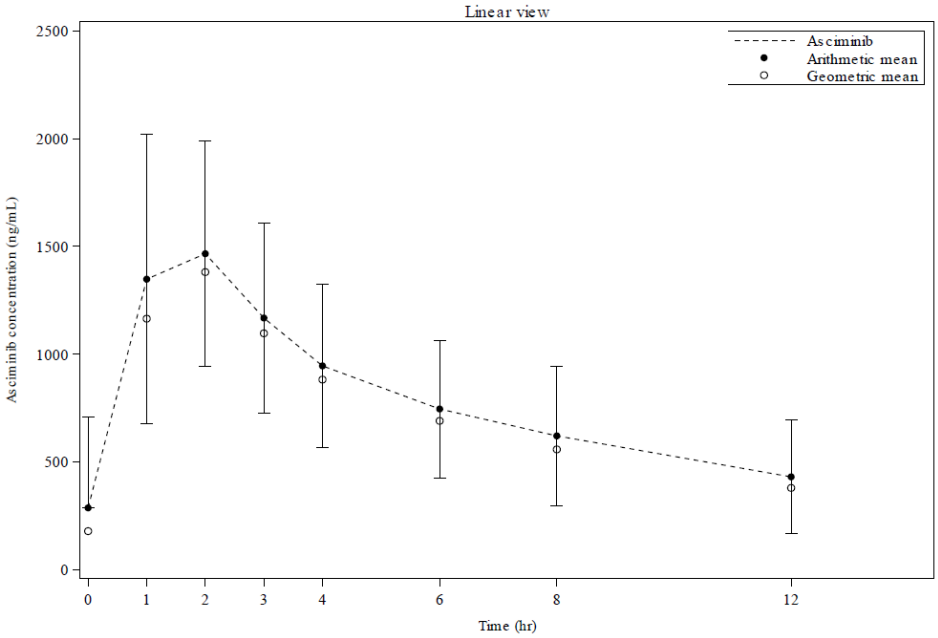
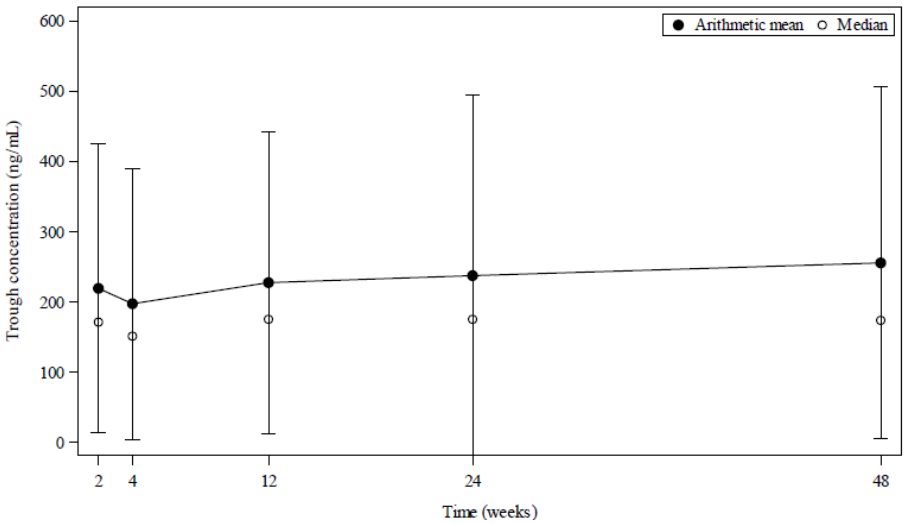


Figure 14.2-3.1

Figure 3: Asciminib trough concentration-time profiles in 1L Ph+ CML-CP, study J12301 - Full and sparse PK sampling



TKI-pretreated patients with CML-CP (3L+)

Study A2301 in TKI-pretreated patients with 3L+ CML-CP

Study A2301 is an ongoing Phase IIIb, multi-centre, open-label, active-controlled randomised of oral asciminib 40 mg BID vs. bosutinib 500 mg QD in the treatment of TKI-pretreated patients with 3L+ CML-CP, submitted as pivotal study for the initial MAA. Of 233 patients randomised in a 2:1 ratio 157 were randomised to asciminib. PK data were included in the popPK and ERR analyses.

PopPK modelling

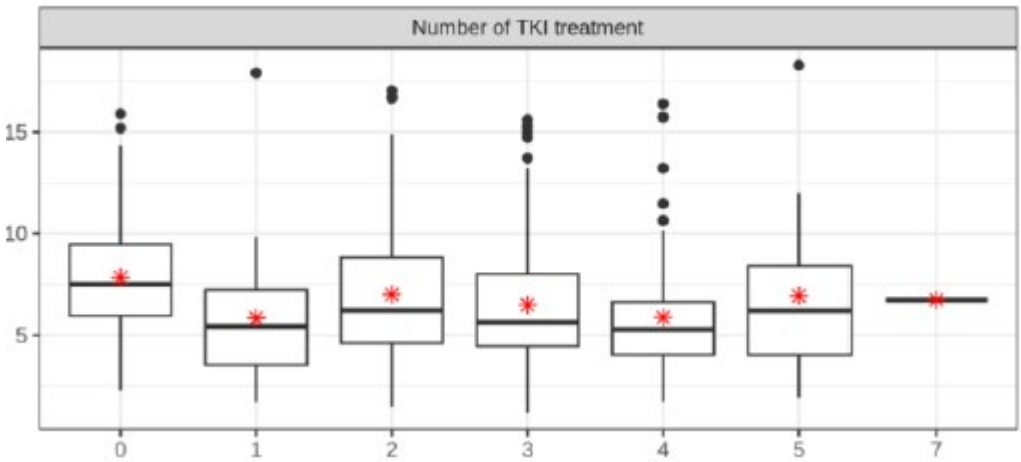
The newly submitted revised popPK model comprised of the following studies: A2103 (renal impairment in HV), A2105 (hepatic impairment in HV), X2101 (FIH), A2301, and J12301.

Lines of TKI pre-treatment

Relationships between these potential covariates and asciminib clearance were investigated. The typical individual in the initially submitted model was a 51.6-year-old and 70 kg non-Asian male patient whose baseline aGFR is 90 mL/min, on a total daily dose of 80 mg using the FMI formulation. Asciminib clearance for this typical individual was 6.89 L/h, and the combined volumes of central and peripheral compartments were approximately 109 L (V1 of 56.7 L and V2 of 51.9 L). The clearance of 6.89 L/h predicted by the final model was in line with both the clearance predicted by the original popPK model (6.31 L/h), and by the independent model developed by the FDA (9.48 L/h).

From this popPK model, no correlation was seen between clearance and number of prior TKI treatments, suggesting that there is no difference in asciminib PK between 1L and 3L+ patients (Figure 4).

Figure 4: Correlation between clearance and number of TKI pre-treatments



Alternative dosing 80 mg QD vs. 40 mg BID in 3L+ CML-CP

The 80 mg QD dosing regimen was originally proposed as an alternative regimen to 40 mg BID in 3L+ CML-CP, based on simulations from the dataset with a limited number of patients treated with 80 mg QD (n=18) in study X2101. As the popPK dataset now includes n=197 patients from 1L CML-CP Study J12301 where the 80 mg QD dosing regimen was studied, the final popPK model was used to update the PK profile comparison of the two regimens.

In the initially submitted model, the simulated average $AUC_{0\text{-}24h}$ values were comparable between the two regimens, while the average 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, consistent with the results described in the original popPK analysis.

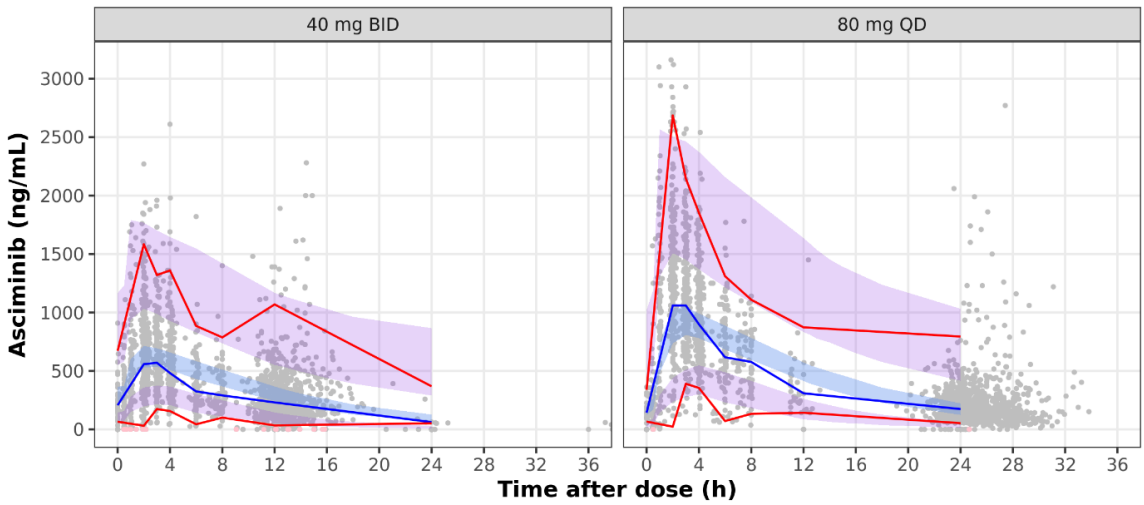
Clearance was very similar between the 40 mg BID (n=192) and 80 mg QD (n=215) dose regimens.

Upon request, the MAH further revised the model to include regimen as covariate to account for potential differences between dosing frequencies using only the 80mg QD and 40mg BID data to avoid confounding by higher doses with nonlinear PK (Table 4).

Table 4 *Summary of PopPK vs NCA derived asciminib PK parameters at 40 mg BID and 80 mg QD at steady state*

	PopPK simulated 40 mg b.i.d.				**PopPK simulated 80 mg QD**		
	$AUC_{0\text{-}12h}$ = AUC_{tau} (ng.h/mL)	**$AUC_{0\text{-}24h}$ (ng.h/mL) (2*$AUC_{0\text{-}12h}$)**	**Cmax (ng/mL)**	**Cmin (ng/mL)**	**$AUC_{0\text{-}24h}$ = AUC_{tau} (ng.h/mL)**	**Cmax (ng/mL)**	**Cmin (ng/mL)**
Geomean (geomean %CV)	5422 (43)	10844 (43)	624 (41)	270 (63)	11639 (43)	956 (42)	142 (99)
Mean ± SD	5902 ± 2556	11804 ± 5111	675 ± 280	315 ± 180	12672 ± 5491	1036 ± 426	194 ± 164
Median	5441	10881	631	273	11692	959	145
90% CI	[2755, 10363]	[5511, 20725]	[325, 1207]	[107, 650]	[5910, 22278]	[483, 1799]	[39, 499]
	NCA 40 mg BID (X2101)				**NCA 80 mg QD (X2101)**		
	AUC_{tau} (ng.h/mL)	**$AUC_{0\text{-}24h}$ (ng.h/mL) (2*AUC_{tau})**	**Cmax (ng/mL)**	**Cmin (ng/mL)**	**AUC_{tau} (ng.h/mL)**	**Cmax (ng/mL)**	**Cmin (ng/mL)**
Geomean (geomean %CV)	5262 (48.49)	10524	793 (48.92)	263 (67.53)	15112 (27.85)	1781 (23.34)	193 (39.58)

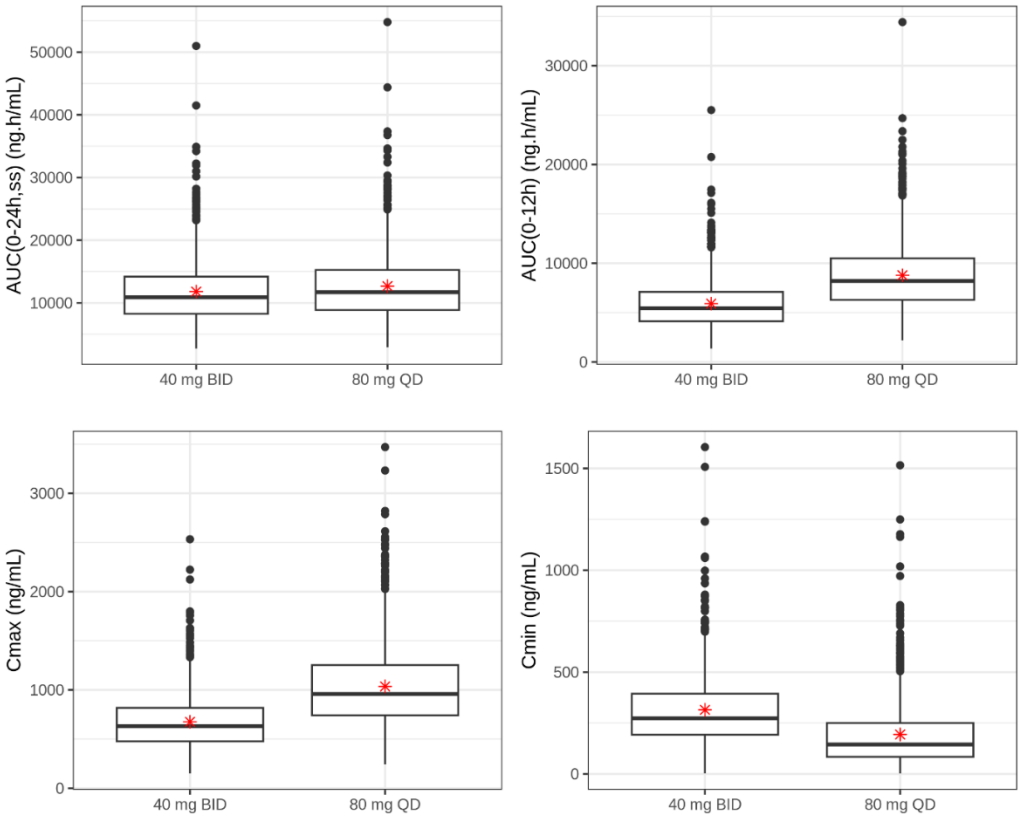
Figure 5: *Visual predictive check showing overlay of observed and predicted PK profiles*



vob/CABL001A/mas/mas_3/model/pgm_008/PlotOverlayObsVsPred2.R -> /output_008/VPCABL001PK3A.png
Model: vob/CABL001A/mas/mas_3/model/pgm_008/PopPK/Run13A.mlxtran

Grey dots: observations. Blue solid lines: 50th percentiles of the observed PK data; red solid lines: 2.5th and 97.5th percentiles of observed PK data. Blue shades: 95% confidence interval of 50th percentiles of the predictions from 200 replicates. Red shades: 95% confidence interval of 2.5th and 97.5th percentiles of the predictions.

Figure 6: Boxplots comparing PopPK-predicted PK parameters of asciminib 40 mg BID and 80 mg QD at steady state



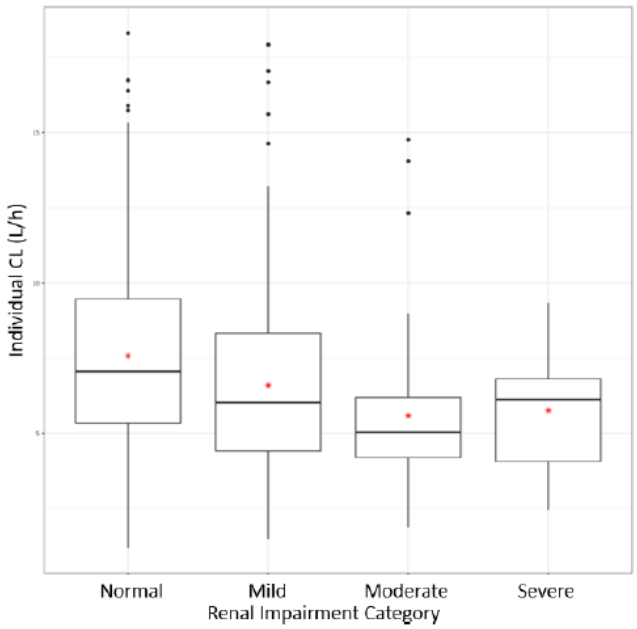
2.3.3. Special populations

Renal impairment

The revised PopPK analysis included 348 subjects with normal renal function, 233 subjects with mild renal impairment, 48 subjects with moderate renal impairment, and 8 subjects with severe renal impairment, based on aGFR (absolute GFR) at baseline by MDRD.

Clearance was lower in patients with mild, moderate and severe renal impairment compared to those with normal renal function (Figure 7). However, these results should be interpreted with caution, given the limited number of subjects in the moderate (n=48, 7.5%) and severe (n=8, 1.3%) renal impairment categories. The impact of renal function was not statistically significant, suggesting that no dose adjustment is necessary.

Figure 7: Correlation between renal impairment category and clearance



Derived from popPK report Figure 7-3

Hepatic impairment / liver function

The patients in the CML studies were enrolled based on liver function tests and classified according to NCI liver function criteria.

The popPK report highlighted that while for the primary analysis of the dedicated hepatic impairment study A2103 subjects were assigned to hepatic function groups based on the Child-Pugh classification, for the purposes of exploratory analysis in phase III study A2301 and for the analyses in the popPK report, subjects were (re-)classified according to the NCI-ODWG liver function criteria. There seemed to be a low degree of concordance between the assessments made by Child-Pugh classification and NCI criteria in study A2301 which led to discrepancies in the popPK in proportions of A2103 subjects in the various hepatic function categories (subject numbers enrolled by Child-Pugh per severity class 8:8:8:8; re-classified by NCI 17:6:4:5 normal/mild/moderate/severe subjects).

No correlation between liver function by NCI-ODWG criteria and clearance was observed in the popPK model.

2.3.4. Genetic differences in pharmacokinetics

As asciminib is mainly metabolized via UGTs (UGT2B7 [28%], UGT2B17 [16%], UGT1A3/4 [14%]) (in total ~60%) and CYP3A4 (~35%), previously the effect of UGT2B7 and UGT2B17 genetic variants on the PK of asciminib (Ctrough) in samples from study A2301 was analysed and polymorphisms for both UGTs did not have a clinically relevant effect on PK.

In **study J12301** (report DMPK-RC4009521-OTHER), of 200 patients 149 patients had valid data for UGT2B7 and 151 patients had valid data for UGT2B17. For UGT2B7 there were four different phenotypes: intermediate (5/149, 3%), normal (58/149, 39%), rapid (58/149, 39%), and ultra-rapid metabolizer (28/149, 19%). For UGT2B17 there were three different phenotypes: intermediate (66/151, 44%), normal (44/151, 29%), and poor metabolizer (41/151, 27%).

Among the different UGT2B7 phenotypes, no statistically significant difference was observed (Kruskal-Wallis test, p-value of 0.064), neither for different UGT2B7 allele combinations (Table 5).

Table 5 Summary statistics of Ctrough levels (ng/mL) by UGT2B7 phenotype, study J12301

Statistics	Intermediate Metabolizer	Normal Metabolizer	Rapid Metabolizer	Ultrarapid Metabolizer
N	5	57	55	28
QC pass	5 (100%)	57 (100%)	55 (100%)	28 (100%)
Mean (SD)	165 (178)	195 (109)	222 (136)	232 (110)
Median (Min-Max)	117 (56-245)	168 (146-194)	196 (172-222)	209 (175-249)
Geometric mean	108	161	182	209
95% CI for geometric mean	61-480	50-496	91-866	80-480

Among the different UGT2B17 phenotypes, no statistically significant difference was observed (Kruskal-Wallis test, *p*-value = 0.762) neither for different UGT2B17 allele combinations (Table 6).

Table 6 Summary statistics of Ctrough (ng/mL) levels by UGT2B17 phenotype, study J12301

Statistics	Intermediate Metabolizer	Normal Metabolizer	Poor Metabolizer
N	64	42	41
Mean (SD)	214 (114)	216 (154)	198 (96)
Median (Min-Max)	186 (163-213)	183 (155-215)	177 (153-206)
Geometric mean	179	161	185
95% CI for geometric mean	50-487	80-866	60-456

2.3.5. Pharmacodynamics

Mechanism of action

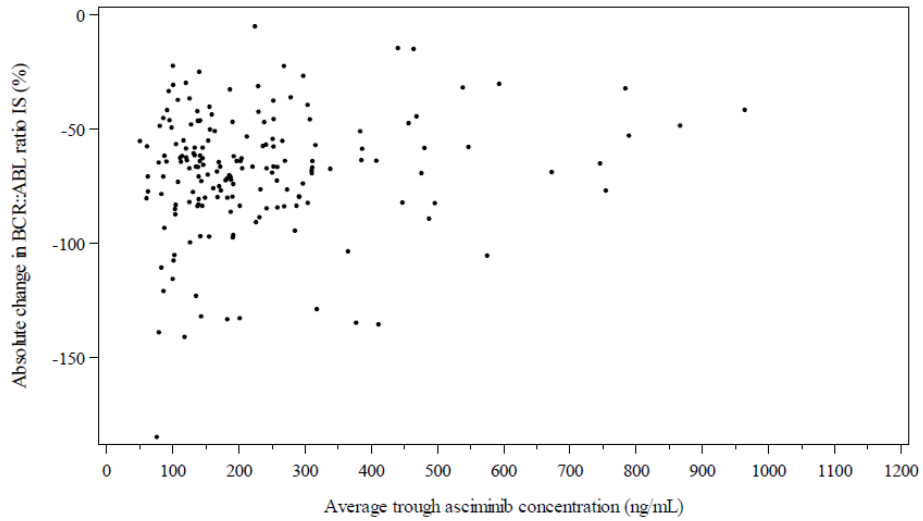
Asciminib is a potent inhibitor of BCR::ABL1 tyrosine kinase. BCR::ABL1 is a chimeric oncoprotein with the constitutively active ABL1 tyrosine kinase domain. Asciminib, by specifically targeting the allosteric myristoyl binding pocket on the SH1 domain of ABL1, inhibits the ABL1 kinase activity of the BCR::ABL1 fusion protein.

Primary and secondary pharmacology

Primary pharmacology

1L study J12301 evaluated BCR::ABL ratio IS (%) change from baseline vs. average trough asciminib concentration at week 48 (*Figure 8*a).

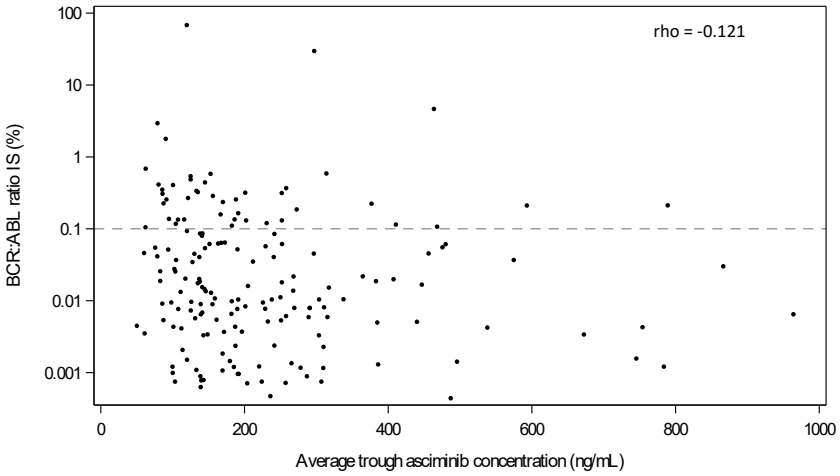
Figure 8a: BCR::ABL ratio IS (%) change from baseline vs. average trough asciminib concentration at week 48 - 1L study J12301



Updated CSR J12301 w96 Figure 14.2-6.1

In Figure 8b, the individual BCR::ABL IS (%) values at Week 48 vs. average trough concentrations (Cmin) are provided. In line with change from baseline, a shallow correlation (rho = -0.121) is apparent between BCR::ABL IS (%) and average Cmin.

Figure 8b: Average asciminib trough concentrations vs. BCR::ABL1 ratio (IS%) at week 48 – 1L study J12301



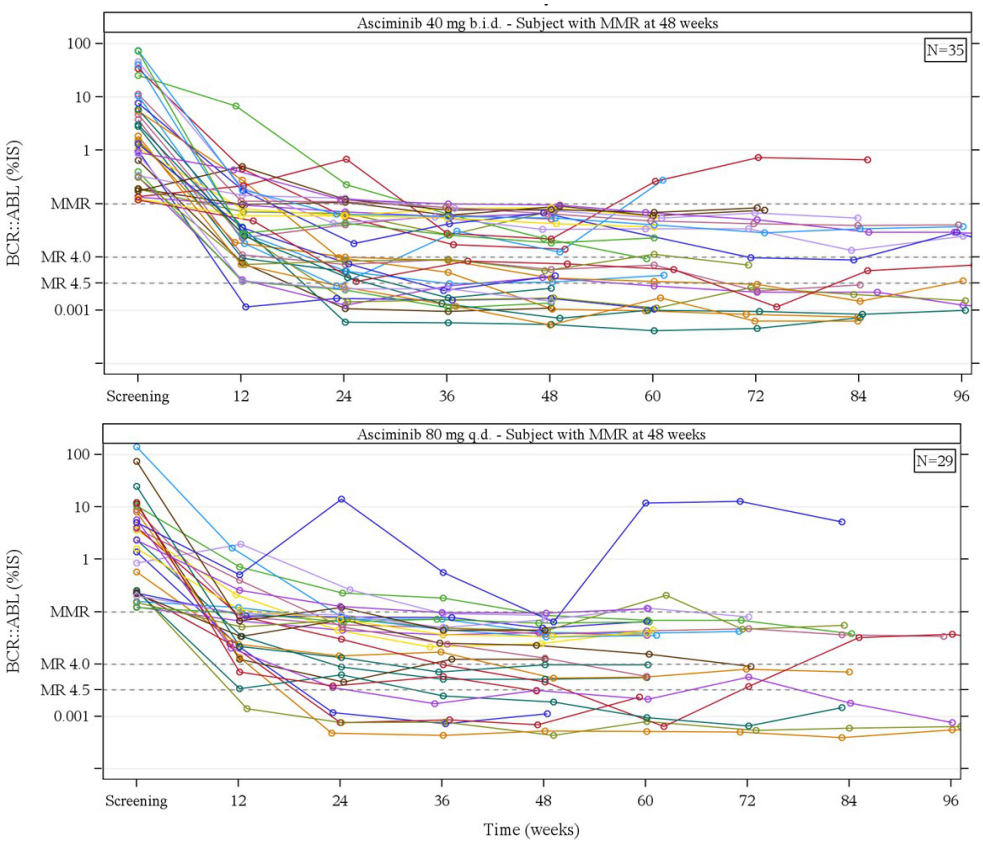
Source: Response to 1. RSI, Figure 2-3

Study A2302 in TKI-pretreated 3L+CML-CP patients - 40 mg BID vs. 80 mg QD

Study A2302 was a phase IIIb, multi-centre, open-label, treatment optimization study of oral asciminib in TKI-pretreated patients with CML-CP (3L+) to estimate the MMR rate at Week 48 of all subjects (40 mg BID and 80 mg QD) with CML-CP following two or more prior TKI treatments and with no evidence of MMR at baseline. No PK sampling was performed but sampling for biomarkers.

For the patients without MMR at baseline the BCR::ABL1 (%IS) ratio plot in MMR (≤ 0.1%) at Week 48 in each dose group is shown in *Figure 9*. The BCR::ABL1 ≤ 1% rate was numerically higher in the 40 mg BID group (range: 61.2% to 64.7%) than the 80 mg QD group (range: 53.6% to 64.3%) at each timepoint except Week 36.

Figure 9: BCR::ABL1 (% IS) plot over time (Full analysis set) – Study A2302



Source: Study A2302 W48 CSR - Figure 14.2-1.4

Secondary pharmacology

Treatment-emergent secondary *BCR::ABL1* gene mutations

In **1L study J12301** at baseline, the majority of patients in both treatment arms had no mutations in the *BCR::ABL1* gene (97.0% in the asciminib arm vs. 96.6% of participants in the IS-TKI arm). Four patients in total had single mutations observed at baseline. No new post-baseline mutations were detected (until the Week 96 data cut off) in these 4 patients.

At Week 96 DCO, there were 10 (5.0%) patients in the asciminib arm with postbaseline treatment-emergent *BCR::ABL1* gene mutations, typically appearing at Weeks 24 - 36. (Table 7). Of these 10 patients, 9 discontinued treatment and 1 had treatment ongoing. The reasons for treatment discontinuation included treatment failure per ELN criteria 2020 in 6 participants; and unsatisfactory therapeutic effect, progressive disease, and confirmed loss of MMR in 1 participant each.

The mutations observed in the asciminib arm were distinct and non-overlapping with the IS-TKI arm. All post-baseline mutations in the asciminib arm were in the myristoyl pocket or functionally adjacent area of the KD domain, while a majority of postbaseline mutations in the IS-TKI arm were in the P-loop, adjacent to the ATP binding site. Valine and threonine exchanges at A337 were the most frequently observed mutations in asciminib arm (7 out of 10 patients with treatment-emergent mutations in the asciminib arm).

Table 7: Post-baseline treatment-emergent BCR::ABL1 gene mutations (FAS)

Post-baseline mutations	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 (%)
A337T[1]/A344P[1]/I502N[1]/P465Q[1]	0	1 (1.0)	1 (0.5)	0	0	0
A337T[1]/F497L[1]	1 (1.0)	0	1 (0.5)	0	0	0
A337T[1]/L340Q[1]	0	1 (1.0)	1 (0.5)	0	0	0
A337T[1]/V506M[1]	1 (1.0)	0	1 (0.5)	0	0	0
A337T[1]	1 (1.0)	0	1 (0.5)	0	0	0
A337V[1]	0	1 (1.0)	1 (0.5)	0	0	0
A337V[1]/V506M[1]	1 (1.0)	0	1 (0.5)	0	0	0
A433D[1]	1 (1.0)	1 (1.0)	2 (1.0)	0	0	0
E255V[2]/G250E[2]/L248V[2]	0	0	0	1 (1.0)	0	1 (0.5)
E450G/L248V[2]	0	0	0	1 (1.0)	0	1 (0.5)
E459K[2]	0	0	0	1 (1.0)	0	1 (0.5)
F317L[2]	0	0	0	1 (1.0)	0	1 (0.5)
L340Q[1]	0	1 (1.0)	1 (0.5)	0	0	0
Y253H[2]	0	0	0	0	3 (2.9)	3 (1.5)
Total	5 (5.0)	5 (5.0)	10 (5.0)	4 (3.9)	3 (2.9)	7 (3.4)

[1] Mutations in the myristoyl pocket or functionally adjacent area of the KD domain (Eide et al 2019).
[2] Mutations in the P-loop (Soverini et al 2011).
A participant with multiple mutations is counted only once.
Total row shows the number of participants with any treatment emergent *BCR::ABL1* gene mutations.
Source: Table 14.2-11.4

Table 11-18 CSR J12301 week 96

In **3L+ study A2302** at baseline, 25 (14.8%) participants had at least one BCR::ABL1 gene mutation of which 2 (1.2%) participants had more than one mutation. Post-baseline, 90 participants were assessed for mutations at any timepoint post-baseline, and the mutations are presented in *Table 8*.

Table 8: Post-baseline BCR::ABL1 gene mutations by central lab (Full analysis set) – Study A2302

	Asciminib 40 mg b.i.d. N=85 n (%)	**Asciminib 80 mg QD N=84 n (%)**	**All participants N=169 n (%)**
Total participants assessed for mutation at any timepoint post baseline (m)	44	46	90
Mutation			
p.Met244Val(244M>V)	4 (9.09)	2 (4.35)	6 (6.67)
p.Thr315Ile(315T>I)	0	3 (6.52)	3 (3.33)
p.Phe317Leu(317F>L)	1 (2.27)	1 (2.17)	2 (2.22)
p.Phe359Val(359F>V)	0	2 (4.35)	2 (2.22)
p.Ala433Thr(433A>T)	0	1 (2.17)	1 (1.11)
p.Ala68Pro(68A>P)	0	1 (2.17)	1 (1.11)
p.Gln252His(252Q>H)	0	1 (2.17)	1 (1.11)
p.Glu453Lys(453E>K)	0	1 (2.17)	1 (1.11)
p.Glu459Lys(459E>K)	1 (2.27)	0	1 (1.11)
p.Gly250Glu(250G>E)	1 (2.27)	0	1 (1.11)
p.Phe359Ile(359F>I)	1 (2.27)	0	1 (1.11)
p.Pro465Ala(465P>A)	1 (2.27)	0	1 (1.11)
Not all randomised participants were analysed for post baseline mutation. Percentages calculated taking Total participants assessed for mutation at any timepoint post baseline (m) as denominator.			

Table 9: Newly emergent or persistent mutations in the asciminib treatment arm in Study J12301 and Study A2302(Week 48 cut-off)

Study J12301 (1L)	**Study A2302 (3L+)**
New:	*New:*
A337T	A68P
A337V	P465A
A344P	A433T
A433D	F359V
F497L	M244V
I502N	Q252H
L340Q	*Persisted:*
P465Q	E453K
V506M	F317L
Persisted:	G250E
M244V	

2.3.6. PK/PD modelling / exposure-response relationships

The PK-PD dataset included in total 430 patients with CML-CP from study J12301 (data cut- off date of 28-Nov-2023), A2301 (data cut-off date of 22-Mar-2023), and X2101 (data cut-off date of 14-Mar-2023). Patients with the T315I mutation were excluded. At baseline, 327 of the 430 patients (76%) had BCR::ABL1 IS levels >10%. The ERR analysis for efficacy was a retrospective modelling that utilized data from clinical trials of which none were designed to investigating relationships between PK metrics and clinical outcomes.

Exposure - Efficacy

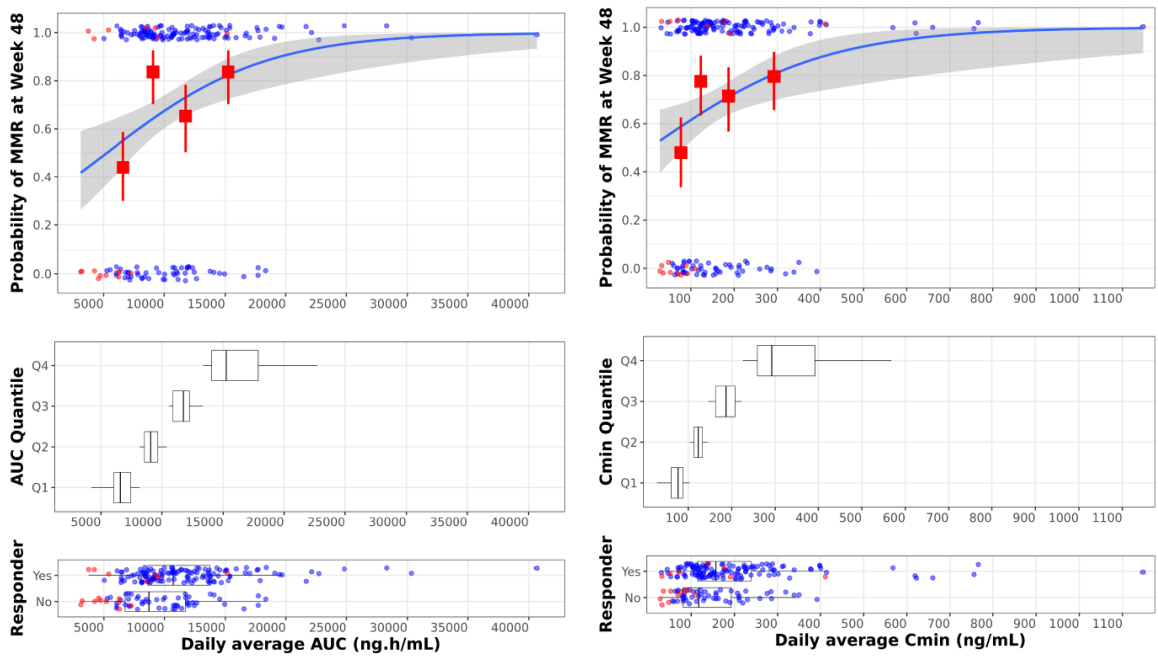
First line (1L) CML-CP

The result of the logistic regression showed positive relationship between exposure metrics (average daily AUC0-24 and Cmin) 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 (~45%) for the first quartile (Q1) of exposure metrics and no correlation for quartiles Q2-Q4 of AUC0-24 and Cmin. The response was constant between 70% to 80% from Q2-Q4, suggesting the response has reached plateau by Q2. Relatively more patients in Q1 exposure had a relative dose intensity (RDI) ≤75% as represented by red dots, contributing to the lower MMR rate. (Figure 10)

The mean (CV%) predicted steady-state AUC0-24 and Cmin from the PopPK model would be close to Q3 average daily AUC and Cmin in Figure 3, respectively. Overall, the dose of 80 mg QD provided sufficient exposure for showing robust and sustained efficacy in patients with newly diagnosed Ph+ CML-CP without T315I mutation.

Figure 10: Exposure-efficacy relationship between the probability of achieving MMR at Week 48 and daily average AUC0-24 (left) and Cmin (right) from prior 48 weeks (top); distribution of quartiles (middle); spread between responders and non-responders (bottom) – 1L Study J12301



Source ERR model report Figures 5-1 and 5-2

3L+ CML-CP

For 3L+ CML, the ERR model-predicted MMR rates for asciminib 80 mg QD and 40 mg BID at Week 24 and Week 48, assuming maintenance of uninterrupted dosing, were as follows (Table 10):

Table 10: ERR model-predicted MMR rates for asciminib 80 mg QD and 40 mg BID at Week 24 and Week 48 in 3L+

Dosing regimen	Time of readout	Predicted MMR rates mean [95% CI]	Observed MMR rates Estimate [95% CI]	Reference
40 mg b.i.d.				
	Week 24	36.1% [33.0, 39.6]	35.3% [25.2, 46.4]	A2302 (n=85)
			25.5% [18.9, 33.0]	ASCEMBL (n=157)
	Week 48	42.6% [38.4, 46.0]	42.4% [31.7, 53.6]	A2302 (n=85)
			29.3% [22.3, 37.1]	ASCEMBL (n=157)
80 mg q.d.				
	Week 24	32.8% [29.2, 36.0]	29.8% [20.3, 40.7]	A2302 (n=84)
	Week 48	39.6% [35.4, 43.0]	34.5% [24.5, 45.7]	A2302 (n=84)

Note: Observed MMR rates in A2302 and ASCEMBL trials are in third line setting. ASCEMBL trial only evaluated 40 mg b.i.d.

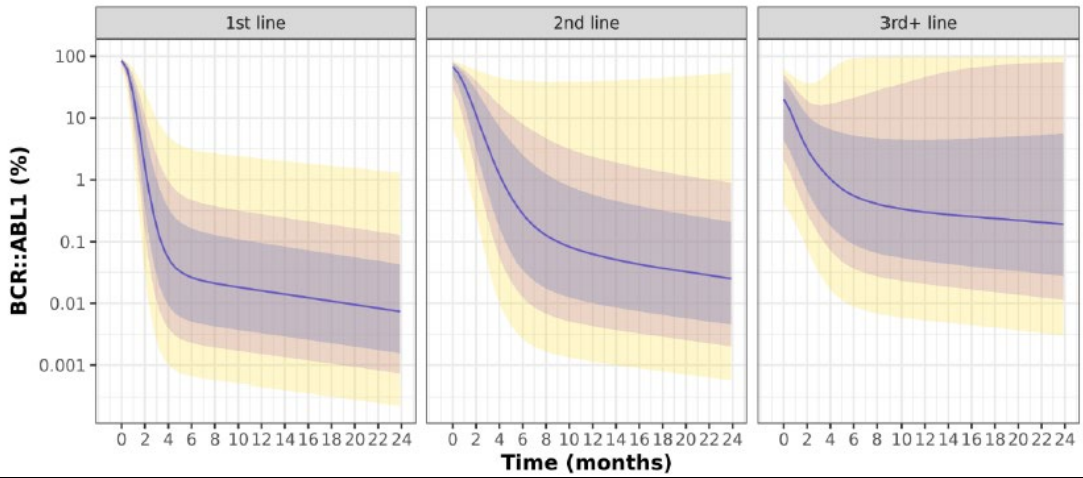
2L CML-CP

As asciminib 2L data were not available, extrapolation into the 2L setting assumed that nilotinib and asciminib had similar differences in model parameters between 1L and 2L settings and the longitudinal BCR::ABL1 in the 2L for asciminib was simulated using the same difference in model parameters as that for nilotinib (model also submitted). For the extrapolation into 2L, the predicted MMR rate, assuming a total daily dose of 80 mg without dose interruption, ranged from 54 to 63% ± 2% at Week 48 and 66 to 74% ± 2% at Week 96, respectively.

Line-independent 80 mg total-daily dose regimen

Assuming a total daily dose of 80 mg (80 mg QD or 40 mg BID) without interruption, time courses of BCR::ABL1 rates in the 1L to 3L+ setting were simulated with the EER model, including the extrapolation into 2L setting (Figure 10a).

Figure 10a: EER model-predicted time-course of BCR::ABL1 in 1L, 2L, and 3L settings after a total daily dose of 80 mg asciminib



This plot presents the simulation based on Scenario 2 with parameters listed in [Exposure-efficacy Report-Table 4-2].
Blue line represents median; Purple shaded area represents 25th and 75th prediction percentiles; Pink shaded area represents 15th and 85th prediction percentiles; Yellow shaded area represents 5th and 95th prediction percentiles.
Source: Exposure-efficacy Report-Figure 5-10

Safety

According to the **A2302** CSR the number of patients with 80 mg QD with TEAEs to those with 40 mg BID (88.1 vs. 90.5%) of which fatigue was increased >3-fold (14.3 vs 3.6%). No difference was observed in AEs leading to discontinuation or dose reduction.

In the **safety ERR model** safety events from 1L and 3L+ studies over the full administered dose levels were evaluated. The PK-Safety Set included 550 participants (40.0% female and 60.0% male); 353 were pretreated and 197 newly diagnosed participants. 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 was as expected. 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.

2.3.7. Discussion on clinical pharmacology

This group of variations concerned an extension of indication to newly diagnosed (1L) CML-CP patients with 80 mg QD or 40 mg BID with PK data from study J12301 as well as the addition of the 80 mg QD dose regimen as alternative to the approved 40 mg BID for the 3L+ CML-CP population with PK data from study A2302. In addition, new modelling for popPK and exposure-response was included to also support an intrapolation to a 2L indication without clinical PK data and for an overall line independent dosing with either 40 mg BID or 80 mg QD, i.e. a total-daily-80 mg-dose regimen.

Pharmacokinetics

Primary PK parameter for the 1L population with 80 mg QD in study J12301 were in the same ranges as known from the approved populations in later treatment lines. The steady-state (geo-mean) Cmax was 1470 ng/mL (geo-mean CV% 38.2%), AUClast (i.e. AUC0-12) was 8590 ng*hr/mL (CV% 42.2%), Cmin ranged between 161 -192 ng/ml and Tmax was at 2.0 hours. The PK parameters derived from NCA and popPK model (with the updated model) could be regarded similar, i.e. within the observed inter-individual variability for asciminib.

From popPK modelling and on basis of a "daily dose of 80 mg" as underlying regimen, estimated clearance was 6.89 l/h and did not differ relevantly between 0 – 7 lines of TKI-pre-treatments. However, it is highlighted that in response to a respective question during initial MAA for comparison between the regimens 80 mg QD and 40 mg BID, the MAH had updated the popPK model to include regimen (QD/BID) as covariate instead of total daily dose. In the current updated model, again total daily dose was chosen as a covariate on clearance. With the updated model, including regimen as covariate, no statistically significant differences between the two regimens (40mg BID and 80mg QD) were detected. The comparison of PK metrics between regimens showed comparable AUC, i.e. within the observed inter-individual variability for asciminib, but lower Cmin and higher Cmax for 80 mg QD compared to 40 mg BID, as expected.

Modelling of special populations estimated no clinically relevant differences for gender, body weight, race, and elderly warranting dose adjustments in the PK of asciminib, in line with previous

conclusions. For renal impairment, lower clearance was estimated with increasing severity of impairment, i.e. reducing GFR. However, for severe renal impairment the dataset is very limited. Therefore, no additional conclusions could be drawn and the relevant recommendations in the SmPC should remain unchanged.

For hepatic impairment, the popPK dataset comprised both the dedicated HI study and patient studies. As classifications by reduced liver function based on liver function tests and by NCI-ODWG criteria do not correlate, no additional definite conclusions can be drawn with regard to Child-Pugh-categorised hepatic impairment outside from studied parameters. Therefore, the relevant recommendations in the SmPC should remainunchanged.

Asciminib is mainly (~60%) metabolised via UGT enzymes which show genetic polymorphism. The analysis of Ctrough levels for different phenotypes in study J12301 did not result in statistically significant differences between intermediate to ultrarapid metabolisers for UGT2B7 and between intermediate to poor metabolisers for UGT2B17.

Pharmacodynamics

Asciminib is a potent inhibitor of BCR::ABL1 tyrosine kinase targeting the allosteric myristoyl binding pocket on the SH1 domain of ABL1, restoring the inactive kinase conformation. Thus, BCR::ABL IS (%) ratio is used as biomarker/measure for pharmacodynamics and efficacy in CML-CP.

When taking the NCA-derived Cmin range (161-192 ng/ml) from the 1L study J12301 as basis, which is lower than the current popPK-model derived measure, the unbound concentration (f_u 2.7%) is ~4.7 ng/ml which is not relevantly higher than the IC_{50} of 0.6 nM (inhibition of proliferation in cell assay). In other assays the IC_{50} had even been higher.

In 1L study J12301 at 80 mg QD, no correlation of Ctrough levels at week 48 to BCR::ABL IS (%) change from baseline could be observed. Only a very slight Ctrough exposure-response correlation to achieving MMR (i.e. 0.1% IS ratio) at week 48 was detectable, however it could be derived that for deeper molecular responses higher average trough concentrations seem more advantageous.

Corresponding ERR analyses for 1L study J12301 revealed that at the levels of steady-state Cmin a 70-80% probability of MMR at week 48 could be obtained. However, dose reductions to ≤75% RDI with resulting lower Cmin correlated with a lower probability of achieving MMR, or even non-response.

The MAH proposes the 40 mg BID or the 80 mg QD regimen independently of treatment line, i.e. an 80 mg daily-dose regimen, and has correspondingly revised the dosing recommendations in section 4.2 of the SmPC to state: "*The recommended total daily dose of Scemblix is 80 mg. Scemblix can be taken orally either as 80 mg once daily at approximately the same time each day, or as 40 mg twice daily at approximately 12-hour intervals*." Considering that the ERR demonstrated that with higher average Cmin, which would usually be observed with a 40 mg BID regimen rather than with an 80 mg QD regimen of 80 mg total daily dose, a higher probability of MMR would be achievable, this proposal could be supported for the 1L population.

However, on the other hand, the evaluation of BCR::ABL1 (% IS) rate over time in the 3L+ population in study A2302 revealed that the BCR::ABL1 ≤ 1% rate was numerically higher in the 40 mg BID group (range: 61.2% to 64.7%) than the 80 mg QD group (range: 53.6% to 64.3%) at each timepoint except Week 36. Also, the achievement of a comparable response was slower for the 80 mg QD regimen in the 3L+ population.

The observed MMR rate in 3L+ study A2302 at week 48 was nearly 8% higher in the 40 mg BID vs. the 80 mg QD group, supporting the need of continued sufficiently high exposure at the target structures for adequate inhibition and response, which can usually be better achieved with a BID regimen.

Safety ERR data show no obvious association between exposure and most safety events based on the comparable average exposure with the 40 mg BID and 80 mg QD asciminib dose regimens. So, with respect to safety ERR modelling the interchangeability of these two dosing regimens in the 3L+ population could be supported.

When considering molecular response, however, a nearly 8% lower rate of MMR in 3L+ CML treatment could become clinically relevant. So, it might be individually necessary and appropriate to switch the approved BID dosing to a QD dosing regimen in the 3L+ population, as the twice daily fasted intake of asciminib may be difficult for satisfactory compliance in all patients. On the other hand, dose reductions for adverse events could result also in reduced exposure and response rates, as observed in the 1L study, which could impact efficacy.

In addition, the MAH provided model estimates of MMR rate intrapolated to a potential 2L CML-CP population, which can be followed and are acceptable with the proposed 80 mg daily-dose regimen.

Both studies in 1L and 3L+ CML-CP also evaluated treatment-emergent secondary BCR::ABL1 gene mutations. As could be expected for a newly diagnosed untreated population 97% of the patients in study J12301 had no BCR::ABL1 gene mutations at baseline. During treatment new mutations were found in 5% of patients, most of them discontinued treatment for treatment failure/progress. The BCR::ABL1 gene mutations under asciminib treatment were all located in or near the asciminib binding myristoyl pocket. In contrast, the new mutations in the comparator-TKI treatment arm were near the ATP binding site, meaning that treatment-emergent secondary mutations were not overlapping between arms.

In the 3L+ pre-treated patient group in study A2302 15% of patients had mutations of BCR::ABL1 at baseline and the MAH provided summary tabulations of mutations at baseline and newly emergent under treatment for both studies. The post-baseline mutations that occurred during asciminib treatment in the pre-treated CML population were different to those detected in the 1L population. Here, under asciminib treatment new mutations occurred both near the asciminib binding site and near the ATP binding site. In 3 patients new occurrence of T315I was observed under 80 mg QD, but not in the 40 mg BID arm.

Most of these detected new mutations are already known e.g. from imatinib-resistant patients (Soverini, 2011). A337T/V was detected after 1L treatment with asciminib only and is described as an asciminib-specific mutation completely inhibiting BCR::ABL1 (Leyte-Vidal, 2024; Manley, 2020). Other mutations, such as M244V were observed both after 1L and 3L treatment or persisted it. This mutation was also recently published as a further novel resistance mechanism to class IV TKIs such as asciminib. The mutations are all in line with those described as specifically conferring resistance to asciminib in the 2025 ELN recommendations for management of CML (Apperley, 2025). As discussed in the referenced publications, for most asciminib treatment-emergent mutations other TKIs are available which target and can rescue these mutations.

These exploratory small datasets can only support to broaden the picture of resistance mechanisms to asciminib and insofar, it is endorsed that the 1L study J12301 clinical study protocol was amended to collect mutational data during survival follow-up, which will be included in the final CSR (see Annex II).

The above assessment supports dose recommendations under section 4.2 of the on the option to take asciminib either as 80 mg once daily at approximately the same time each day, or as 40 mg twice daily at approximately 12-hour and on the possibilities to switch between the two as necessary for the benefit of the patient.

2.3.8. Conclusions on clinical pharmacology

The clinical pharmacology dataset of asciminib submitted in the current group of variations for supporting the 1L CML-CP treatment with 40 mg BID or 80 mg QD (i.e. an 80 mg total daily dose regimen), the inclusion of the 80 mg QD regimen as alternative for the previously approved 3L+ CML-CP population and the intrapolation of asciminib treatment to the adult 2L CML population, is considered appropriate. The PK data are considered consistent with previous PK data from the patient population in the currently approved setting.

The clinical pharmacology data supporting this group of variations is sufficient to support the posology recommendations.

Study J12301 clinical study protocol was amended to collect mutational data during survival follow-up, and this will be reported in the final CSR (see Annex II).

2.4. Clinical efficacy

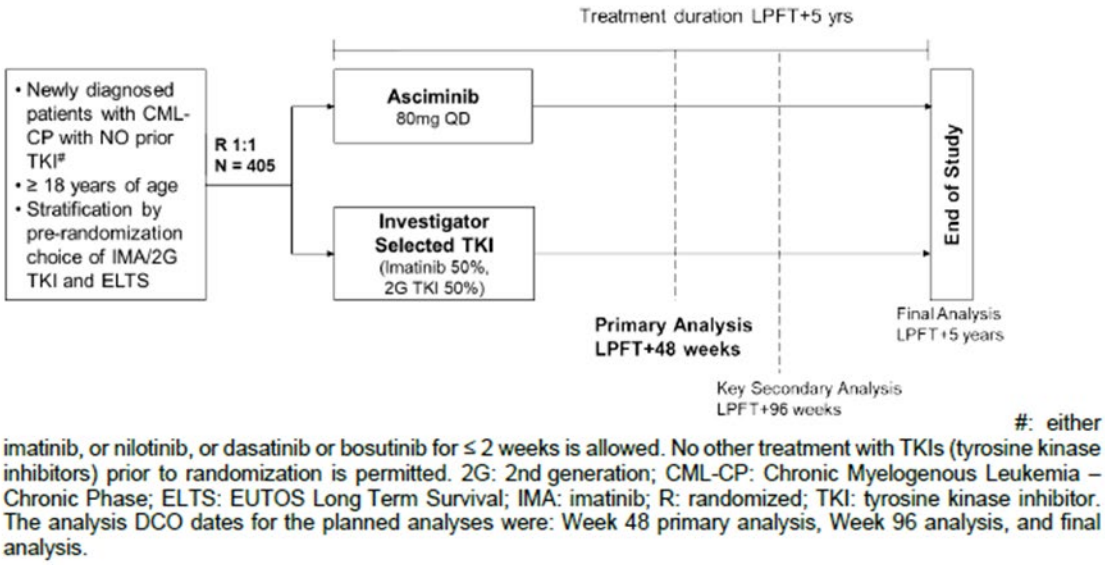
2.4.1. Main study

Phase III study CABL001J12301: Open label, multi-centre, randomised study of oral asciminib vs. Investigator selected TKI to determine efficacy, safety, PK, and tolerability of asciminib 80 mg QD in participants with newly diagnosed Ph+ CML-CP (ASC4FIRST, NCT 04971226)

Methods

Study design

The pivotal study for the extension of indication to CP-CML-CP 1st line treatment is an ongoing phase III, randomised (1:1)-controlled, open-label, multicentre, superiority trial, J12301 (ASC4FIRST), comparing asciminib 80 mg QD monotherapy with investigator's selected TKI (imatinib 400 mg QD, nilotinib 300 mg BID dasatinib 100 mg QD or bosutinib 400 mg QD) in estimated 402 patients with CML-CP.



#: either imatinib, or nilotinib, or dasatinib or bosutinib for ≤ 2 weeks is allowed. No other treatment with TKIs (tyrosine kinase inhibitors) prior to randomization is permitted. 2G: 2nd generation; CML-CP: Chronic Myelogenous Leukemia – Chronic Phase; ELTS: EUTOS Long Term Survival; IMA: imatinib; R: randomized; TKI: tyrosine kinase inhibitor. The analysis DCO dates for the planned analyses were: Week 48 primary analysis, Week 96 analysis, and final analysis.

Figure 11: Design study J12301 (ASC4FIRST)

Table 11 Overview of Phase III registration study - Study J12301

Key features	CABL001J12301
Phase	III
Study design	Open label, multi-centre, randomised study of oral asciminib vs. Investigator selected TKI to determine efficacy, safety, PK, and tolerability of asciminib 80 mg QD in participants with newly diagnosed Ph+ CML-CP QD in participants with newly diagnosed Ph+ CML-CP.
No. participants (total)	405
Population	Adult, treatment-naive participants with newly diagnosed Ph+ CML-CP (within 3 months of diagnosis)
Treatment duration	Participants in the study will continue to receive the assigned treatment until the End of Study (5 years from last participant first treatment), or until premature discontinuation due to treatment failure, disease progression or intolerance or due to Investigator or participant decision.
Treatment(s)	asciminib 80 mg QD imatinib 400 mg QD nilotinib 300 mg BID dasatinib 100mg QD bosutinib 400mgQD
Completed/Ongoing	Ongoing FPFV: 06-Oct-2021 Data cut-off date for the Week 48 primary analysis: 28-Nov-2023 Data cut-off date for the Week 96 key secondary analysis: 22-Oct-2024

Justification for the selected dose

The asciminib dose of 80 mg QD for participants with newly diagnosed Ph+ CML-CP was selected based on the 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 modelling-based exposure-response and exposure-safety analyses.

Study participants

The population consisted of adult participants with newly diagnosed Ph+ CML-CP (diagnosed within 3 months prior to enrolment). The definition of Ph+ CML-CP was according to the ELN 2020 criteria.

Key inclusion criteria:

- Male or female participants ≥ 18 years of age
- Signed informed consent must be obtained prior to any study related screening procedures being performed.
- Participants with CML-CP within 3 months of diagnosis.
- Diagnosis of CML-CP (ELN 2020 criteria) with cytogenetic confirmation of the Philadelphia chromosome
    - < 15% blasts in peripheral blood and bone marrow
    - < 30% blasts plus promyelocytes in peripheral blood and bone marrow
    - < 20% basophils in the peripheral blood
    - Platelets count ≥ 100,000/mm3
    - No evidence of extramedullary leukemic involvement, except for hepatosplenomegaly
- Evidence of typical BCR::ABL1 transcript [e14a2 and/or e13a2] at the time of screening which are amenable to standardized RQ-PCR quantification.
- ECOG performance status of 0, or 1.
- Adequate end organ function as defined by 1) Total bilirubin (TBL) < 3 × ULN; participants with Gilbert's syndrome may only be included if TBL ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN 2) CrCl ≥ 30 mL/min as calculated using Cockcroft-Gault formula 3) Serum lipase ≤ 1.5 × ULN. For serum lipase > ULN - ≤ 1.5 × ULN, value must be considered not clinically significant and not associated with risk factors for acute pancreatitis
- Participants must have the following laboratory values within normal limits or corrected to within normal limits with supplements prior to randomization: 1) Potassium (potassium increase of up to 6.0 mmol/L is acceptable if associated with CrCl* ≥ 90 mL/min) 2) Total calcium (corrected for serum albumin); (calcium increase of up to 12.5 mg/dl or 3.1 mmol/L is acceptable if associated with CrCl* ≥ 90 mL/min) 3) Magnesium (magnesium increase of up to 3.0 mg/dL or 1.23 mmol/L if associated with CrCl ≥ 90 mL/min) 4) For participants with mild to moderate renal impairment (CrCl* ≥ 30 mL/min and < 90 mL/min) - potassium, total calcium (corrected for serum albumin) and magnesium should be ≥ LLN or corrected to within normal limits with supplements prior to randomisation.

Key exclusion criteria

- Previous treatment of CML with any other anticancer agents including chemotherapy and/or biologic agents or prior stem cell transplant, with the exception of hydroxyurea and/or anagrelide. Treatment with either imatinib, or nilotinib, or dasatinib or bosutinib for ≤ 2 weeks

is allowed. No treatment with other tyrosine kinase inhibitors prior to randomization is permitted.

- Known cytopathologically confirmed CNS infiltration (in absence of suspicion of CNS involvement, lumbar puncture not required)
- Impaired cardiac function or cardiac repolarization abnormality including but not limited to any one of the following:
    - History within 6 months prior to starting study treatment of myocardial infarction (MI), angina pectoris, coronary artery bypass graft (CABG).
    - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II- and third-degree AV block).
    - QTc ≥ 450 ms (male participants), ≥ 460 ms (female participants) on the average of three serial baseline ECG (using the QTcF formula) as determined by central reading. If QTcF ≥ 450 ms and electrolytes are not within normal ranges, electrolytes should be corrected and then the participant re-screened for QTc.
- Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
    - Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia.
    - Concomitant medication(s) with a "Known risk of Torsades de Pointes" per //.crediblemeds.org/ that cannot be discontinued or replaced 7 days prior to starting study drug by safe alternative medication.
    - Inability to determine the QTcF interval.
- Severe and/or uncontrolled concurrent medical disease that in the opinion of the Investigator could cause unacceptable safety risks or compromise compliance with the protocol (e.g., uncontrolled diabetes, active or uncontrolled infection; uncontrolled arterial or pulmonary hypertension, uncontrolled clinically significant hyperlipidemia).
- History of significant congenital or acquired bleeding disorder unrelated to cancer.
- Major surgery within 4 weeks prior to study entry or who have not recovered from prior surgery.
- History of other active malignancy within 3 years prior to study entry with the exception of previous or concomitant basal cell skin cancer and previous carcinoma in situ treated curatively.
- History of acute pancreatitis within 1 year prior to randomization or medical history of chronic pancreatitis.
- History of chronic liver disease leading to severe hepatic impairment, or ongoing acute liver disease.

Treatments

The treatments administered in this study included:

Arm 1: Asciminib 80 mg QD under fasting conditions

For participants randomised to the asciminib treatment arm, dose escalation beyond 80 mg QD for asciminib was not permitted.

Arm 2: IS-TKI that included one of the below treatments as per the PRS-TKI (imatinib or the 2G TKI nilotinib or dasatinib or bosutinib).

- Imatinib 400 mg QD administered with food
- Nilotinib 300 mg BID (total daily dose of 600 mg) administered under fasting conditions
- Dasatinib 100 mg QD administered with or without food
- Bosutinib 400 mg QD administered with food

Objectives

Table 12 Objectives and related endpoints for efficacy

Primary objectives	Endpoints for primary objectives
• The study has **2 primary objectives**: To compare the efficacy of asciminib vs. IS-TKI, • With respect to the proportion of participants that are in MMR at Week 48 • Within the stratum of participants with imatinib as their PRS-TKI, with respect to the proportion of participants that are in MMR at Week 48 *The study was declared positive and met both the primary objectives*	MMR **at** Week 48 (Yes/No)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• The study has 2 **key secondary objectives:** • These objectives are the same as the 2 primary objectives except that they are analyzed at the Week 96 time point	MMR **at** Week 96 (Yes/No)
• **Other secondary objectives for efficacy**: To estimate the efficacy of asciminib vs. IS-TKI, within the stratum of participants with a 2G TKI as their PRS-TKI, with respect to the proportion of participants that are in: • MMR at Week 48 • MMR at Week 96	MMR **at** Week 48/Week 96 (Yes /No)
• To compare the efficacy of asciminib vs. IS-TKI, with respect to additional parameters of efficacy • To compare the efficacy of asciminib vs. IS-TKI, within the stratum of participants with imatinib as their PRS-TKI, with respect to additional parameters of efficacy • To estimate the efficacy of asciminib vs. IS-TKI, within the stratum of participants with a 2G TKI as their PRS-TKI, with respect to additional parameters of efficacy	• MMR **at** all scheduled data collection time points (except at Week 48 and at Week 96) • MMR **by** all scheduled data collection time points • MR4.0 and MR4.5, **at** and **by** all scheduled data collection time points • CHR, **at** and **by** all scheduled data collection time points • *BCR::ABL1* (IS) ≤ 1% **at** and **by** all scheduled data collection time points • CCyR **by** Week 48 and **by** Week 96 • Duration of MMR, MR4.0, MR4.5 • Time to first MMR, first MR4.0, first MR4.5 • TTF • FFS • EFS

	• PFS • OS
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• **Exploratory objectives for Biomarkers[a]**: To characterize mutations in the *BCR::ABL1* gene and other myeloid associated genes at baseline and during therapy and their association with molecular response	• Proportion of patients who develop any *BCR::ABL1* mutations and myeloid associated mutations at baseline, upon loss of response and at end of treatment (EOT)
[a] Exploratory biomarker endpoints planned in the study are presented in the CSR and SCE	
Source: 1L SCE-Table 1-2	

Outcomes/endpoints

Table 13 Criteria for response and relapse

Response/Relapse	Definition
	Molecular response MR2.0:*BCR::ABL1(*IS)≤ 1% **MMR (MR3.0):** *BCR::ABL1* (IS) ≤ 0.1% **MR4.0:** *BCR::ABL1* (IS) ≤ 0.01% or **MR4.5**: BCR::ABL1 (IS) ≤ 0.0032% **DMR:** MR4.0 or MR 4.5 **EMR:** *BCR::ABL1* (IS) ≤ 10% at Week 12
Cytogenetic response	**CCyR:** No Ph-positive metaphases (corresponding to MR2.0)
Hematologic response for	**CHR:** Defined as all of the following present ≥ 4 weeks: • Complete normalization of peripheral blood counts with leukocyte count <10 x 10^9/L • Platelet count <450 x 10^9/L • Basophils <5% • No blasts and promyelocytes in peripheral blood • Myelocytes + metamyelocytes <5% in peripheral blood • No evidence of extramedullary disease, including spleen and liver

Source: Clinical overview, page 44, tab. 4-2

Estimand

Table 14 Estimand table for primary objectives

Population	Newly diagnosed adult Ph+ CML-CP patients
Treatment condition	Treatment with asciminib vs. the (1) IS-TKI and (2) imatinib as IS-TKI regardless of dose modifications, dosing errors, deviation in any intake of concomitant medications, intake of prohibited medication, and taking or not taking a TKI different from their PRS-TKI in the comparator arm.
Endpoint (variable)	composite endpoint of MMR at Week 48, without meeting any treatment failure criteria prior to Week 48 and without discontinuation due to any reasons prior to Week 48
Population-level summary	stratum adjusted difference in the proportion of participants that were in MMR at Week 48 and corresponding 95% CI
Intercurrent events and strategy to handle them	
Treatment discontinuation or treatment failure prior to week 48	Composite (counted as failure)
Taking a TKI different from their PRS-TKI	Treatment policy
dose reduction, interruption, allowed dose escalations	Treatment policy
Dosing errors	Treatment policy
Deviation in any intake of concomitant medications	Treatment policy
Prohibited medication	Treatment policy

Similar estimands are defined for the key secondary efficacy endpoints targeting MMR at week 96.

Sample size

The proportions of participants expected to achieve the primary endpoint of being in MMR at Week 48 were assumed to be 0.525 for asciminib, 0.28 for imatinib, and 0.45 for any 2G TKI. The proportions of participants expected to achieve the secondary endpoint of MMR at Week 96 were assumed to be 0.635 for asciminib, 0.43 for imatinib, and 0.56 for any 2G TKI. The study design planned for a 50% versus 50% enrolment of imatinib versus 2G TKIs into the control arm. Therefore, the proportion of participants expected to achieve the primary endpoint of MMR at Week 48 was assumed to be 0.365 for the IS-TKI arm. Similarly, the proportion of participants expected to achieve the primary endpoint of MMR at Week 96 was assumed to be 0.495 for the IS-TKI arm.

Based on a 1-sided 2.5% level of significance, with 402 participants and 1:1 randomization ratio between arms (i.e. 201 participants in the asciminib arm and 201 participants in the IS-TKI arm) the study had 94.6% power to reject at least one of the null hypotheses (H1 or H2). At this sample size, the local power to reject the null hypothesis for H1 is 88.5% and local power to reject the null hypothesis for H2 is 92.7%.

Randomisation

Randomisation was planned in a 1:1 ratio to Arm 1 (asciminib 80 mg QD) or Arm 2 (IS-TKI). No cross-over across arms and no change of study treatment within the Arm 2 was allowed. Stratification was applied according to:

- ELTS score (low vs. intermediate vs. high)

- PRS-TKI (imatinib vs. 2G TKI): prior to randomisation a selection of imatinib or 2G TKI was made by the investigator

Blinding (masking)

This study was a randomised open label study. Treatment was open to participants, investigator staff, persons performing the assessments, and the Novartis Clinical Trial Team (CTT). Except review of unblinded safety data by a DMC, no aggregate statistical analyses by treatment arm were performed prior to the database lock. The enrolment into the strata of imatinib versus 2G TKIs based on the PRS-TKIs was managed by IRT to be approximately 50% versus 50%.

Statistical methods

The statistical analysis plan was finalized prior to the conduct of the primary analysis (week 48) and unblinding of the database. The primary analysis at week 48 was based on all data collected in the database up to the DCO date of 28-Nov-2023 with database lock on 19-Dec-2023 (all participants had been on study treatment for at least 48 weeks or discontinued earlier). The week 96 analysis was done when all participants had been on study treatment for at least 96 weeks or discontinued earlier (DCO 22-Oct-2024).

Analyses sets

The Full Analysis Set (FAS) comprised of all participants to whom study treatment has been assigned by randomization.

The IMA Full Analysis Set (FAS_{IMA}) comprised of all participants from the FAS, whose PRS-TKI is imatinib.

The 2GTKI Full Analysis Set (FAS_{2GTKI}) comprised of all participants from the FAS, whose PRS-TKI is a 2G TKI.

The Safety Set comprised of all participants who received at least one dose of any study treatment. Participants were analyzed according to the actual study treatment received, where actual treatment received was defined as the randomised treatment if the participant took at least one dose of that treatment, or the first treatment received if the randomised treatment was never received.

In line with the ITT principle and the targeted estimand, the FAS sets will be used for efficacy evaluations unless specified otherwise.

Analyses of primary and key secondary MMR endpoints

Participants discontinuing the randomised treatment due to any reason prior to Week 48 and/or 96, or participants meeting any treatment failure criteria (as per European Leukemia Network (ELN) 2020 criteria, (ELN 2020)) prior to Week 48 and/or 96, were counted as not being in MMR at Week 48 and/or 96, respectively. When a participant had a missing Week 48 RQ-PCR evaluation but was in MMR both at Week 36 and Week 60, then the participant was imputed as in MMR at Week 48; similarly, when a participant had a missing Week 96 RQ-PCR evaluation but was in MMR both at Week 84 and Week 108, then the participant was imputed as in MMR at Week 96. If any evaluations were performed at unscheduled visits closer to the Week 48 and/or 96 visit (before or after), respectively, these were taken into account for the imputation. Within the overall population (FAS) and within the stratum of participants that have imatinib as their PRS-TKI (FAS_{IMA}), comparison of treatment groups for primary/key secondary MMR endpoints was performed with a one-sided stratified Cochran-Mantel-Haenszel (CMH) test. For the overall population both randomization stratification factors (ELTS risk

group and PRS-TKI [imatinib vs. 2G TKI]) were taken into account while for the other only the ELTS risk group was used. Estimates of the common risk difference were provided.

A **sensitivity analysis** of the primary and key secondary endpoints was also conducted at Week 48 and Week 96. The CMH Chi-square test of MMR rate was repeated without the imputation rule used in the main primary and key secondary analyses for participants who had missing RTPCR evaluations at Week 48 and/or 96. In such cases these participants were considered non-responders for MMR at Week 48 and/or at Week 96.

Supplementary analyses of the primary and key secondary endpoints were also conducted at Week 48 and Week 96:

- In the first supplementary analysis, participants were analysed using the PRS-TKI as recorded in the baseline eCRF.
- In the second supplementary analysis, the one-sided stratified CMH test based on the ELTS and PRS-TKI strata in the IRT system was repeated (as for the primary estimand) after excluding participants who (1) had been a screen failure but randomised by mistake, (2) had atypical transcript at baseline [Study J12301 W48 CSR].
- Supplemental estimands for the endpoint of MMR at Week 48 and 96 based on the treatment policy, composite and hypothetical strategies have been produced.

Subgroup analyses for the primary and key secondary endpoints were conducted to assess the homogeneity of the treatment effect across subgroups (e.g., based on demographic and baseline disease characteristics, ELTS prognostic categories, geographic regions etc.)

Analysis of the key secondary safety endpoint

The analysis of TTDAE was performed using the Safety Set. The comparison is between all participants receiving asciminib as their actual treatment and all participants receiving the 2G TKIs as their actual treatment. The formal comparison of the cause-specific hazard for the event of interest was implemented via the log-rank test. The cumulative incidence curve for the event of interest was to be plotted. The estimated cumulative incidence rates and 95% CI at specified scheduled visits was presented for each treatment group (asciminib and the 2G TKI).

As **supplementary analysis,** competing risk analysis via the sub-distribution hazard approach was performed. These supplementary analyses were to be provided for information purpose only for participants receiving asciminib vs those receiving 2G-TKI. In this analysis, discontinuation due to AE (including death due to AE) is the event of interests, and discontinuation due to other reasons is the competing risks. Patients who were still ongoing at the time of the analysis are considered censored.

In addition, the following analyses based on the Safety Set were to be conducted:

- The cause-specific hazard and the cumulative incidence function to be estimated for the time to discontinuation of study treatment due to AE for participants receiving asciminib vs those receiving all comparator treatments.
- The cause-specific hazard and the cumulative incidence function to be estimated for the time to discontinuation of study treatment due to AE for participants receiving asciminib vs those receiving imatinib.

Multiplicity control

The family wise error rate for the tests was controlled at 2.5% level via the graphical gatekeeping procedure ().

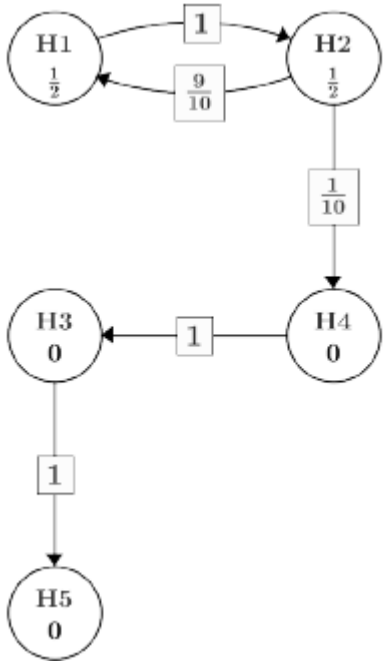


Figure 12: Testing hierarchy (graphical gatekeeping procedure)

H1 and H2 refer to the hypotheses for the primary endpoint (MMR at week 48) in the overall population and in the stratum of participants that have imatinib as their pre-randomization selection of TKI, respectively. Correspondingly H3 and H4 refer to the hypotheses for the key secondary endpoints MMR at week 96. H 5 corresponds to the hypothesis for the secondary safety endpoint (TTDAE).

The three families of hypotheses were to be tested in the following manner. The null hypotheses in family F1 (H1 and H2) will be examined first and tested using the weighted parametric tests (Bretz et al 2011); the hypotheses in family F2 (H3 and H4) will be tested using the fixed-sequence testing approach; followed by the hypothesis in family F3 (H5) will be tested using the fixed-sequence testing approach. The null hypotheses in key secondary end-point family F2 can be tested if the null hypothesis for H2 (or for both H1 and H2) in the primary end-point family F1 is rejected. The null hypotheses in secondary safety end-point family F3 can be tested if the null hypothesis for both H4 and H3 in the key secondary end-point family F2 are rejected.

Adjusted p-values in line with the above approach are provided.

Results

Participant flow

Overall, 475 participants with newly diagnosed CML-CP were screened in this study from 116 centres in 29 countries worldwide (Figure 13).

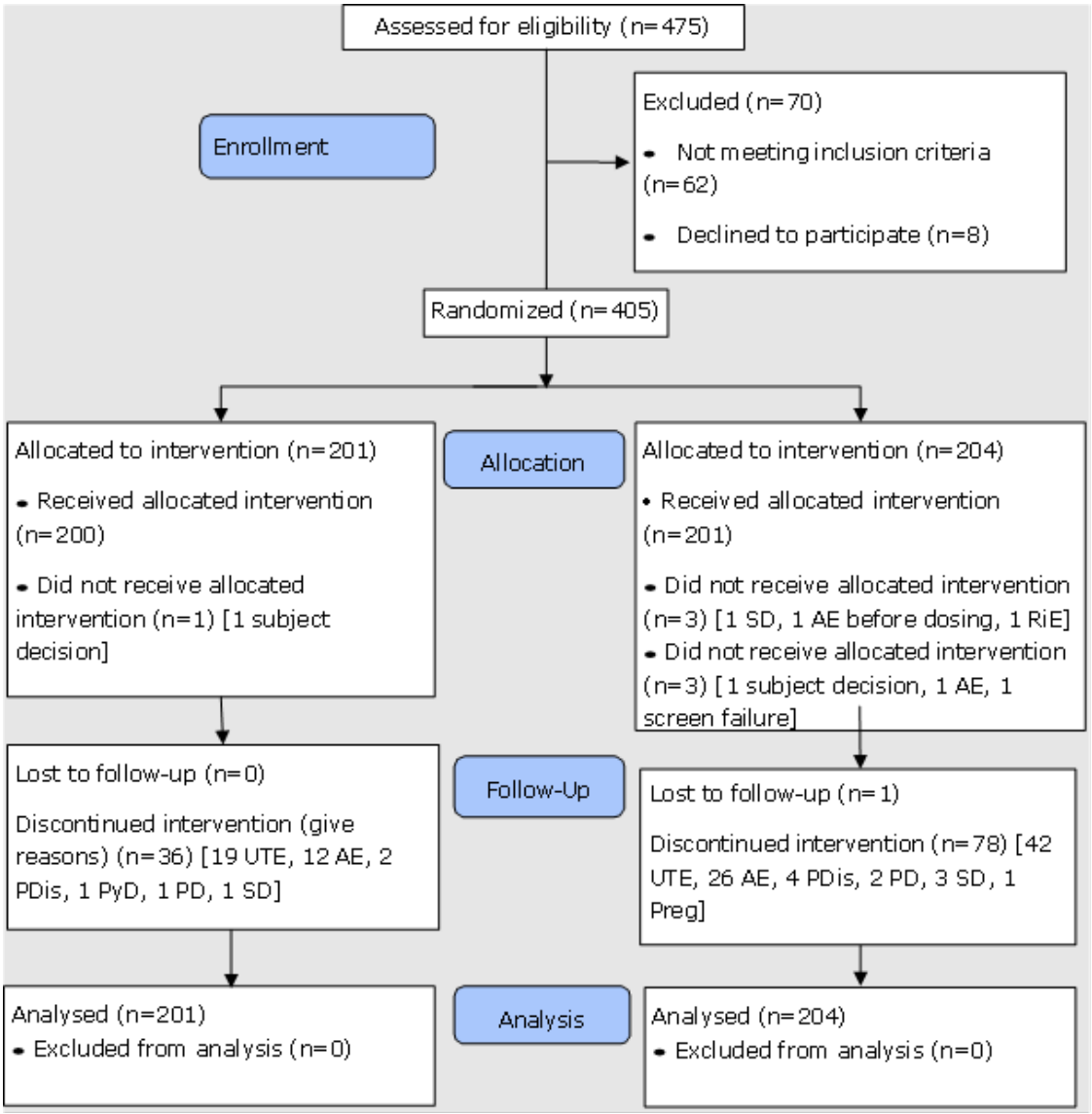


Figure 13: Study J12301 Participant flow

Recruitment

First patient first visit was on 6 October 2021 and last patient first visit on 5 December 2022. The randomisation period took 13.5 months. The analysis cut-off date was 28 November 2023. In the IS TKI arm, 99 patients received imatinib, 49 patients received nilotinib,42 dasatinib and 11 bosutinib.

Conduct of the study

There were two protocol amendments for study J12301. There were no changes in study conduct and no changes in the planned analysis.

Table 15 Protocol amendments

Version and date	Summary of key changes

Amendment 01 09-May-2022	The main purpose of this protocol amendment was to further clarify requirements for eligibility, dose administration and pregnancy testing in view of the comparator arm being approved TKIs selected by Investigators. In addition, BCR-ABL≤1% was added as a secondary endpoint. Also added details 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	The main purpose of this protocol amendment was to clarify dose modification guidelines for hepatotoxicity for asciminib and dose discontinuation rule as applicable to both treatment arms.

Baseline data

Demographics and patient-baseline characteristics are presented in *Table 16*. These were generally balanced between the all- asciminib arm and the all-comparators arm.

Table 16 Demographics and baseline characteristics (FAS)

Baseline Characteristic Categories/Statistics	Asciminib Imatinib Stratum N=101	Asciminib 2G TKI Stratum N=100	Asciminib All Asciminib N=201	IS TKI Imatinib Stratum N=102	IS TKI 2G TKI Stratum N=102	IS TKI All Comparators N=204
Age (years)						
n	101	100	201	102	102	204
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
Q1-Q3	49.0-66.0	35.0-59.5	39.0-63.0	46.0-66.0	33.0-56.0	39.0-64.0
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 group1 -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)
Age group2 -n (%)						
<65 years	69 (68.3)	86 (86.0)	155 (77.1)	70 (68.6)	85 (83.3)	155 (76.0)
≥ 65 years	32 (31.7)	14 (14.0)	46 (22.9)	32 (31.4)	17 (16.7)	49 (24.0)
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)

Baseline Characteristic Categories/Statistics	Asciminib Imatinib Stratum N=101	Asciminib 2G TKI Stratum N=100	Asciminib All Asciminib N=201	IS TKI Imatinib Stratum N=102	IS TKI 2G TKI Stratum N=102	IS TKI All Comparators N=204
Not Reported	4 (4.0)	6 (6.0)	10 (5.0)	14 (13.7)	2 (2.0)	16 (7.8)
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)
Charlson Comorbidity Index (CCI) (%)						
2	22 (21.8)	56 (56.0)	78 (38.8)	30 (29.4)	58 (56.9)	88 (43.1)
3	21 (20.8)	15 (15.0)	36 (17.9)	21 (20.6)	17 (16.7)	38 (18.6)
4	26 (25.7)	16 (16.0)	42 (20.9)	17 (16.7)	14 (13.7)	31 (15.2)
5	16 (15.8)	5 (5.0)	21 (10.4)	15 (14.7)	2 (2.0)	17 (8.3)
6	7 (6.9)	7 (7.0)	14 (7.0)	9 (8.8)	7 (6.9)	16 (7.8)
7	5 (5.0)	0	5 (2.5)	5 (4.9)	3 (2.9)	8 (3.9)
8	1 (1.0)	1 (1.0)	2 (1.0)	2 (2.0)	1 (1.0)	3 (1.5)
9	2 (2.0)	0	2 (1.0)	0	0	0
Missing	1 (1.0)	0	1 (0.5)	3 (2.9)	0	3 (1.5)
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
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)

Baseline Characteristic Categories/Statistics	Asciminib			IS 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
2G TKI stratum	0	100 (100)	100 (49.8)	0	102 (100)	102 (50.0)
Pre-randomization selection TKI (eCRF)						
Imatinib stratum	101 (100)	0	101 (50.2)	100 (98.0)	0	100 (49.0)
2G TKI stratum	0	100 (100)	100 (49.8)	1 (1.0)	102 (100)	103 (50.5)
Missing	0	0	0	1 (1.0)	0	1 (0.5)
Reason for TKI selection						
Age	13 (12.9)	16 (16.0)	29 (14.4)	16 (15.7)	15 (14.7)	31 (15.2)
Co-morbidities	9 (8.9)	1 (1.0)	10 (5.0)	6 (5.9)	6 (5.9)	12 (5.9)
Local practice / guidelines clinical experience	33 (32.7)	42 (42.0)	75 (37.3)	29 (28.4)	46 (45.1)	75 (36.8)
Other	14 (13.9)	13 (13.0)	27 (13.4)	20 (19.6)	11 (10.8)	31 (15.2)
Risk category	23 (22.8)	13 (13.0)	36 (17.9)	24 (23.5)	18 (17.6)	42 (20.6)
Treatment objective	9 (8.9)	15 (15.0)	24 (11.9)	6 (5.9)	6 (5.9)	12 (5.9)
Missing	0	0	0	1 (1.0)	0	1 (0.5)

Source: Study J12301 W48 CSR-Table 14.1-4.1

An overview of disease history is provided in *Table 17*. Baseline characteristics were generally balanced between the all- asciminib arm and the all-comparators arm. Three patients in the asciminib arm and one patient in the IS-TKI arm had BCR::ABL1 gene mutations.

Table 17 Disease history (FAS)

Disease history	Asciminib			IS-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
Q1-Q3	3.57-6.43	3.43-6.79	3.43-6.71	3.57-7.00	3.00-6.14	3.29-6.86
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
Q1-Q3	0.14-0.71	0.14-1.00	0.14-0.86	0.14-1.00	0.14-0.57	0.14-0.71
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
Q1-Q3	3.14-6.14	3.22-6.43	3.14-6.14	3.57-7.07	3.00-6.14	3.29-6.86
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)

	Asciminib			IS-TKI		
Disease history	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
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)
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)

Prior use of anti-neoplastic therapy and TKIs before randomization refers to treatment with hydroxyurea and/or anagrelide and either imatinib, or nilotinib, or dasatinib or bosutinib for ≤ 2 weeks allowed per protocol.
Source: Study J12301 W48 CSR-Table 14.1-4.5

Numbers analysed

The numbers of participants in each analysis set for study J12301 are summarised in *Table 18*.

Table 18 Analysis Sets (FAS)

	Asciminib			Investigator Selected TKI		
Analysis Set	Imatinib Stratum n (%)	2G TKI Stratum n (%)	All Asciminib n (%)	Imatinib Stratum n (%)	2G TKI Stratum n (%)	All Comparators n (%)
Safety Set*	100	100	200	99	102	201
Full Analysis Set	101	100	201	102	102	204
Imatinib Full Analysis Set (FAS_{IMA})	101	0	101	102	0	102
2G TKI Full Analysis Set ($FAS_{2G\ TKI}$)	0	100	100	0	102	102
MMR Responder Set	77	80	157	52	67	119
MR4.0 Responder Set	53	44	97	18	37	55
MR4.5 Responder Set	31	25	56	8	23	31
Pharmacokinetic Analysis Set	95	99	194	0	0	0

Percentages are computed using the number of <ANALYSIS SET> in each treatment group as the denominator.
* Number of participants reported in Safety set is based on the actual received treatment

Outcomes and estimation

Primary endpoints and key secondary endpoints

Co primary endpoints

Study J12301 had two primary endpoints. The primary endpoint 1, MMR at week 48 in the overall population (FAS) for asciminib vs. IS-TKI was positive: the MMR rate at Week 48 was higher in the asciminib arm with 67.7% compared to 49.0% in the IS-TKI arm. The common treatment difference

between the arms of the overall population was 18.88% (95% CI: 9.59, 28.17; one sided p-value: <0.001; Table 19, Figure 14).

The primary endpoint 2, MMR rate at Week 48 in the imatinib stratum was 69.3% for asciminib^{IMA}, compared to 40.2% in the IS-TKI^{IMA} (imatinib). The common treatment difference in the MMR rate in the imatinib stratum was 29.55% (95% CI: 16.91, 42.18; one-sided adjusted p-value: < 0.001, Figure 15).

Key secondary endpoints

The key secondary endpoint 1, MMR rate at Week 96 in the overall population (FAS) remained higher in the asciminib arm with 74.1% compared to 52.0% in the IS- TKI arm (difference between arms 22.42%; 95% CI: 13.55, 31.29; p-value: < 0.001; Table 19)

The key secondary endpoint 2, MMR rate after week 96 in the imatinib stratum (FAS_{IMA}) was positive with 76.2% vs. 47.1% patients achieving MMR in with asciminib vs. imatinib-treatment, respectively. The common treatment difference was 29.7% (95% CI, 17.6-41.8; p<0.001).

In the following, results are presented according to the respective population (overall population (FAS) or imatinib stratum (FAS_{IMA}).

Table 19 Primary endpoint 1 MMR rate at Week 48 and key secondary endpoint 1 MMR rate at Week 96 (overall population, FAS)

	Week 48		Week 96	
	Asciminib	IS-TKI	Asciminib	IS-TKI
	All Asciminib N=201	All Comparators N=204	All Asciminib N=201	All Comparators N=204
Response - n (%)	136 (67.66)	100 (49.02)	149 (74.13)	106 (51.96)
95% CI for response[a]	(60.72, 74.07)	(41.97, 56.10)	(67.50, 80.03)	(44.87, 58.99)
Unstratified difference in response rates (vs. comparator) (%)	18.64	-	22.17	-
95% CI for unstratified difference in response rates[b]	(9.21, 28.07)	-	(13.02, 31.31)	-
Common treatment difference (%)[c]	18.88	-	22.42	-
95% CI for common treatment difference[c]	(9.59, 28.17)	-	(13.55, 31.29)	-
CMH 1-sided test p-value[d]	<.001	-	<.001	-
CMH 1-sided test adjusted p-value[e]	<.001	-	<.001	-

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 IS-TKI arm, respectively, are imputed as responders. Subjects without PCR assessment at Week 96 are considered non-responders unless they are in MMR at both Week 84 and Week 108. Zero and 0 subjects in Asciminib arm and in IS TKI arm, respectively, are imputed as responders.[a] Clopper-Pearson 95% CI; [b] Wald 95% CI [c] Common treatment difference and common risk difference are synonymous. The common treatment difference and its 95% CI estimated using the Mantel-Haenszel method after stratifying for (a) pre-randomization selected TKI, and (b) baseline ELTS risk groups (both IRT data).

[d] CMH 1-sided test stratified by the same stratification factors.[e] 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%.

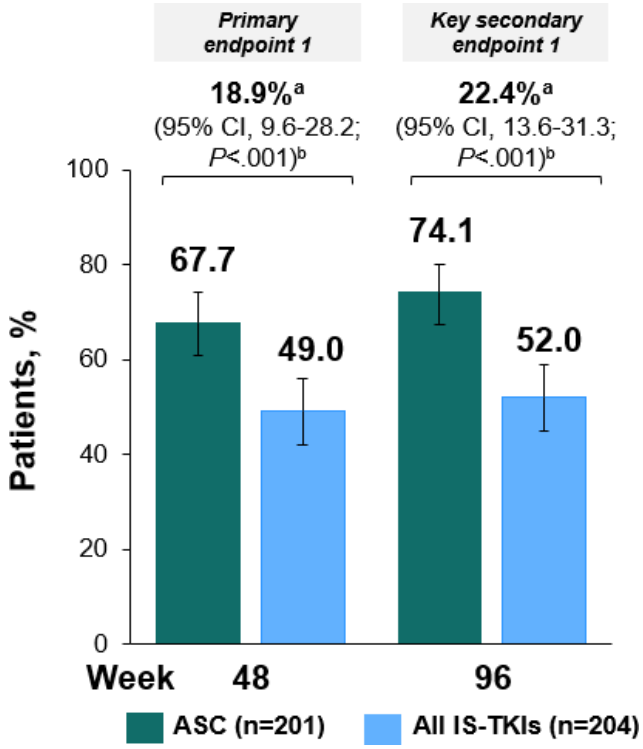


Figure 14: *MMR rate at Week 48 (primary endpoint 1) and Week 96 (key secondary endpoint 1) in the overall population (FAS)*

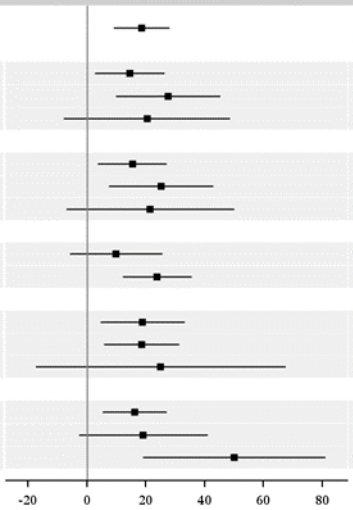
Error bars represent 95% CIs. The common treatment difference and its 95% CI were estimated using the Mantel- Haenszel method after stratifying for a pre-randomization-selected TKI and baseline ELTS risk groups (both IRT data). b Adjusted 1-sided P value was calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted P value is ⩽.025. Source: SoE, p 34

Subgroup analyses for the co- primary endpoint 1

Subgroup analysis for relevant patient-/ and disease characteristics are provided in Table 20 for the co-primary endpoint 1 and in Table 21 for the key secondary endpoint 1. In general, a concordant effect can be observed among important subgroups.

Table 20 Forest plot of risk difference with 95% confidence interval for MMR at Week 48 from subgroup analysis (FAS)

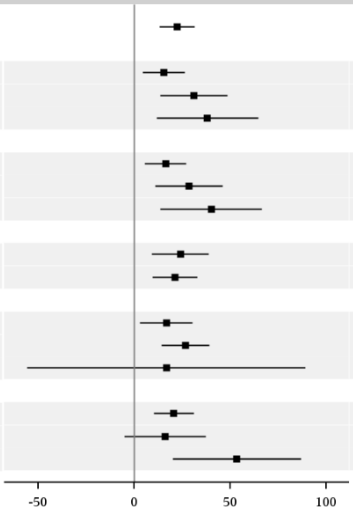
Subgroup	Asciminib All Asciminib n/N (%)	INVTKI All Comparators n/N (%)	Risk difference (95% CI)
All subjects	136/201 (67.7)	100/204 (49.0)	18.6 (9.2, 28.1)
ELTS based on randomization data			
Low	88/122 (72.1)	72/125 (57.6)	14.5 (2.8, 26.3)
Intermediate	36/56 (64.3)	21/57 (36.8)	27.4 (9.7, 45.2)
High	12/23 (52.2)	7/22 (31.8)	20.4 (-7.9, 48.6)
ELTS based on CRF data			
Low	90/122 (73.8)	73/125 (58.4)	15.4 (3.7, 27.0)
Intermediate	35/57 (61.4)	21/58 (36.2)	25.2 (7.5, 42.9)
High	11/22 (50.0)	6/21 (28.6)	21.4 (-7.0, 49.9)
Sex			
Female	45/70 (64.3)	43/79 (54.4)	9.9 (-5.8, 25.6)
Male	91/131 (69.5)	57/125 (45.6)	23.9 (12.1, 35.6)
Race			
Asian	58/90 (64.4)	41/90 (45.6)	18.9 (4.6, 33.2)
White	75/108 (69.4)	56/110 (50.9)	18.5 (5.8, 31.3)
Others	3/3 (100)	3/4 (75.0)	25.0 (-17.4, 67.4)
Age category			
18-65 years	100/155 (64.5)	75/155 (48.4)	16.1 (5.2, 27.0)
65-75 years	27/36 (75.0)	19/34 (55.9)	19.1 (-2.8, 41.0)
≥ 75 years	9/10 (90.0)	6/15 (40.0)	50.0 (19.0, 81.0)



n: The number of subjects who responded. N: The total number of subjects in the subgroup and treatment group. INVTKI = Investigator Selected TKI (IS-TKI). Source: [Study J12301 W48 CSR-Figure 14.2-1.7.1]

Table 21 Forest plot of risk difference with 95% confidence interval for MMR at Week 96 from subgroup analysis (FAS)

Subgroup	Asciminib All Asciminib n/N (%)	INVTKI All Comparators n/N (%)	Risk difference (95% CI)
All subjects	149/201 (74.1)	106/204 (52.0)	22.2 (13.0, 31.3)
ELTS based on randomization data			
Low	98/122 (80.3)	81/125 (64.8)	15.5 (4.6, 26.5)
Intermediate	37/56 (66.1)	20/57 (35.1)	31.0 (13.5, 48.5)
High	14/23 (60.9)	5/22 (22.7)	38.1 (11.6, 64.7)
ELTS based on CRF data			
Low	100/122 (82.0)	82/125 (65.6)	16.4 (5.6, 27.1)
Intermediate	36/57 (63.2)	20/58 (34.5)	28.7 (11.2, 46.2)
High	13/22 (59.1)	4/21 (19.1)	40.0 (13.5, 66.6)
Sex			
Female	54/70 (77.1)	42/79 (53.2)	24.0 (9.2, 38.7)
Male	95/131 (72.5)	64/125 (51.2)	21.3 (9.7, 32.9)
Race			
Asian	66/90 (73.3)	51/90 (56.7)	16.7 (2.9, 30.4)
White	81/108 (75.0)	53/110 (48.2)	26.8 (14.4, 39.2)
Others	2/3 (66.7)	2/4 (50.0)	16.7 (-55.8, 89.1)
Age category			
18-65 years	113/155 (72.9)	81/155 (52.3)	20.6 (10.1, 31.2)
65-75 years	28/36 (77.8)	21/34 (61.8)	16.0 (-5.2, 37.3)
≥ 75 years	8/10 (80.0)	4/15 (26.7)	53.3 (19.9, 86.7)



n: The number of subjects who responded. N: The total number of subjects in the subgroup and treatment group. 95% Wald CI for Risk Difference. Risk Difference is Asciminib vs INVTKI. INVTKI = Investigator Selected TKI (IS-TKI). Source: [Study J12301 W96 CSR-Figure 14.2-1.7.1a]

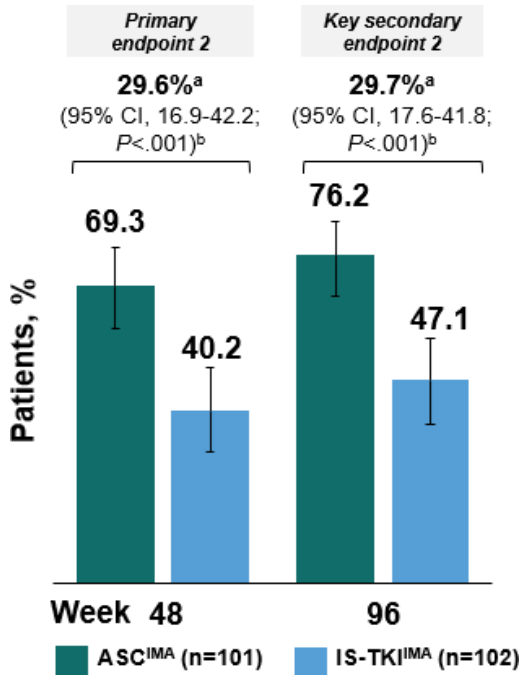


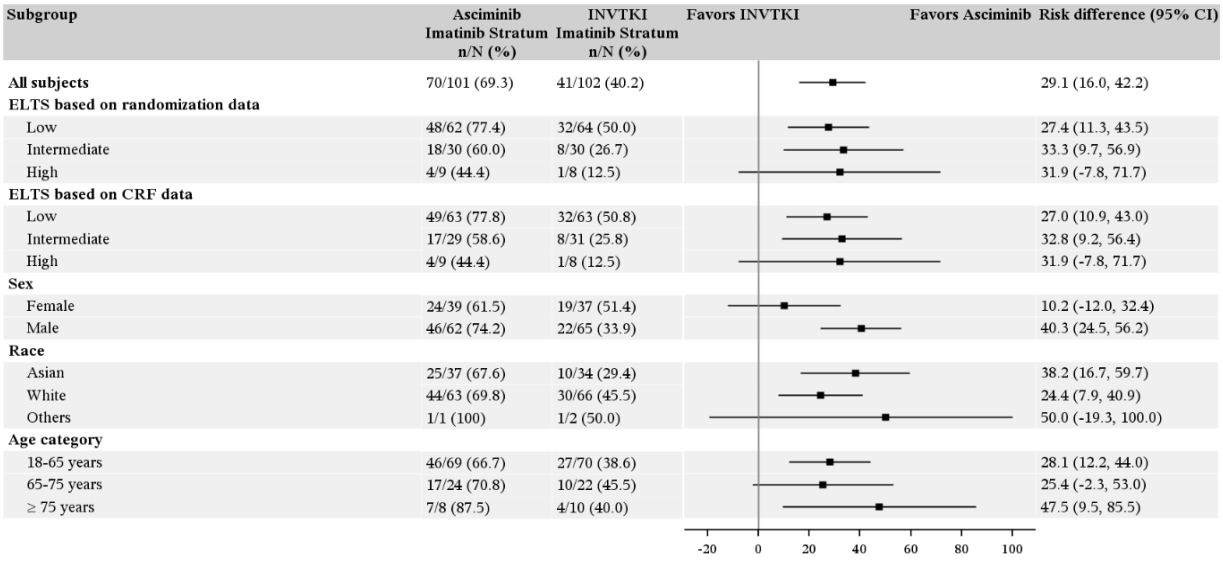
Figure 15: MMR rate at Week 48 (primary endpoint 2) and Week 96 (key secondary endpoint 2) in the imatinib stratum (FAS_{IMA})

Error bars represent 95% CIs. The common treatment difference and its 95% CI were estimated using the Mantel- Haenszel method after stratifying for a pre-randomization-selected TKI and baseline ELTS risk groups (both IRT data). b Adjusted 1-sided P value was calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted P value is ≤.025. Source: SoE, p39

Analyses for the primary endpoint 2 and key secondary endpoint 2

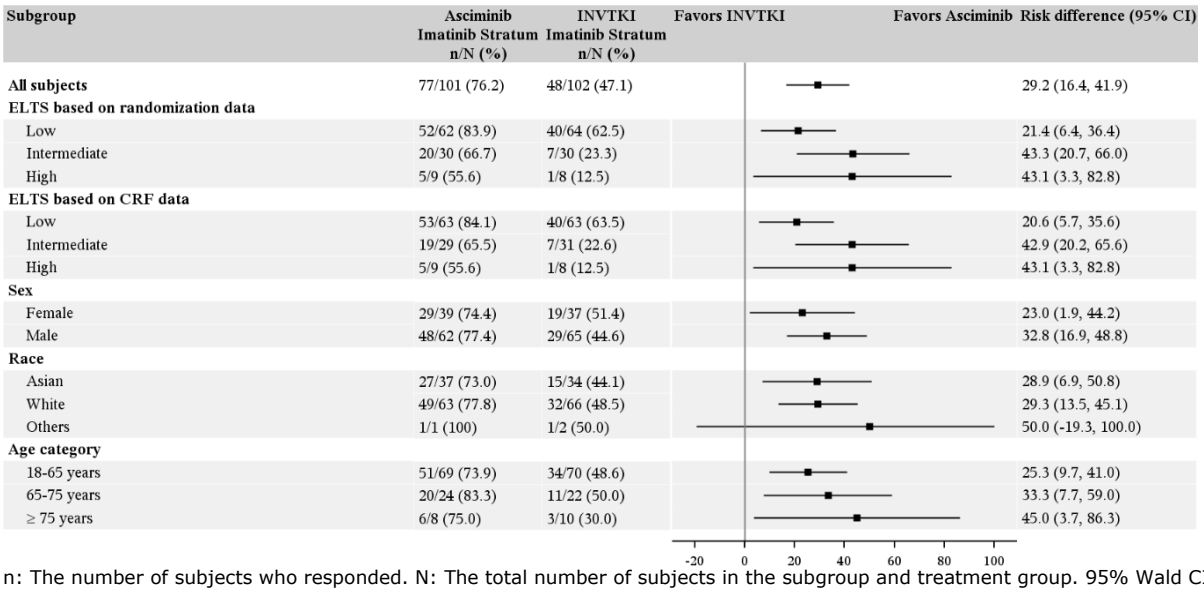
Subgroup analysis for relevant patient-/ and disease characteristics are provided for the FAS_{IMA} population regarding the primary endpoint 2 and key secondary endpoint 2.

Figure 16: *Forest plot of risk difference with 95% confidence interval for MMR at Week 48 from subgroup analysis (FAS_{IMA})*



n: The number of subjects who responded. N: The total number of subjects in the subgroup and treatment group. INVTKI = Investigator Selected TKI (IS-TKI). Source: [Study J12301 W48 CSR-Figure 14.2-1.7.2]

Figure 17: Forest plot of risk difference with 95% confidence interval for MMR at Week 96 from subgroup analysis



n: The number of subjects who responded. N: The total number of subjects in the subgroup and treatment group. 95% Wald CI for Risk Difference. Risk Difference is Asciminib vs INVTKI. INVTKI = Investigator Selected TKI (IS-TKI). Source: [Study J12301 W96 CSR-Figure 14.2-1.7.2a]

Sensitivity analysis of MMR rate at week 48 in the overall population without imutation

The imputation rule in case of missing reports of BCR::ABL1 transcript levels at Week 48 was used for primary analysis in one participant in the asciminib arm and two participants in the IS-TKI arm. The MMR rate at Week 48 (without imputation) in the overall population (FAS) was 67.2% in the asciminib arm and was 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.

There were no participants with missing reports of BCR::ABL1 transcript levels at Week 96, consequently no sensitivity analysis concerning the imputation rule was performed for week 96.

Time to first MMR for the primary endpoints and key secondary endpoints

MMR was achieved earlier in the asciminib arm compared to the IS-TKI arm (KM estimated median time to first MMR: 24.3 weeks vs. 36.4 weeks, *Figure 18*) and earlier in comparison to imatinib (24.1 weeks vs. 48.6 weeks, *Figure 19*).

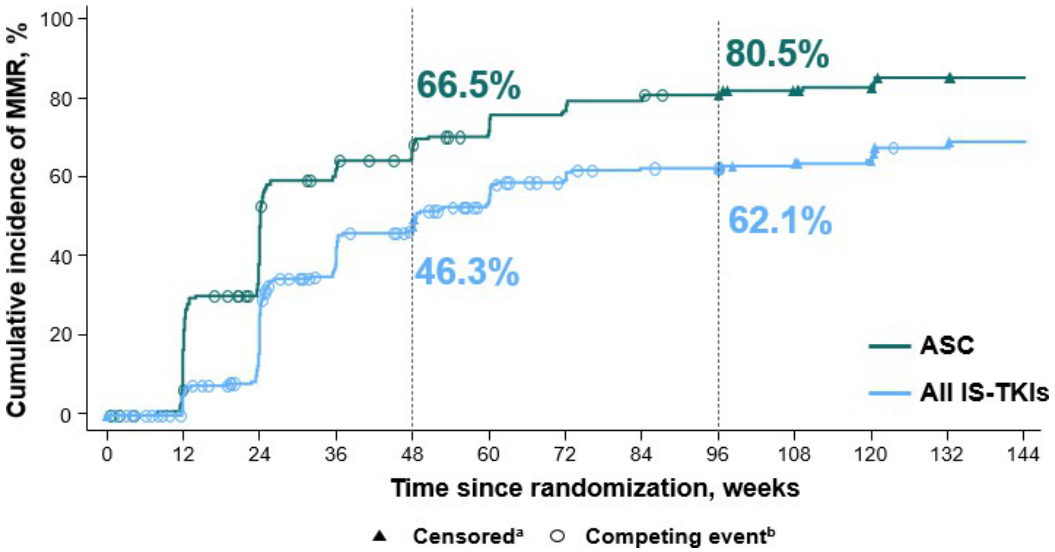


Figure 18: ***Cumulative incidence function of time to first MMR (FAS)***
a Nonresponders were censored at their last molecular assessment date. b Discontinuation from treatment for any reason without prior achievement of MMR was considered a competing event. Source: SoE, figure 3-11

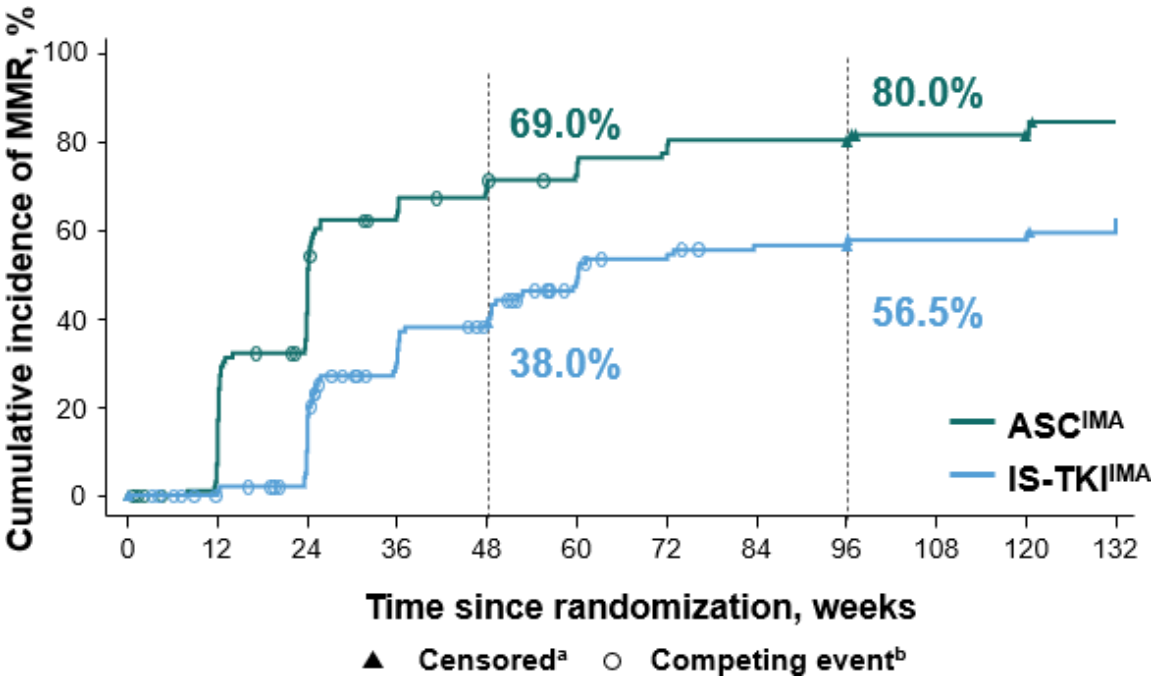


Figure 19: ***Cumulative incidence function of time to first MMR (FAS_{IMA})***
a Nonresponders were censored at their last molecular assessment date. b Discontinuation from treatment for any reason without prior achievement of MMR was considered a competing event. Source: SoE, figure 3-12

Duration of MMR

Ninety-seven percent in the asciminib arm and 97.7% in the IS-TKI arm of participants who achieved MMR continued to remain in MMR at Week 96.

Asciminib vs. IS-TKI

By the Week 96 data cut-off, 166 participants in the asciminib arm and 131 in the IS-TKI arm achieved MMR at least once, and 5/166 (3.0%) participants in the asciminib arm and 3/131 (2.3%) in the IS-TKI arm lost MMR. Three of 82 (3.7%) participants in ASC^{IMA} and two of 59 (3.4%) participants in IS-TKI^{IMA} lost MMR. Two of 84 (2.4%) participants in ASC^{2G} and one in 72 (1.4%) participants in IS-TKI^{2G} lost MMR.

Among the 5 participants who lost response in the asciminib arm:

- 4 (2 each from the imatinib and the 2G TKI strata) had confirmed loss of MMR and subsequently discontinued treatment.
- 1 (from the imatinib stratum) discontinued treatment due to a protocol deviation before the loss of MMR could be confirmed.

Among the 3 participants who lost response in the IS-TKI arm:

- 2 (1 each from the imatinib and the 2G TKI strata) had confirmed loss of MMR and subsequently discontinued treatment.
- 1 (from the imatinib stratum) discontinued treatment due to an AE before the loss of MMR could be confirmed.

Ancillary analyses

Other secondary efficacy results

MMR Rate at Week 48 and at week 96 for ASC^{2G} vs. IS-TKI^{2G}

Within the 2G TKI stratum, the MMR rate at Week 48 was higher in ASC^{2G} (66.0%) compared to IS-TKI^{2G} (57.8%). The common treatment difference in the MMR rate was 8.17% (95% CI: -5.14, 21.47; per the CMH one-sided test, stratified by baseline ELTS risk groups). MMR rate at Week 96 increased further and was higher in ASC^{2G} (72.0%) while it remained similar in IS-TKI^{2G} (56.9%). The treatment difference was 15.14% at Week 96 (95% CI: 2.32, 27.95; per the CMH one-sided test, stratified by baseline ELTS risk groups).

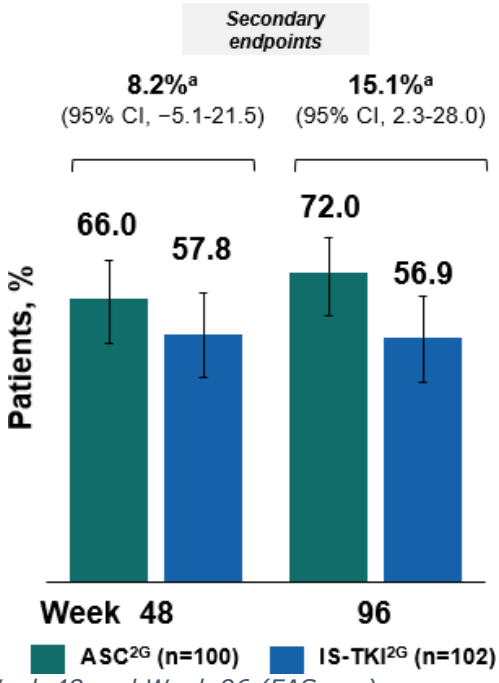


Figure 20: MMR rate at Week 48 and Week 96 (FAS_{2GTKI})

Error bars represent 95% CIs. The common treatment difference and its 95% CI were estimated using the Mantel- Haenszel method after stratifying for a baseline ELTS risk group (IRT data). Source: Source: Study J12301 W48 CSR-Table 14.2-1.1.1.3 and Study J12301 W96 CSR-Table 14.2-1.1.1.3a

Within the 2G TKI stratum MMR was reached numerically faster (KM estimated median time to first MMR: 24.3 weeks vs. 36.1 weeks):

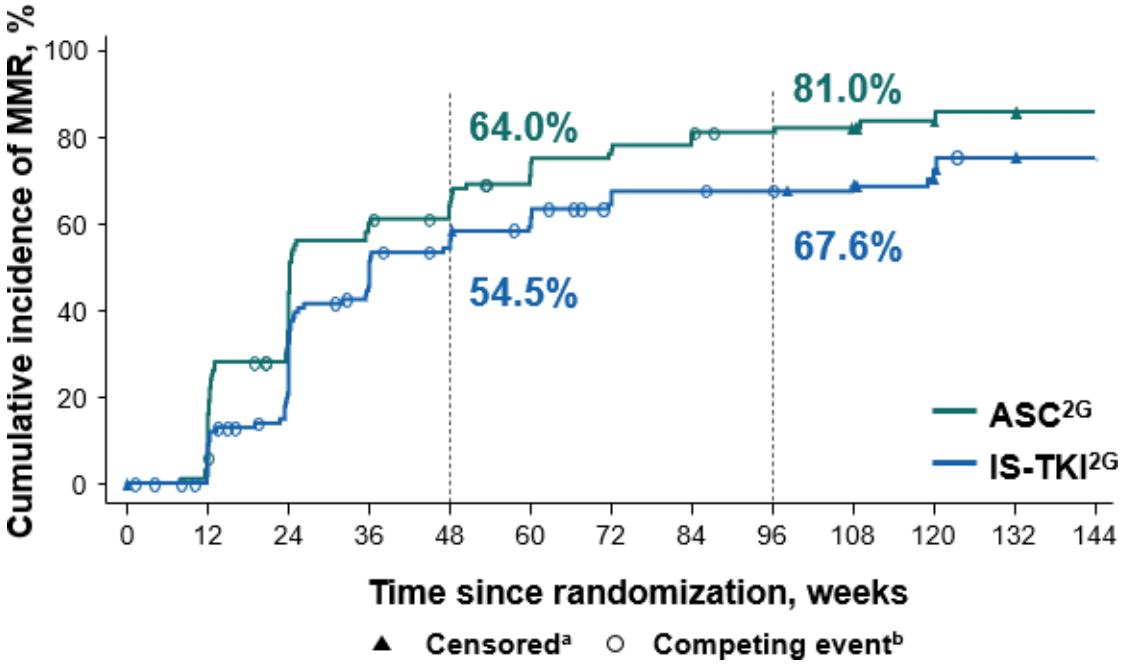


Figure 21: ***Cumulative incidence function of time to first MMR (FAS_{2GTKI})***

a Nonresponders were censored at their last molecular assessment date. b Discontinuation from treatment for any reason without prior achievement of MMR was considered a competing event. Source: SoE, figure 3-13

A higher MMR rate was achieved through Week 96 in the asciminib arm compared to the IS-TKI arm *at or by* each scheduled timepoints assessed (overall and within each stratum, Table 22)

Table 22 MMR rate at and by scheduled time points (FAS)

MMR rate *at* scheduled time points (FAS)					MMR rate *by* scheduled time points (FAS)			
	Asciminib	IS-TKI			Asciminib	IS-TKI		
	All Asciminib N=201	All Comparator N=204	Between treatments[b]		All Asciminib N=201	All Comparators N=204	Between treatments[b]	
MMR[a]	n (%)	n (%)	Common treatment difference (%)	95% CI	n (%)	n (%)	Common treatment difference (%)	95% CI
Week 12	60 (29.85)	15 (7.35)	**22.55**	(15.32, 29.79)	60 (29.85)	15 (7.35)	**22.55**	(15.32, 29.79)
Week 24	116 (57.71)	69 (33.82)	**24.12**	(14.95, 33.29)	118 (58.71)	69 (33.82)	**25.12**	(16.01, 34.22)
Week 36	125 (62.19)	91 (44.61)	**17.83**	(8.42, 27.24)	128 (63.68)	92 (45.10)	**18.83**	(9.50, 28.16)
Week 48	**136 (67.66)**	**100 (49.02)**	**18.88**	**(9.59, 28.17)**	**140 (69.65)**	**104 (50.98)**	**18.92**	**(9.78, 28.07)**
Week 60	144 (71.64)	109 (53.43)	**18.46**	(9.44, 27.47)	151 (75.12)	117 (57.35)	**18.05**	(9.30, 26.80)
Week 72	145 (72.14)	112 (54.90)	**17.53**	(8.52, 26.53)	158 (78.61)	123 (60.29)	**18.61**	(10.16, 27.06)
Week 84	148 (73.63)	105 (51.47)	**22.40**	(13.42, 31.38)	161 (80.10)	124 (60.78)	**19.61**	(11.30, 27.93)
Week 96	**149 (74.13)**	**106 (51.96)**	**22.42**	**(13.55, 31.29)**	**163 (81.09)**	**125 (61.27)**	**20.13**	**(11.93, 28.32)**

[a] Clopper-Pearson 95% CI for observed rates; Wald 95% CI for the unstratified difference between observed rates.

[b] Common treatment difference and common risk difference are synonymous. The common treatment difference and its 95% CI estimated using the Mantel-Haenszel method after stratifying for (a) pre-randomization selected TKI, and (b) baseline ELTS risk groups (both IRT data). Source: Study J12301 W96 CSR-Table 14.2-1.1.1 and Study J12301 W96 CSR-Table 14.2-1.2.1

An exploratory multivariate analysis of treatment effect after adjusting for baseline stratification and other important variables between treatment arms was assessed by logistic regression (*Table 23*).

Table 23 Odds ratio of MMR rate at Week 48 adjusted for the stratification factors and other important variables (FAS)

Adjusted for stratification factors (PRS-TKI and ELTS risk group)		
	Odds ratio	95% CI
Treatment		
Asciminib vs Investigator Selected TKI	2.26	(1.50, 3.42)
Adjusted for stratification factors (PRS-TKI and ELTS risk group) and other important variables		
	Odds ratio	95% CI
Treatment		
Asciminib vs Investigator Selected TKI	2.26	(1.48, 3.47)
Pre-Randomization selection TKI (IRT)		
2G TKI vs Imatinib	1.78	(1.13, 2.81)
ELTS Score (IRT)		
Intermediate vs Low	0.43	(0.25, 0.71)
High vs Low	0.26	(0.13, 0.53)
Sex		
Female vs Male	1.19	(0.73, 1.94)
Race		
Asian vs White	0.83	(0.53, 1.31)
Other vs White	4.47	(0.51, 38.93)
Age Group		
65 - < 75 years vs 18 - < 65 years	1.67	(0.84, 3.32)
≥ 75 years vs 18 - < 65 years	1.94	(0.70, 5.39)
Framingham estimated 10-year CDV risk category		
Intermediate (estimated risk between 10% and 20%) vs Low (estimated risk < 10%)	0.78	(0.43, 1.41)
High (estimated risk ≥ 20%) vs Low (estimated risk < 10%)	1.78	(0.90, 3.51)

Including imputed MMR responders at Week 48.

Source: Table 14.2-1.7.1, Table 14.2-1.8.1

Early molecular response (EMR) at Week 12

In Study J12301, 89.6% of participants in the asciminib arm achieved the treatment milestone EMR compared to 70.1% of participants in the IS-TKI arm overall (89.6% vs. 70.1%), including effects within the imatinib stratum (88.1% vs. 59.8%), and within the 2G TKI stratum (91.0% vs. 80.4%; *Table 24*).

Table 24 ***BCR::ABL1 ratio (% IS) at Week 12***

	FAS		FAS_{IMA}		FAS_{2GTKI}	
	Asciminib	IS-TKI	Asciminib	IS-TKI	Asciminib	IS-TKI
	All Asciminib	All Comparators	Imatinib Stratum	Imatinib Stratum	2G-TKI Stratum	2G-TKI Stratum
	N=201	N=204	N=101	N=102	N=100	N=102
	n·(%)	n·(%)	n·(%)	n·(%)	n·(%)	n·(%)
Individual category						
<=0.0032%	2·(1.0)	1·(0.5)	2·(2.0)	0	0	1·(1.0)
>0.0032% - <=0.01%	4·(2.0)	2·(1.0)	1·(1.0)	0	3·(3.0)	2·(2.0)
>0.01% - <=0.1%	54·(26.9)	12·(5.9)	29·(28.7)	2·(2.0)	25·(25.0)	10·(9.8)
>0.1% - <=1%	92·(45.8)	56·(27.5)	43·(42.6)	22·(21.6)	49·(49.0)	34·(33.3)
>1% - <=10%	28·(13.9)	72·(35.3)	14·(13.9)	37·(36.3)	14·(14.0)	35·(34.3)
>10%	13·(6.5)	47·(23.0)	6·(5.9)	34·(33.3)	7·(7.0)	13·(12.7)
Missing	8·(4.0)	14·(6.9)	6·(5.9)	7·(6.9)	2·(2.0)	7·(6.9)
Assessment not evaluable (1)	0	0	0	0	0	0
Discontinued due to unsatisfactory therapeutic effect/ PD/death (2)	1·(0.5)	3·(1.5)	1·(1.0)	2·(2.0)	0	1·(1.0)
Discontinued due to other reasons (2)	3·(1.5)	6·(2.9)	3·(3.0)	3·(2.9)	0	3·(2.9)
Missing assessment	4·(2.0)	5·(2.5)	2·(2.0)	2·(2.0)	2·(2.0)	3·(2.9)
Cumulative over categories						
<=0.0032%	2·(1.0)	1·(0.5)	2·(2.0)	0	0	1·(1.0)
<=0.01%	6·(3.0)	3·(1.5)	3·(3.0)	0	3·(3.0)	3·(2.9)
<=0.1%	60·(29.9)	15·(7.4)	32·(31.7)	2·(2.0)	28·(28.0)	13·(12.7)
<=1%	152·(75.6)	71·(34.8)	75·(74.3)	24·(23.5)	77·(77.0)	47·(46.1)
<=10%	**180·(89.6)**	**143·(70.1)**	**89·(88.1)**	**61·(59.8)**	**91·(91.0)**	**82·(80.4)**

N: The total number of participants in the treatment group. It is the denominator for percentage (%) calculation.
n: Number of participants who are at the corresponding category.
(1) Assessments from samples with dates after treatment failure criteria were met.
(2) Discontinued on or before the current time point.
PD: Progression of disease.

Source: SoE, table 3-15

MR2.0 at and by all scheduled data collection time points

Achievement of BCR::ABL1 ≤1% (MR 2.0, corresponding to CCyR) at 12 months was achieved by 87.06% in the asciminib arm and 68.14% in the IS-TKI arm (difference 14.78%; 95% CI 7.44; 22.12). The effect was observed at and by all assessed timepoints from week 8 to week 96 (

Table 25). Regarding the FAS_{IMA} population, the MR2.0 rate by Week 48 in $ASCI^{IMA}$ subgroup was 91.1% vs. 69.6% in IS-TKI^{IMA} subgroup (treatment difference of 22.00%, 95% CI: 11.95, 32.06). For FAS_{2GTKI}

MR2.0 rate by Week 48 in ASC^{2G} of 94.0% vs. 84.3% in IS-TKI^{2G} (treatment difference: 9.67%, 95% CI: 1.45, 17.89).

Table 25 MR2.0 (BCR::ABL1 <=1%) rate at and by scheduled time points (FAS)

MR2.0 (*BCR::ABL1* <=1%) rate *at* scheduled time points (FAS)					MR2.0 (*BCR::ABL1* <=1%) rate *by* scheduled time points (FAS)			
	Asciminib All Asciminib N=201	IS-TKI All Comparators N=204	Between treatments[b]		Asciminib All Asciminib N=201	IS-TKI All Comparators N=204	Between treatments[b]	
MR2.0[a]	n (%)	n (%)	Common treatment difference (%)	95% CI	n (%)	n (%)	Common treatment difference (%)	95% CI
Week 8	31 (15.42)	6 (2.94)	**12.52**	(7.02, 18.03)	31 (15.42)	6 (2.94)	**12.52**	(7.02, 18.03)
Week 12	152 (75.62)	71 (34.80)	**41.06**	(32.69, 49.44)	152 (75.62)	72 (35.29)	**40.58**	(32.18, 48.98)
Week 24	178 (88.56)	130 (63.73)	**25.11**	(17.40, 32.81)	182 (90.55)	132 (64.71)	**26.13**	(18.72, 33.54)
Week 36	176 (87.56)	139 (68.14)	**19.68**	(12.08, 27.28)	184 (91.54)	143 (70.10)	**21.70**	(14.55, 28.84)
Week 48	**175 (87.06)**	**148 (72.55)**	**14.78**	**(7.44, 22.12)**	**186 (92.54)**	**157 (76.96)**	**15.85**	**(9.30, 22.40)**
Week 60	175 (87.06)	146 (71.57)	**15.75**	(8.30, 23.20)	186 (92.54)	157 (76.96)	**15.85**	(9.30, 22.40)
Week 72	172 (85.57)	139 (68.14)	**17.70**	(9.92, 25.48)	186 (92.54)	157 (76.96)	**15.85**	(9.30, 22.40)
Week 84	170 (84.58)	130 (63.73)	**21.09**	(13.05, 29.13)	186 (92.54)	157 (76.96)	**15.85**	(9.30, 22.40)
Week 96	**167 (83.08)**	**126 (61.76)**	**21.55**	**(13.31, 29.80)**	**186 (92.54)**	**157 (76.96)**	**15.85**	**(9.30, 22.40)**

[a] Clopper-Pearson 95% CI for observed rates; Wald 95% CI for the unstratified difference between observed rates.

[b] Common treatment difference and common risk difference are synonymous. The common treatment difference and its 95% CI estimated using the Mantel-Haenszel method after stratifying for (a) pre-randomization selected TKI, and (b) baseline ELTS risk groups (both IRT data).

Source: Study J12301 W96 CSR-Table 14.2-1.13.1] and [Study J12301 W96 CSR-Table 14.2-1.14.1

Source: SoE, p 55

MR4.0 at and by all scheduled data collection time points

The MR4.0 rate at and by each scheduled time point was higher for the asciminib arm compared to the IS-TKI arm. Differences were observed in week 24 (23.4% in the asciminib arm compared to 9.8% in the IS-TKI arm, common treatment difference (Δ) of 13.66%, 95% CI: 6.63, 20.68) week 48 (40.8% in the asciminib arm vs. 22.1% in the IS-TKI arm; Δ: 18.91%, 95% CI: 10.30, 27.52) and week 96 (52.7% in the asciminib arm vs. 34.3% in the IS-TKI arm; Δ: 18.62%, 95% CI: 9.34, 27.91, *Table 26*). Regarding MR4.0 rate, the numerical difference between arms by week 48 was 30.22% (95% CI: 18.61, 41.83; 56.4% vs. 28.4%) for the FASIMA and 7.54% (95% CI; -4.77, 19.86; 36.0% vs. 28.4%) for the FAS2G in favour of asciminib.

Table 26 MR4.0 rate at and by scheduled time points (FAS)

MR4.0 rate *at* scheduled time points (FAS)					MR4.0 rate *by* scheduled time points (FAS)			
	Asciminib All Asciminib N=201	IS-TKI All Comparators N=204	Between treatments[b]		Asciminib All Asciminib N=201	IS-TKI All Comparators N=204	Between treatments[b]	
MR4.0[a]	n (%)	n (%)	Common treatment difference (%)	95% CI	n (%)	n (%)	Common treatment difference (%)	95% CI
Week 12	6 (2.99)	3 (1.47)	**1.49**	(-1.35, 4.34)	6 (2.99)	3 (1.47)	**1.49**	(-1.35, 4.34)
Week 24	47 (23.38)	20 (9.80)	**13.66**	(6.63, 20.68)	47 (23.38)	20 (9.80)	**13.66**	(6.63, 20.68)
Week 36	63 (31.34)	30 (14.71)	**16.77**	(8.85, 24.69)	66 (32.84)	31 (15.20)	**17.78**	(9.74, 25.81)
Week 48	**78 (38.81)**	**42 (20.59)**	**18.38**	**(9.96, 26.79)**	**82 (40.80)**	**45 (22.06)**	**18.91**	**(10.30, 27.52)**
Week 60	82 (40.80)	51 (25.00)	**15.94**	(7.13, 24.75)	92 (45.77)	56 (27.45)	**18.48**	(9.50, 27.46)
Week 72	85 (42.29)	53 (25.98)	**16.46**	(7.58, 25.34)	96 (47.76)	61 (29.90)	**18.04**	(8.96, 27.13)
Week 84	91 (45.27)	55 (26.96)	**18.47**	(9.47, 27.47)	101 (50.25)	67 (32.84)	**17.60**	(8.43, 26.77)
Week 96	**98 (48.76)**	**56 (27.45)**	**21.48**	**(12.40, 30.56)**	**106 (52.74)**	**70 (34.31)**	**18.62**	**(9.34, 27.91)**

[a] Clopper-Pearson 95% CI for observed rates; Wald 95% CI for the unstratified difference between observed rates.

[b] Common treatment difference and common risk difference are synonymous. The common treatment difference and its 95% CI estimated using the Mantel-Haenszel method after stratifying for (a) pre-randomization selected TKI, and (b) baseline ELTS risk groups (both IRT data).

Source: Study J12301 W96 CSR-Table 14.2-2.4.1] and [Study J12301 W96 CSR-Table 14.2-2.5.1

The cumulative incidence function for time to first MR4.0 was separately observed in the FAS_{IMA} – population and to a lower extent in the FAS_{2GTKI} population (*Figure 22*, *Figure 23*, *Figure 24*). At Week 96, the majority of participants (97.4% in the asciminib arm and 97.4% in the IS-TKI arm) who achieved MR4.0 continued to remain in MR4.0.

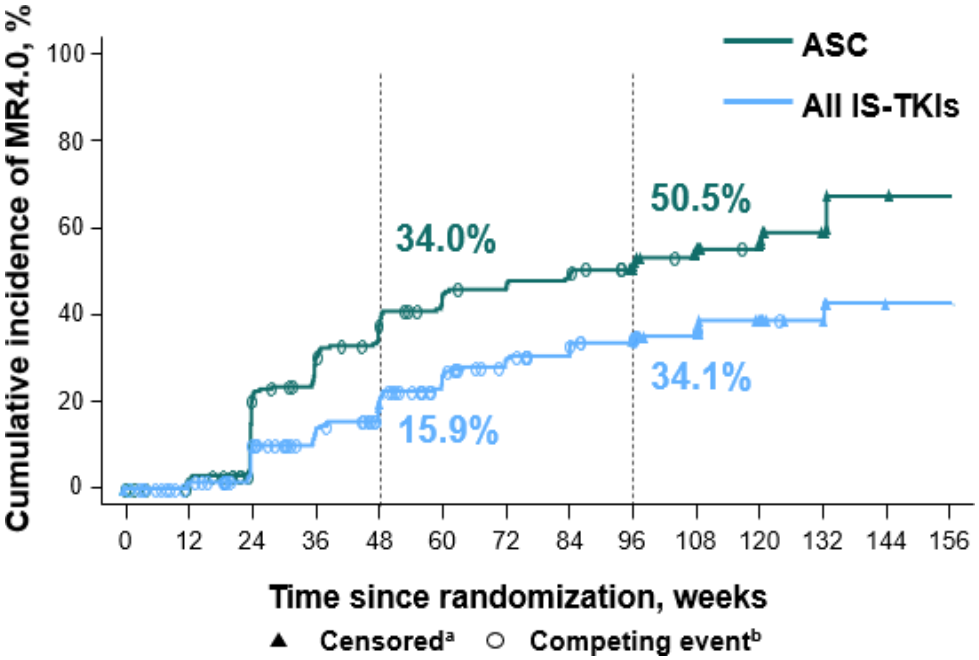


Figure 22: ***Cumulative incidence function of time to first MR4.0 (FAS)***

a Nonresponders were censored at their last molecular assessment date. b Discontinuation from treatment for any reason without prior achievement of MR4.5 is considered a competing event for cumulative incidence of MR4.5. Source: SoE, p 60

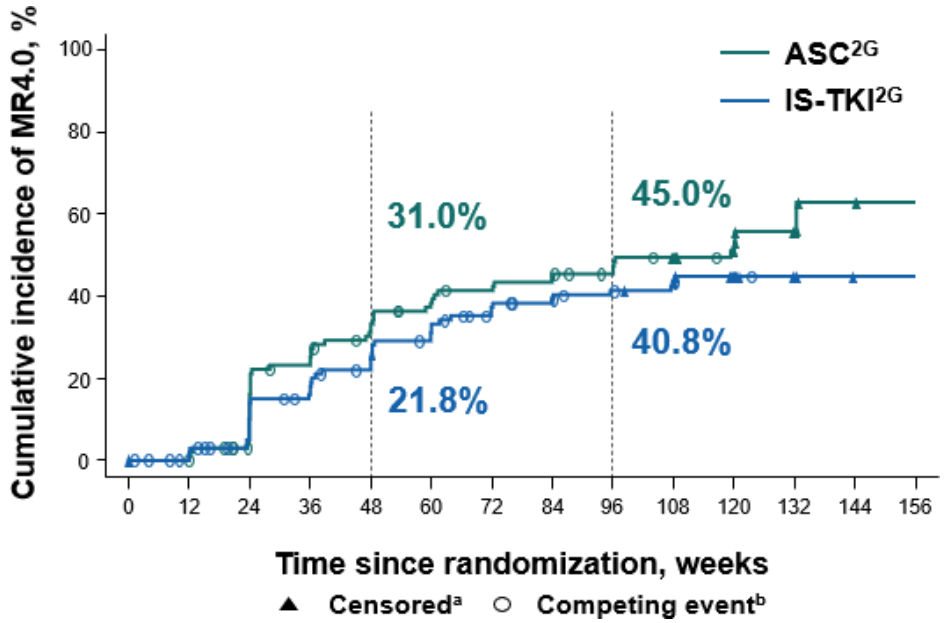


Figure 23:

Cumulative incidence function of time to first MR4.0 (FAS_{2GTKI})

a Nonresponders were censored at their last molecular assessment date. b Discontinuation from treatment for any reason without prior achievement of MR4.0 is considered a competing event for cumulative incidence of MR4.0. Source: SoE, p 61

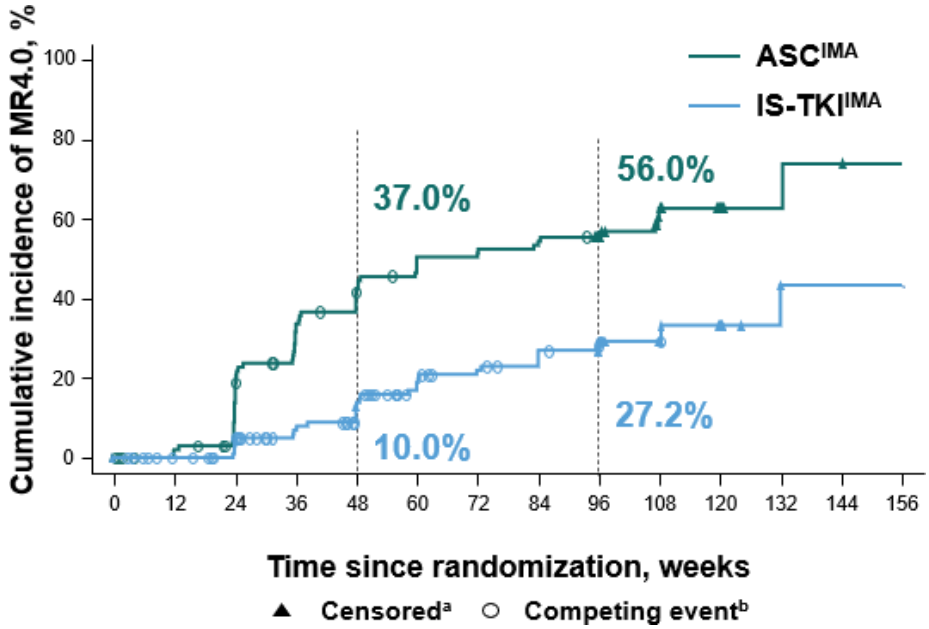


Figure 24: ***Cumulative incidence function of time to first MR4.0 (FAS_{IMA})***

a Nonresponders were censored at their last molecular assessment date. b Discontinuation from treatment for any reason without prior achievement of MR4.0 is considered a competing event for cumulative incidence of MR4.0. Source: SoE; p 59

MR4.5 at and by all scheduled data collection time points

MR4.5 rates at and by different time points were higher in the asciminib arm compared to IS-TKI and are presented in *Table 27*.

For the FAS_{IMA} population, MR4.5 rate was 14.9% vs. 2.9% after 24 weeks, 21.8% vs. 5.9% after 48 weeks and 40.6% vs. 15.7% after 96 weeks for ASC^{IMA} and IS-TKI^{IMA}, respectively.

For the FAS_{2GTKI} population, MR4.5 rate was 14.0% vs. 7.8% after 24 weeks, 18.0% vs. 17.7% after 48 weeks and 32.0% vs. 27.5% after 96 weeks for ASC^{IMA} and IS-TKI^{IMA}, respectively.

At Week 96, the majority of participants (98.9% in the asciminib arm vs. 98.1% in the IS-TKI arm) who achieved MR4.5 continued to remain in MR4.5.

Table 27 MR4.5 rate at and by scheduled time points (FAS)

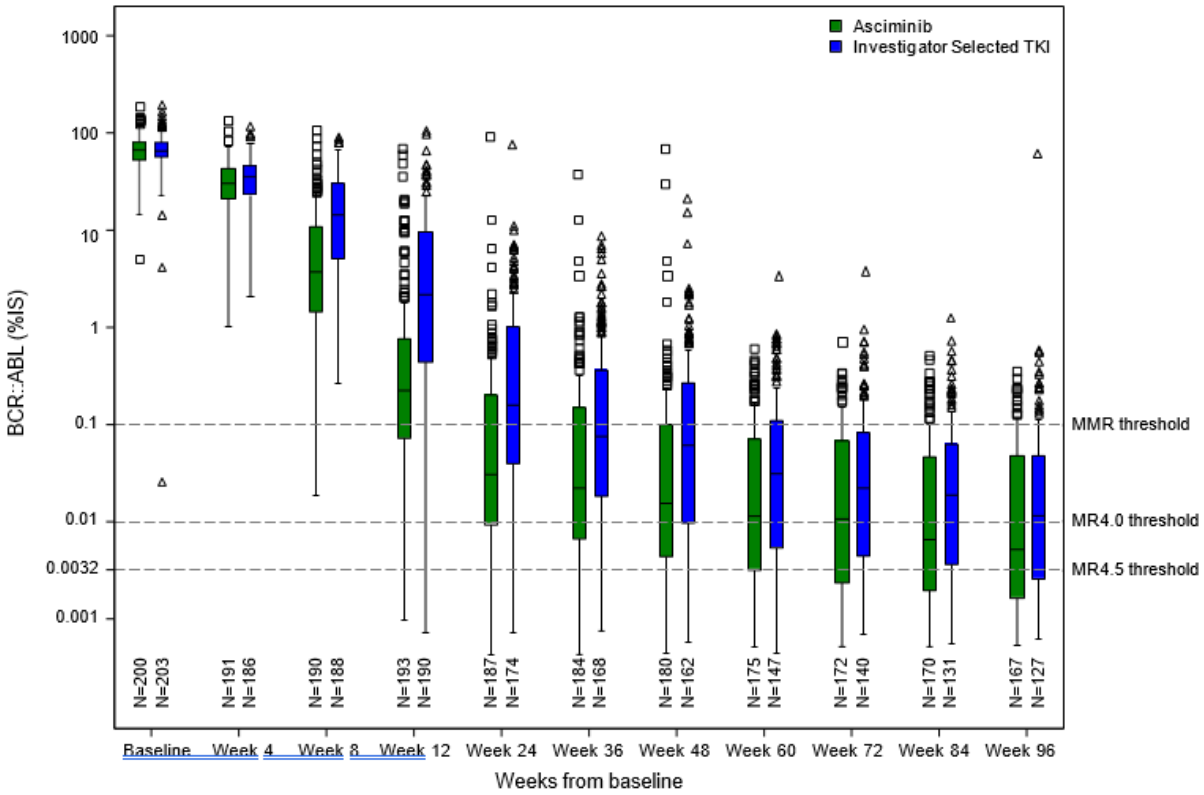
MR4.5 rate at scheduled time points (FAS)					MR4.5 rate by scheduled time points (FAS)			
	Asciminib All Asciminib N=201	IS-TKI All Comparators N=204	Between treatments[b]		Asciminib All Asciminib N=201	IS-TKI All Comparators N=204	Between treatments[b]	
MR4.5[a]	n (%)	n (%)	Common treatment difference (%)	95% CI	n (%)	n (%)	Common treatment difference (%)	95% CI
Week 12	2 (1.00)	1 (0.49)	**0.51**	(-1.17, 2.20)	2 (1.00)	1 (0.49)	**0.51**	(-1.17, 2.20)
Week 24	29 (14.43)	11 (5.39)	**9.11**	(3.43, 14.80)	29 (14.43)	11 (5.39)	**9.11**	(3.43, 14.80)
Week 36	32 (15.92)	19 (9.31)	**6.71**	(0.34, 13.07)	34 (16.92)	21 (10.29)	**6.73**	(0.17, 13.28)
Week 48	**34 (16.92)**	**18 (8.82)**	**8.20**	**(1.78, 14.62)**	**40 (19.90)**	**24 (11.76)**	**8.26**	**(1.26, 15.25)**
Week 60	44 (21.89)	24 (11.76)	**10.20**	(3.09, 17.32)	48 (23.88)	29 (14.22)	**9.77**	(2.26, 17.28)
Week 72	51 (25.37)	31 (15.20)	**10.30**	(2.65, 17.95)	60 (29.85)	37 (18.14)	**11.86**	(3.78, 19.94)
Week 84	57 (28.36)	31 (15.20)	**13.27**	(5.50, 21.04)	64 (31.84)	40 (19.61)	**12.36**	(4.10, 20.62)
Week 96	**62 (30.85)**	**36 (17.65)**	**13.26**	**(5.07, 21.46)**	**73 (36.32)**	**44 (21.57)**	**14.86**	**(6.29, 23.43)**

[a] Clopper-Pearson 95% CI for observed rates; Wald 95% CI for the unstratified difference between observed rates.
[b] Common treatment difference and common risk difference are synonymous. The common treatment difference and its 95% CI estimated using the Mantel-Haenszel method after stratifying for (a) pre-randomization selected TKI, and (b) baseline ELTS risk groups (both IRT data).

MR4.5 was achieved earlier in the asciminib arm compared to the IS-TKI arm overall (KM estimated median time to first MR4.5: 120.3 weeks vs. 131.9 weeks), within the imatinib stratum (108.1 weeks vs. NE), and within the 2G TKI stratum (122.1 weeks vs. 131.9 weeks).

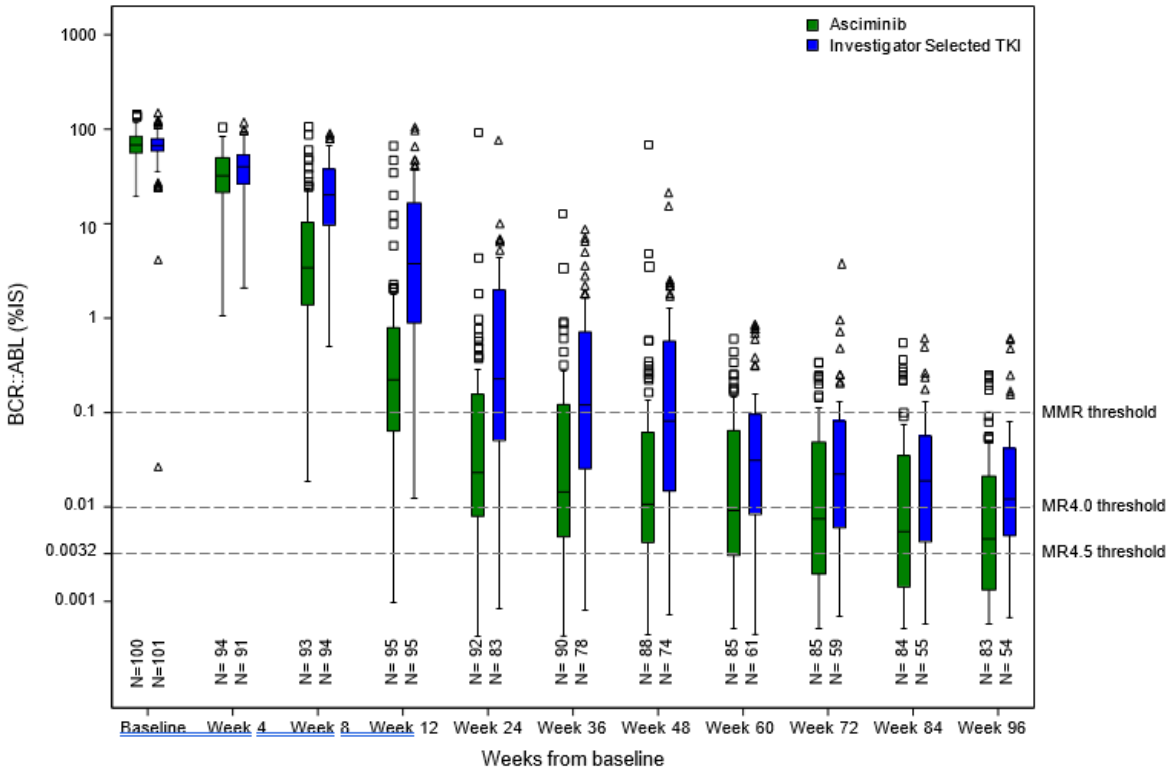
Overview of BCR::ABL1 ratio (%IS) kinetics

BCR::ABL1 levels comparing asciminib vs. IS-TKIs are demonstrated in *Figure 25*, *Figure 26* and Figure 27.



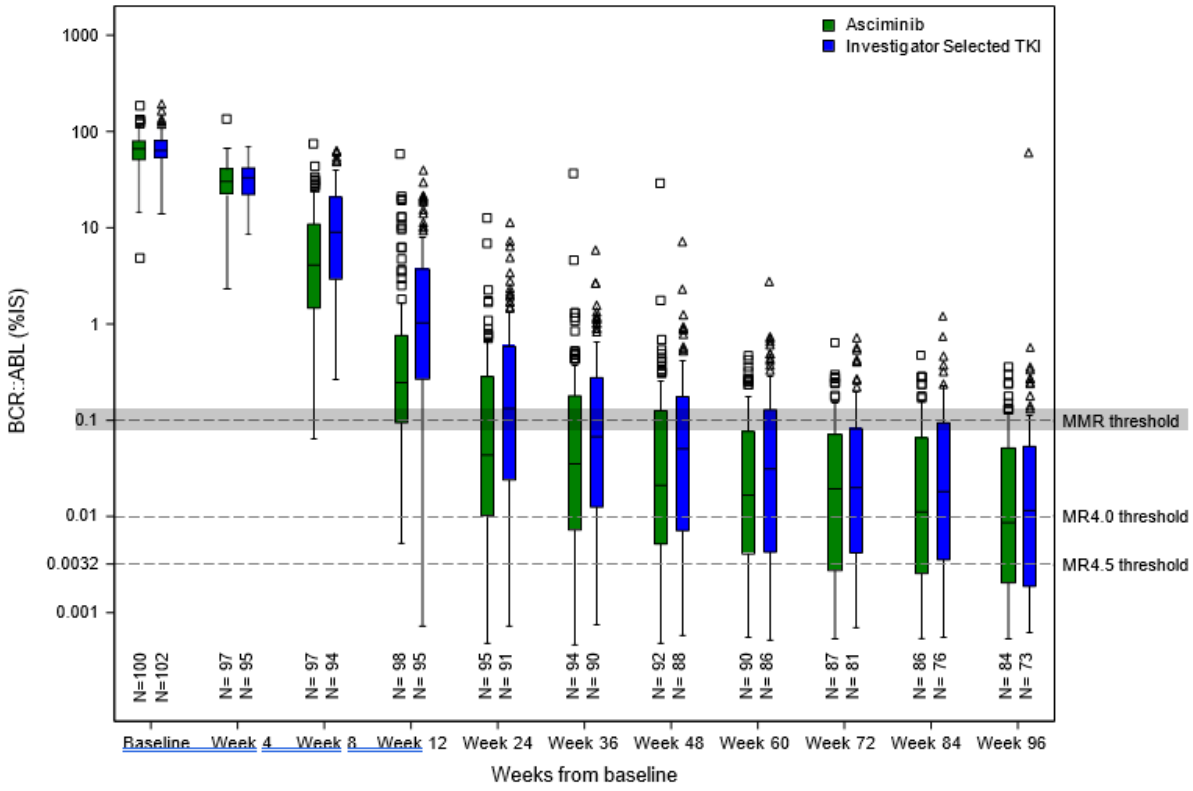
N: number of participants with available assessments.
Values after treatment failure or end of treatment visit are not displayed.
Squares and triangles denote outliers

Figure 25: ***BCR::ABL1 ratio (% IS) summary plot over time (FAS)***
Source: SoE, figure 3-20



N: number of participants with available assessments.
Values after treatment failure or end of treatment visit are not displayed.
Squares and triangles denote outliers

Figure 26: ***BCR::ABL1 ratio (% IS) summary plot over time (FAS$_{IMA}$)***



N: number of participants with available assessments.
Values after treatment failure or end of treatment visit are not displayed.
Squares and triangles denote outliers
Source: [Study J12301 W96 CSR-Figure 14.2-2.2.3]

Figure 27: ***BCR::ABL1 ratio (% IS) summary plot over time ($FAS2_{GTKI}$)***

Complete haematological response

By Week 48, as expected, CHR was achieved in 94.5% of participants in the asciminib arm and 94.1% in the IS-TKI arm.

Cytogenetic response

Due to current medical practice, bone marrow examination for cytogenetic assessment during the course of the study was not mandatory and only performed if clinically indicated. As a result, very few participants (n = 2) had the cytogenetic assessment performed by Week 96.

Other time to event-endpoints

Time to treatment failure:

The KM probability of treatment failure was lower in the asciminib arm compared to the IS-TKI arm (HR=0.37; 95% CI: 0.25, 0.55). By 1 year since randomisation, the KM estimated probability (%) of being treatment failure-free higher in the asciminib arm (88.0%, 95% CI: 82.6, 91.8) compared to the IS-TKI arm (74.1%, 95% CI: 67.5, 79.6). By 2 years since randomisation, the KM estimated probability (%) of being treatment failure-free was higher in the asciminib arm (82.9%, 95% CI: 76.9, 87.5) compared to the IS- TKI arm (61.5%, 95% CI: 54.4, 67.9). The median time to treatment failure was not estimable for either arm.

For the FAS_{IMA} population, (ASCIMA vs. IS-TKIIMA), The KM probability of treatment failure was lower in ASCIMA compared to IS-TKIIMA (HR=0.27; 95% CI: 0.15, 0.47). By 1 year since randomization, the KM estimated probability (%) of being treatment failure-free was higher in ASCIMA (86.0%, 95% CI: 77.5 - 91.5) compared to IS-TKIIMA (63.0%, 95% CI: 52.8, 71.6). By 2 years since randomization, the KM estimated probability (%) of being treatment failure-free was higher in ASCIMA (83.0%, 95% CI: 74.1, 89.1) compared to IS-TKIIMA (52.8%, 95% CI: 42.5, 62.0). The median time to treatment failure was not estimable for either arm.

For the FAS_{2GTKI} population, (ASC^{2G} vs. $IS\text{-}TKI^{2G}$), the KM probability of treatment failure was lower in ASC2G compared to IS-TKI2G (HR=0.54; 95% CI: 0.30, 0.95). By 1 year since randomization, the KM estimated probability (%) of being treatment failure-free was higher in ASC2G (90.0%, 95% CI: 82.2, 94.5) compared to IS-TKI2G (85.1%, 95% CI: 76.6, 90.8). By 2 years since randomization, the KM estimated probability (%) of being treatment failure-free was higher in ASC2G (83.0%, 95% CI: 74.1, 89.1) compared to IS-TKI2G (70.3%, 95% CI: 60.3, 78.2). The median time to treatment failure was not estimable for either arm.

Event free survival (EFS):

The probability of EFS (including 1) treatment failure as defined in ELN criteria 2) confirmed loss of MMR at any time while the study 3) discontinuation from study treatment due to AE 4) progression to AP / BP 5) death due to any cause) remained higher in the asciminib arm compared to the IS-TKI arm through Week 96. At the Week 96 data cut-off, the number of participants with a relevant EFS event was half in the asciminib arm (29/201 participants, 14.4%) arm compared to the IS-TKI arm (60/204 participants, 29.4%, KM plot Figure 28). The number of participants with a competing risk for the EFS endpoint was lower in the asciminib (7/201 participants, 3.5%) compared to the IS-TKI arm (20/204 participants, 9.8%). By 48 weeks since randomization, the estimated probability of EFS was higher in the asciminib arm (91.0%, 95% CI: 86.5, 94.5) compared to the IS-TKI arm (83.6%, 95% CI: 78.1, 88.3). By 96 weeks since randomization, the estimated probability of EFS was higher in the asciminib arm (86.5%, 95% CI: 81.4, 90.8) compared to the IS-TKI arm (71.1%, 95% CI: 64.8, 77.3).

For the FAS_{IMA} population, the probability of EFS remained higher in ASCIMA compared to IS-TKIIMA through Week 96. At the Week 96 data cut-off, the number of participants with a relevant EFS event was half in ASCIMA (17/101 participants, 16.8%) compared to IS-TKIIMA (36/102 participants, 35.3%) [Study J12301 W96 CSR. No participant in ASCIMA and 12/102 (11.8%) participants in IS-TKIIMA had a competing risk for the EFS endpoint. By 48 weeks since randomization, the estimated probability of EFS was higher in ASCIMA (88.0%, 95% CI: 80.8, 93.5) as compared to IS-TKIIMA (78.0%, 95% CI: 69.4, 85.6) [Study J12301 W96 CSR]. By 96 weeks since randomization, the estimated probability of EFS was higher in ASCIMA (Figure 29)

For the FAS2GTKI population, the probability of EFS remained generally higher in ASC2G compared to IS-TKI2G. At the Week 96 data cut-off, the number of participants with a relevant EFS event was half in ASC2G (12/100 participants, 12.0%) arm compared to IS-TKI2G (24/102 participants, 23.5%) [Study J12301 W96 CSR]. The number of participants with a competing risk for the EFS endpoint was similar in ASC2G (7/100 participants, 7.0%) and IS-TKI2G (8/102 participants, 7.8%). By 48 weeks since randomization, the estimated probability of EFS was higher in ASC2G (94.0%, 95% CI: 88.1, 97.6) as compared to IS-TKI2G (89.1%, 95% CI: 82.1, 94.2) [Study J12301 W96 CSR]. By 96 weeks since randomization, the estimated probability of EFS was higher in ASC2G (90.0%, 95% CI: 83.2, 94.9) compared to IS-TKI2G (77.2%, 95% CI: 68.6, 84.9).

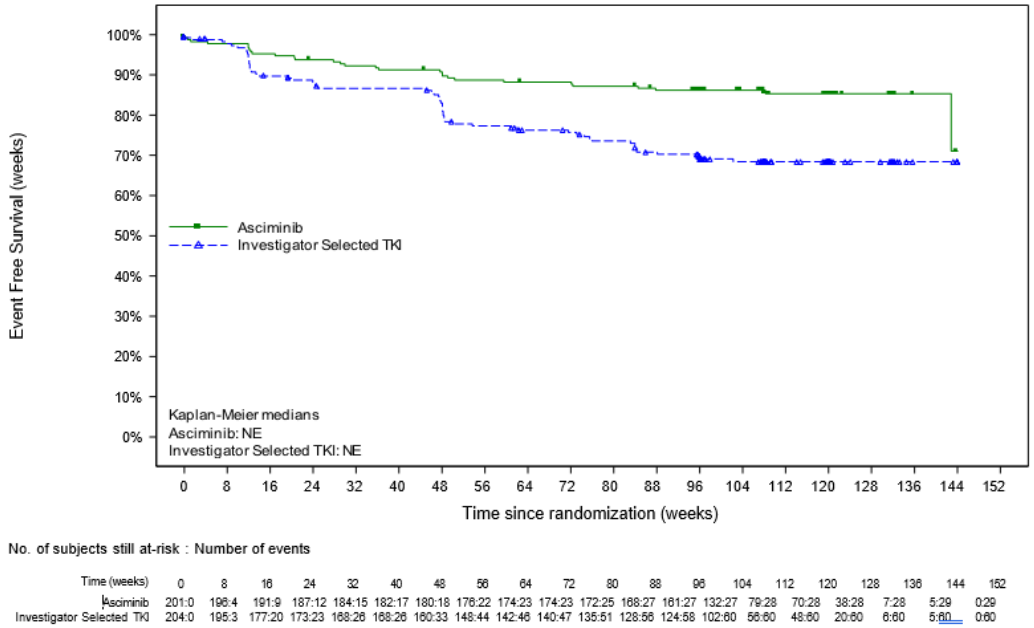


Figure 28 Kaplan-Meier survival plot of event free survival (Full Analysis Set)

Figure 2-6 Kaplan-Meier survival plot of event free survival (Imatinib Full Analysis Set)

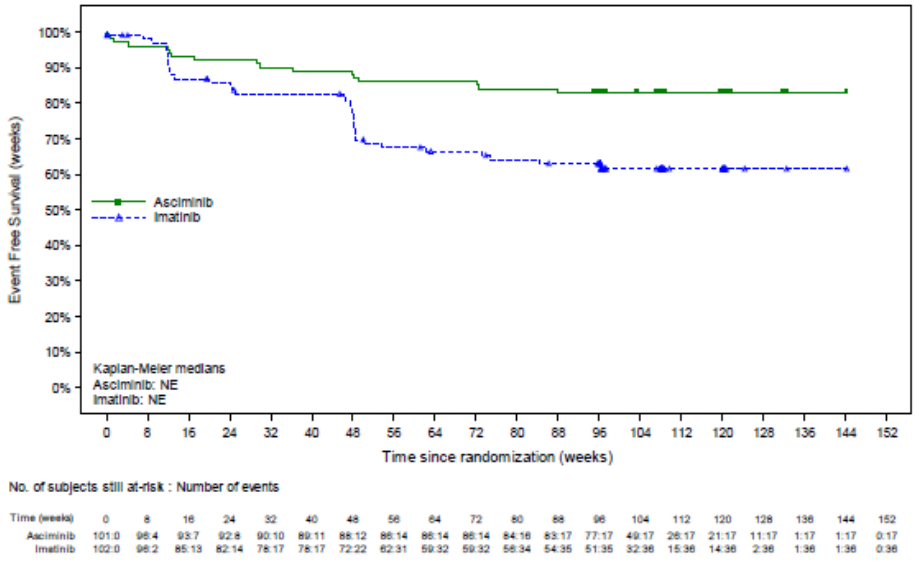


Figure 29 Kaplan-Meier survival plot of event free survival (Imatinib)

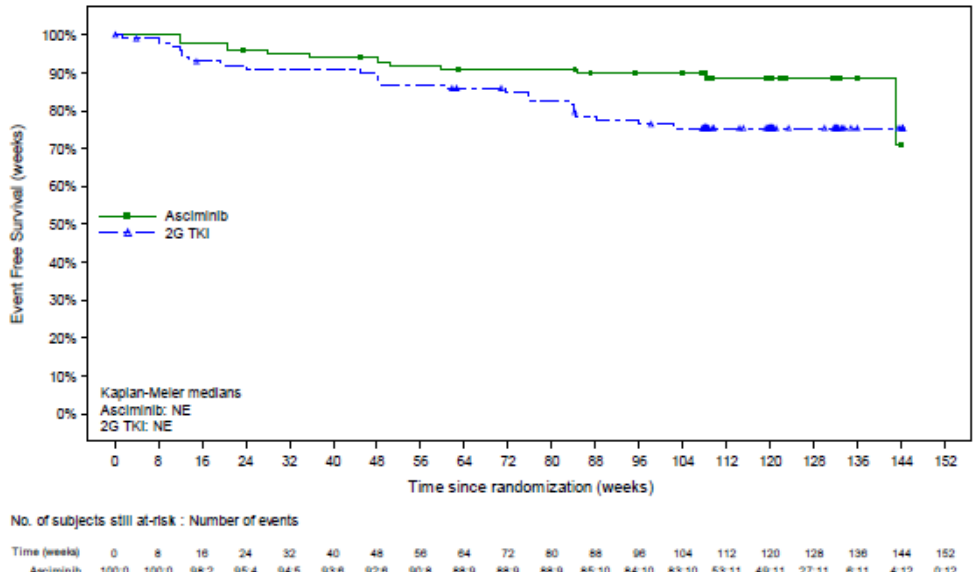


Figure 30 Kaplan-Meier survival plot of event free survival (2G TKI)

Progression free survival (PFS)

A total of 5/201 (2.5%) participants in the asciminib arm and 8/204 participants (3.9%) in the IS-TKI arm had PFS events.

Overall survival (OS)

There were no on-treatment deaths (up to 30 days after end of treatment) in either of the treatment arms. A total of 2/201 (1.0%) participants in the asciminib arm and 4/204 (2.0%) in the IS-TKI arm died during the study.

Other exploratory variables

Details of participants with baseline BCR::ABL1 mutations are shown in *Table 28*.

Table 28 Details of participants with baseline BCR::ABL1 gene mutations identified

Treatment	Ongoing or treatment discontinuation[a]	Reason of treatment discontinuation[a]	Best molecular response[b]	Molecular Response at/ immediately prior to EOT[b]
Asciminib	Ongoing	/	W72: MR2.0 (0.24%)	/
Asciminib	Ongoing	/	W72: MR4.0 (0.01%)	/
Asciminib	Discontinued treatment Within W1	Adverse event	W2: 16.01%	W2: 16.01%
Bosutinib	Ongoing	/	W60: MMR (0.03%)	/

Source: SoE study 12301, page 80

Post-baseline treatment-emergent BCR::ABL1 gene mutations were detected 5% of the patients in the asciminib arm and 3.4% of the patients of the IS-TKI arm, see *Table 8*(Secondary pharmacology). Mutations in the asciminib arm were in the myristoyl pocket or in the functionally adjacent area of the

kinase domain, while the majority of mutations in the IS-TKI arm were in the P-loop adjacent to the ATP binding site.

Among the 10 participants in the asciminib arm with post-baseline BCR::ABL1 gene mutations identified, 1 is still receiving treatment, 5 achieved MR2.0 during study treatment with subsequent elevation in BCR::ABL1 at the time of treatment discontinuation. Overall, 8 discontinued due to unsatisfactory therapeutic effect (6 due to treatment failure per ELN, 1 due to confirmed loss of MMR, and 1 due to other reason (per Investigator's assessment)) and 1 discontinued due to disease progression.

Among the 7 participants in the IS-TKI arm with post-baseline BCR::ABL1 gene mutations identified, 1 is still receiving treatment and achieved MMR, 1 achieved MMR and 2 achieved MR2.0 during the study treatment. Overall, 6 discontinued due to unsatisfactory therapeutic effect (5 due to treatment failure per ELN, and 1 due to confirmed loss of MMR).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 29 Summary of Efficacy for trial CABL001J12301/ ASC4FIRST

Title: A phase III, multi-center, open-label, randomised study of oral asciminib versus Investigator selected TKI in patients with newly diagnosed Philadelphia Chromosome Positive Chronic Myelogenous Leukemia in Chronic Phase		
Study identifier	CABL001J12301, EU CT 2023-508838-33-00, NCT04971226, ASC4FIRST	
Design	Randomised, open-label, active-controlled, multi-centre Phase III study Randomization 1:1 to asciminib or Investigator selected TKI (IS-TKI; imatinib or nilotinib or dasatinib or bosutinib) Prior to randomization, the Investigator selected the TKI to be used in the event of randomization to the comparator arm. Stratification based on: 1) ELTS score (low versus intermediate versus high) 2) Pre-randomization selected TKI (PRS-TKI; imatinib versus 2G TKI (nilotinib or	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	5 years from last participant first treatment (LPFT) not applicable not applicable
Hypothesis	Superiority	
Treatments groups	Asciminib	Treatment: Asciminib 80 mg QD under fasting conditions Duration: until End of Study (5 y from LPFT) or until premature discontinuation

	Investigator selected TKI (IS-TKI)		Treatment: one of the below IS-TKI • Imatinib 400 mg QD administered with food • Nilotinib 300 mg BID (total daily dose of 600 mg) under fasting conditions • Dasatinib 100 mg QD administered with or without a meal • Bosutinib 400 mg QD administered with food Duration: until End of Study (5 y from LPFT) or until premature
	Treatment groups considering stratification based on PRS-TKI:		
	ASC^{IMA}		Participants randomised to asciminib, within the stratum of participants with imatinib as PRS-TKI N=101
	$IS\text{-}TKI^{IMA}$		Participants randomised to IS-TKI, within the stratum of participants with imatinib as PRS-TKI N=102
	ASC^{2G}		Participants randomised to asciminib, within the stratum of participants with 2G TKI as PRS-TKI N=100
	$IS\text{-}TKI^{2G}$		Participants randomised to IS-TKI, within the stratum of participants with 2G TKI as PRS-TKI N=102
Endpoints and definitions	Primary endpoint	MMR rate **at** Week 48	Major Molecular Response (MMR) rate at Week 48 (asciminib vs. IS-TKI overall and within the imatinib stratum; formally tested)
	Key secondary endpoint	MMR rate **at** Week 96	Major Molecular Response (MMR) rate at Week 96 (asciminib vs. IS-TKI overall and within the imatinib stratum; formally tested)
	Other secondary endpoints	MMR rate **at** Week 48 / 96	Major Molecular Response (MMR) rate at Week 48 / Week 96 (asciminib vs. IS-TKI within the 2G TKI stratum; not formally tested)
		MMR rate **by** Week 48 / 96	Major Molecular Response (MMR) rate by Week 48 / Week 96
		EMR	Early Molecular Response (EMR), BCR::ABL1 Ratio (% IS) <=10% at Week 12
		MR2.0 rate **at** / **by** Week 48 /96	Molecular response 2.0 (MR2.0) (BCR::ABL1 ≤1%) rate at Week 48 / Week 96 and by Week 48 / Week 96
		MR4.0 rate **at** / **by** Week 48 /96	Molecular response 4.0 (MR4.0) rate at Week 48 / Week 96 and by Week 48 / Week 96
		MR4.5 rate **at** / **by** Week 48 /96	Molecular response 4.5 (MR4.5) rate at Week 48 / Week 96 and by Week 48 / Week 96
Database lock	Data cut-off dates: 28-Nov-2023 (Week 48 analysis), 22-Oct-2024 (Week 96		

Results and Analysis							
Analysis description	**Primary (Week 48) and Key Secondary (Week 96) Analysis**						
Analysis population and time point description	Intent to treat; participants were analysed according to the treatment and stratum assigned to at randomization Time points: Week 48, Week 96						
Descriptive statistics and estimate variability / Effect estimate per comparison	Treatment group	**Asciminib**	**IS-TKI**	**ASC^{IMA}**	**IS-TKI^{IMA}**	**ASC^{2G}**	**IS-TKI^{2G}**
	Number of subjects	N=201	N=204	N=101	N=102	N=100	N=102
	MMR rate at Week 48	***Primary objectives***				***Other secondary objectives***	
	n (%)	136 (67.66)	100 (49.02)	70 (69.31)	41 (40.20)	66 (66.00)	59 (57.84)
	Common treatment difference (%) (95% CI)[a]	18.88 (9.59, 28.17)		29.55 (16.91, 42.18)		8.17 (-5.14, 21.47)	
	CMH 1-sided test adjusted p-value[b]	<0.001		<0.001		NA	
	MMR rate at Week 96	***Key secondary objectives***					
	n (%)	149 (74.13)	106 (51.96)	77 (76.24)	48 (47.06)	72 (72.00)	58 (56.86)
	Common treatment difference (%) (95% CI)[a]	22.42 (13.55, 31.29)		29.68 (17.57, 41.79)		15.14 (2.32, 27.95)	
	CMH 1-sided test adjusted p-value[b]	<0.001		<0.001		0.011	
	MMR rate by Week 48						
	n (%)	140 (69.65)	104 (50.98)	71 (70.30)	45 (44.12)	69 (69.00)	59 (57.84)
	Common treatment difference (%) (95% CI)[a]	18.92 (9.78, 28.07)		26.65 (14.06, 39.25)		11.16 (−1.92, 24.25)	
	MMR rate by Week 96						
	n (%)	163 (81.09)	125 (61.27)	81 (80.20)	57 (55.88)	82 (82.00)	68 (66.67)
	Common treatment difference (%) (95% CI)[a]	20.13 (11.93, 28.32)		24.90 (13.38, 36.42)		15.33 (3.75, 26.90)	
	EMR						
	n (%) (cumulative categories)	180 (89.6)	143 (70.1)	89 (88.1)	61 (59.8)	91 (91.0)	82 (80.4)
	MR2.0 rate at Week 48						
	n (%)	175 (87.06)	148 (72.55)	85 (84.16)	63 (61.76)	90 (90.00)	85 (83.33)

Common treatment difference (%) (95% CI)[a]	14.78 (7.44, 22.12)		22.86 (11.52, 34.20)		6.66 (-2.36, 15.68)	
MR2.0 rate by Week 48						
n (%)	186 (92.54)	157 (76.96)	92 (91.09)	71 (69.61)	94 (94.00)	86 (84.31)
Common treatment difference (%) (95% CI)[a]	15.85 (9.30, 22.40)		22.00 (11.95, 32.06)		9.67 (1.45, 17.89)	
MR2.0 rate at Week 96						
n (%)	167 (83.08)	126 (61.76)	83 (82.18)	54 (52.94)	84 (84.00)	72 (70.59)
Common treatment difference (%) (95% CI)[a]	21.55 (13.31, 29.80)		29.64 (17.78, 41.50)		13.43 (2.20, 24.66)	
MR2.0 rate by Week 96						
n (%)	186 (92.54)	157 (76.96)	92 (91.09)	71 (69.61)	94 (94.00)	86 (84.31)
Common treatment difference (%) (95% CI)[a]	15.85 (9.30, 22.40)		22.00 (11.95, 32.06)		9.67 (1.45, 17.89)	
MR4.0 rate at Week 48						
n (%)	78 (38.81)	42 (20.59)	43 (42.57)	15 (14.71)	35 (35.00)	27 (26.47)
Common treatment difference (%) (95% CI)[a]	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 (%)	82 (40.80)	45 (22.06)	46 (45.54)	16 (15.69)	36 (36.00)	29 (28.43)
Common treatment difference (%) (95% CI)[a]	18.91 (10.30, 27.52)		30.22 (18.61, 41.83)		7.54 (-4.77, 19.86)	
MR4.0 rate at Week 96						
n (%)	98 (48.76)	56 (27.45)	53 (52.48)	24 (23.53)	45 (45.00)	32 (31.37)
Common treatment difference (%) (95% CI)[a]	21.48 (12.40, 30.56)		29.30 (16.88, 41.73)		13.62 (0.57, 26.68)	
MR4.0 rate by Week 96						
n (%)	106 (52.74)	70 (34.31)	57 (56.44)	29 (28.43)	49 (49.00)	41 (40.20)

Common treatment difference (%) (95% CI)[a]	18.62 (9.34, 27.91)		28.41 (15.74, 41.08)		8.79 (-4.51, 22.09)	
MR4.5 rate at Week 48						
n (%)	34 (16.92)	18 (8.82)	18 (17.82)	5 (4.90)	16 (16.00)	13 (12.75)
Common treatment difference (%) (95% CI)[a]	8.20 (1.78, 14.62)		13.13 (4.69, 21.56)		3.24 (-6.34, 12.83)	
MR4.5 rate by Week 48						
n (%)	40 (19.90)	24 (11.76)	22 (21.78)	6 (5.88)	18 (18.00)	18 (17.65)
Common treatment difference (%) (95% CI)[a]	8.26 (1.26, 15.25)		16.15 (7.01, 25.29)		0.33 (-10.03, 10.69)	
MR4.5 rate at Week 96						
n (%)	62 (30.85)	36 (17.65)	36 (35.64)	12 (11.76)	26 (26.00)	24 (23.53)
Common treatment difference (%) (95% CI)[a]	13.26 (5.07, 21.46)		24.03 (12.89, 35.17)		2.45 (-9.20, 14.09)	
MR4.5 rate by Week 96						
n (%)	73 (36.32)	44 (21.57)	41 (40.59)	16 (15.69)	32 (32.00)	28 (27.45)
Common treatment difference (%) (95% CI)[a]	14.86 (6.29, 23.43)		25.14 (13.44, 36.84)		4.53 (-7.67, 16.73)	

Notes	Participants without PCR assessment at Week 48 are considered non-responders at Week 48 unless they are in MMR at both Week 36 and Week 60. Participants without PCR assessment at Week 96 are considered non-responders at Week 96 unless they are in MMR at both Week 84 and Week 108. [a] Common treatment difference and common risk difference are synonymous. The common treatment difference and its 95% CI estimated using the Mantel-Haenszel method after stratifying for (1) pre-randomization selected TKI, and/or (2) baseline ELTS risk groups (both IRT data). [b] 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: eCTD, Mod. 5.3.5

Supportive studies

CABL001AUS08 / ASC2ESCALATE: Phase II, single-arm, dose-escalation study of asciminib monotherapy in patients with chronic myeloid leukemia in chronic phase (CML-CP) previously treated with 1 prior tyrosine kinase inhibitor (TKI)

Methods

CABL001AUS08 is an ongoing, uncontrolled, open-label, single-arm, dose escalation multicentre phase II study in participants with CML-CP receiving asciminib 80 mg QD monotherapy as second-line or first-line treatment. Both cohorts have completed enrolment, with 101 participants in 2nd line (2L) treatment by 17-Sep-2024 and 95 participants in 1st line (1L) treatment by 25-Jul-2024. Endpoints were BCR::ABL =10%, MR2 rate, MMR rate, MR4 and MR4.5 rates at six months in patient with adequate follow up.

The results of the interim analysis 4 (DCO 15 November 2024) for the 2nd line cohort are described below.

Study participants

No detailed information given about eligibility criteria.

Results

Analysis sets

Information about analysis sets is given in Table *30*.

Table 30 Analysis sets for 2L cohort (FAS)

	2L Cohort N=101
Analysis set	**n (%)**
Safety set	101 (100)
Full analysis set	101 (100)
Efficacy evaluable set at 6 months	63 (62.4)

Baseline characteristics

Overall, 101 patients in the 2L CML-CP were enrolled. However, efficacy and safety data is available for 63 patients, and the magnitude of the characteristics are generally comparable. Baseline characteristics of those patients with available efficacy is presented below in *Table 31*.

In the uncontrolled SAT, mean age of the patients was 49.5 years, weight was 89.3 kg, 54% of participants were male. Pretreatment was with all four approved TKI, with the majority treated by dasatinib (47.6%) and imatinib (36.5%). In 96.8% of patients, no resistance mutations were detected. Mean time from diagnosis was 118.8 days (SD 107.83).

Table 31 Demographics, baseline and disease characteristics for 2L Cohort (Efficacy evaluable set at 6 month)

Characteristic Categories/Statistics	**2L Cohort N=63**
Age group -n (%)	
< 65 years	46 (73.0)
>= 65 years	17 (27.0)
Age (years)	
Mean (SD)	49.5 (17.37)

Median	48.0
Q1-Q3	35.0-67.0
Min-Max	19 - 79
Sex -n (%)	
Male	34 (54.0)
Female	29 (46.0)
Race -n (%)	
White	56 (88.9)
Black or African American	2 (3.2)
Asian	1 (1.6)
Unknown	4 (6.3)
Ethnicity -n (%)	
Hispanic or Latino	8 (12.7)
Not Hispanic or Latino	54 (85.7)
Unknown	1 (1.6)
Weight (kg)	
n	63
Mean (SD)	89.3 (23.84)
Median	88.0
Q1-Q3	71.7-106.9
Min-Max	44 - 137
Height (cm)	
n	55
Mean (SD)	171.3 (9.85)
Median	170.2
Q1-Q3	165.1-180.3
Min-Max	153 - 191
BMI (kg per m2)	
n	55
Mean (SD)	30.5 (7.72)
Median	28.5
Q1-Q3	25.0-35.0
Min-Max	18 - 55
ECOG Performance Status -n (%)	
0	46 (73.0)
1	16 (25.4)
2	1 (1.6)
Time since initial diagnosis of CML (weeks)	
Mean (SD)	118.8 (107.83)
Median	76.4
Q1-Q3	48.9-166.7
Min-Max	8 - 450
Baseline Mutations -n (%)	
E459G	1 (1.6)
V299L	1 (1.6)

No Mutation Detected	61 (96.8)
Total	63 (100)
Evidence of extramedullary Involvement -n (%)	
Yes	1 (1.6)
No	62 (98.4)
Location of extramedullary Involvement -n (%)	
SPLEEN	1 (1.6)
Prior TKI received	
Yes	63 (100)
Medication:[#]	
Bosutinib	2 (3.2)
Dasatinib	30 (47.6)
Imatinib	23 (36.5)
Nilotinib	9 (14.3)
Duration of prior TKI	
<6mo	9 (14.3)
>=6mo and < 12 mo	11 (17.5)
>=12mo	43 (68.3)
Reason to discontinue last TKI	
Lack of efficacy	37 (58.7)
Lack of tolerability	26 (41.3)

[#] Subject 1077001 has received two prior TKIs (DASATINIB for 41 months, IMATINIB for 1 month). The use of more than 1 prior TKI was identified by the sponsor after the patients were enrolled in the trial and have been documented as protocol deviations. The Baseline Mutations were analyzed by Sanger sequencing. Total shows the number of subjects who have been assessed for gene mutations.
Source: Key outputs report, CABL001AUS08 study, tables 4.4a and 4.5 a

Exposure

For 63 patients with evaluable efficacy at six months, duration of exposure is provided in Table 32.

Table 32 Duration of exposure to study drug for 2L Cohort (Efficacy evaluable set at 6 month)

	2L Cohort N=63
Duration of exposure (weeks)	
Mean (SD)	40.1 (17.22)
Median	40.4
Q1-Q3	27.4-49.6
Min-Max	6 - 100
Duration of exposure categories - n(%)	
Less than 24 weeks	6 (9.5)
At least 24 weeks	57 (90.5)
At least 48 weeks	17 (27.0)
At least 96 weeks	1 (1.6)
Duration of exposure (patient-years)	48.44

Duration of exposure to study treatment (weeks) = [(date of last administration of study medication) – (date of first administration of study medication) + 1] / 7
Duration of exposure (patient-years) is the sum of each subject's treatment exposure in year.

Source: key output summary study AUS08

In an update at IA5, median duration of exposure to study treatment was 51.3 weeks in the second-line cohort, 54.5% (55 patients) had a duration of exposure > 48 weeks.

Outcomes and endpoints

At six months for the 63 evaluable patients, at the time of DCO in the ongoing uncontrolled trial and in order of the depths of remission, BCR::ABL1<=10% rate was 90.5% (95%CI: 80.4%, 96.4%) was MR2 rate 82.5% (95%CI: 70.9%, 91.0%), MMR rate 44.4% (95%CI: 31.9%, 57.5%), the rates of MR4.0 was 25.4% (95%CI: 15.3%, 37.9%) and MR4.5 rate was 9.5% (95% CI: 3.6%, 19.6%), see *Table 33*, *Table 36*, *Table 37*.

Subgroup analyses are provided for patients who either dscontinued previous (1L) treatment due to lack of efficacy or lack of tolerability.

Table 33 Major molecular response (MMR) rate at scheduled visits with adequate follow-up for 2L Cohort (Full Analysis Set)

Visit	n/M (%)	2L Cohort N=101	95% CI
at 1 month	1/94 (1.1)		(0.0, 5.8)
at 3 month	34/86 (39.5)		(29.2, 50.7)
at 6 month	28/63 (44.4)		(31.9, 57.5)
at 9 month	22/42 (52.4)		(36.4, 68.0)

n=Number of subjects who achieved MMR at scheduled visits; M=Number of subjects with adequate follow-up (subjects who have assessments within corresponding analysis time interval or subjects who discontinued earlier).
Exact 95% CI is calculated using Pearson-Clopper 2-sided method. Source: table 5-1.1, Key outputs Satudy AUS08

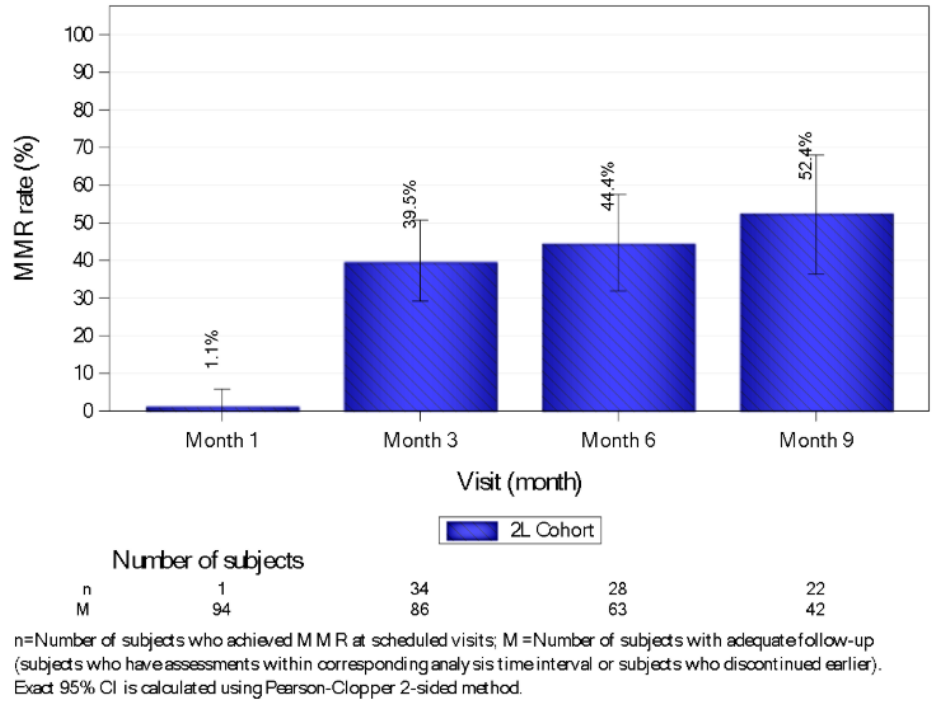


Figure 31: Bar chart with 95% confidence intervals for MMR at visit with adequate follow-up for 2L Cohort (Full Analysis Set)

Subgroup analysis for patients who discontinued last TKI for lack of efficacy

Table 34 MMR rate-Reason to discontinue last TKI: Lack of efficacy (FAS)

	2L Cohort N=101	
Visit	**n/M (%)**	**95% CI**
at 1 month	1/52 (1.9)	(0.1, 10.3)
at 3 month	18/48 (3.75)	(24.0, 52.7)
at 6 month	13/37 (35.1)	(20.2, 52.5)
at 9 month	14/27 (51.9)	(32.0, 71.3)

n=Number of subjects who achieved MMR at scheduled visits; M=Number of subjects with adequate follow-up (subjects who have assessments within corresponding analysis time interval or subjects who discontinued earlier). Exact 95% CI is calculated using Pearson-Clopper 2-sided method. Source: table 5-2.2, Key outputs

Subgroup analysis for patients who discontinued last TKI for lack of tolerability

Table 35 MRR rate -Reason to discontinue last TKI: Lack of tolerability (FAS)

	2L Cohort N=101	
Visit	**n/M (%)**	**95% CI**
at 1 month	0/42	(0.0, 8.4)
at 3 month	16/38 (42.1)	(26.3, 59.2)
at 6 month	15/26 (57.7)	(36.9, 76.7)
at 9 month	8/15 (53.3)	(26.6, 78.7)

n=Number of subjects who achieved MMR at scheduled visits; M=Number of subjects with adequate follow-up (subjects who have assessments within corresponding analysis time interval or subjects who discontinued earlier). Exact 95% CI is calculated using Pearson-Clopper 2-sided method. Source: table 5-2.2, Key outputs

MR2 rate at scheduled visits

Table 36MR2 rate at scheduled visits with adequate follow-up for 2L Cohort (Full Analysis Set)

Visit	n/M (%)	2L Cohort N=101	95% CI
at 1 month	44/94 (46.8)		(36.4, 57.4)
at 3 month	73/86 (84.9)		(75.5, 91.7)
at 6 month	52/63 (82.5)		(70.9, 91.0)
at 9 month	34/42 (81.0)		(65.9, 91.4)

n=Number of subjects who achieved MR2 at scheduled visits; M=Number of subjects with adequate follow-up (subjects who have assessments within corresponding analysis time interval or subjects who discontinued earlier). Exact 95% CI is calculated using Pearson-Clopper 2-sided method. Source: Table 52-1 Key output summary

MR4 rate at scheduled visits

Table 37 MR4 rate at scheduled visits with adequate follow-up for 2L Cohort (Full Analysis Set)

Visit	2L Cohort N=101 n/M (%)	95% CI
at 1 month	0/94	(0.0, 3.9)
at 3 month	10/86 (11.6)	(5.7, 20.4)
at 6 month	16/63 (25.4)	(15.3, 37.9)
at 9 month	10/42 (23.8)	(12.1, 39.5)

Plotted BCR: ABL ratio over time is shown in *Figure 32*.

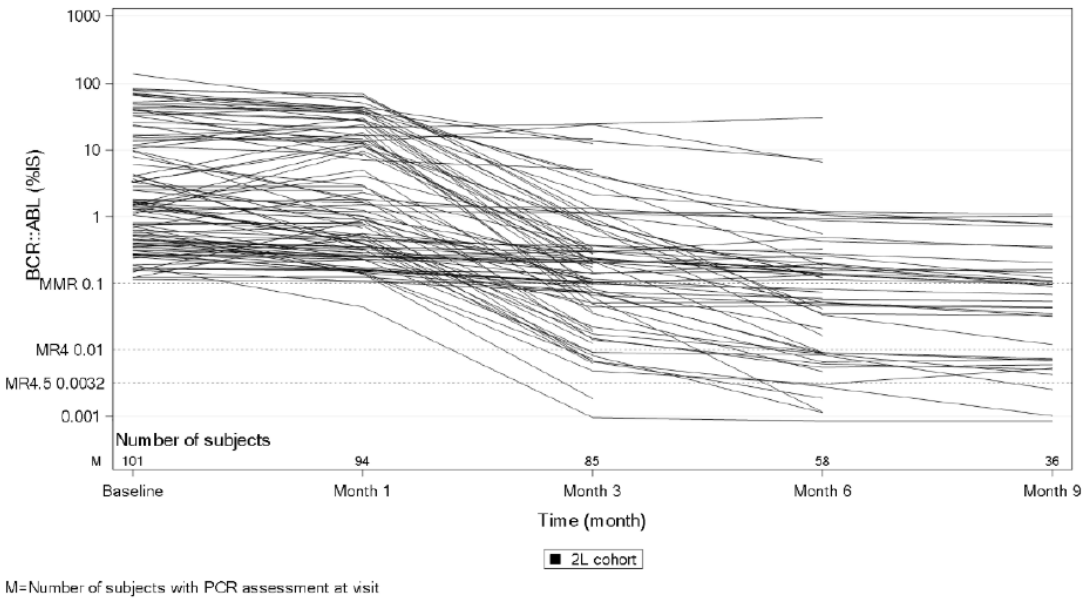


Figure 32: BCR::ABL1 ratio (% IS) plot over time (Full Analysis Set)

At IA5, MMR rate at week 48 in patients with adequate follow-up was 55.6% (40/72; 95% CI: 43.4; 67.3%). Supportive results come from MR2 rate at 48 weeks with 77.8% (56/72; 95% CI: 66.4; 86.7%) and DMR at 48 weeks with 25% (18/72; 95%CI: 15.5%, 36.6%).

CABL001A2302: Phase III study non-comparative, open-label, multi-center, treatment optimisation study (1:1 randomised to 40 mg BID or 80 mg QD) in CML-CP patients after two or more lines of therapy (ASC4OPT)

This study was presented in support of the new posology of 80 mg QD in the 3rd line and beyond.

Methods

Study A2302 is a non-comparative, open-label, multi-center, treatment optimisation study (1:1 randomised to 40 mg BID or 80 mg QD) in CML-CP patients after two or more lines of therapy see Figure 33.

As the study was not designed to assess the comparability between the two dosing regimens, propensity score weighting analysis was conducted to assess differences in MMR rates between the doses in study A2302 and in comparison, to study A 2301 (CABL001A2301, ASCEMBL, pivotal study for use in 3rd line+).

Study design

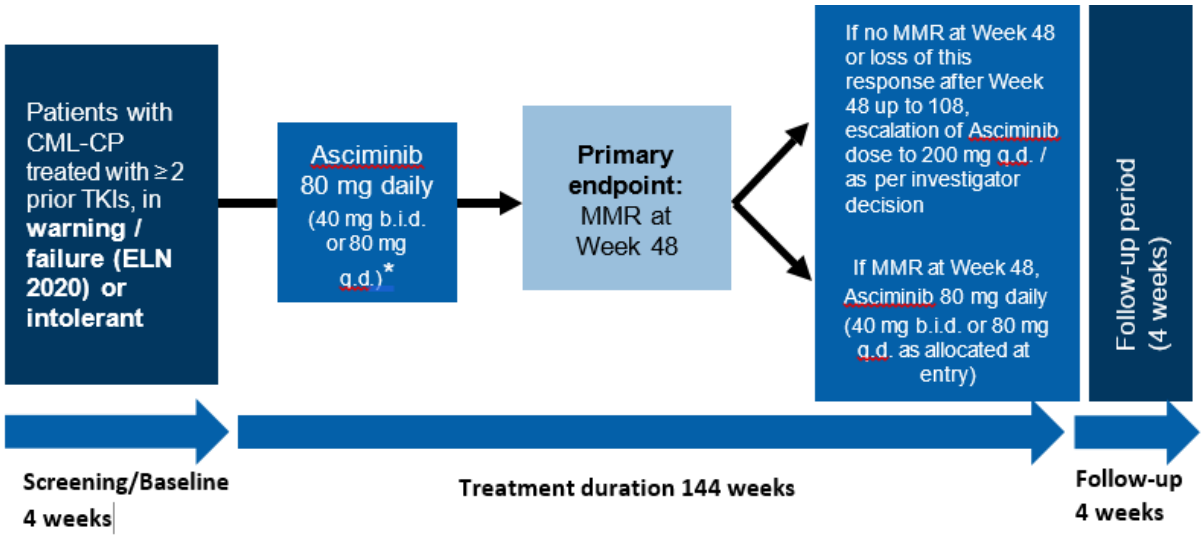


Figure 33: *Design of phase IIIb study A2302 ASC4OPT*

Study population

Participants with chronic myeloid leukemia in chronic phase (CML-CP) who had prior treatment with at least two ATP competitive TKIs and who were either in warning, resistant (ELN 2020 recommendations) or intolerant to the last TKI treatment. Participants who had T315I mutations at any time prior to study entry were excluded.

Treatment

Asciminib administered orally 40 mg BID. or 80 mg QD as 20 mg and 40 mg tablets. The maximum treatment duration for each individual participant is 144 weeks.

Randomisation and stratification

Patients were randomised 1:1 to receive either asciminib 40 mg BID or asciminib 80 mg QD. No stratification was applied.

Outcomes and endpoints

The primary endpoint of the study was major molecular response (MMR) rate at Week 48 for participants without MMR at baseline. Secondary efficacy endpoints are MMR rate for participants without MMR at baseline at all scheduled time-points including weeks 12, 24, 36, 72, 96 and 144 (except week 48), time to MMR, duration of MMR, BCR-ABL1 ratio (% IS) categories at and by scheduled time points, rate of complete cytogenetic response (CCyR) (complete, partial, major, minor, minimal, no response) at weeks 48 and EOT, time to treatment failure, progression free survival and overall survival.

Molecular response (MR) was assessed based on levels of BCR::ABL1 transcripts that were determined by real-time quantitative polymerase chain reaction (RQ-PCR) testing of peripheral blood and analysed at a central testing laboratory. Log reduction in BCR::ABL1 transcripts levels from the standardized baseline value, or the percent ratio of BCR::ABL1 transcripts versus control gene (ABL1) transcripts converted to a reference standard, international scale (IS), were calculated for each sample. Cytogenetic response (CyR) was assessed locally as the percentage of Ph+ metaphases in bone marrow analyses based on at least 20 metaphases examined.

Statistical methodology

The primary efficacy endpoint of the study was the MMR rate at Week 48 evaluated in the overall population (combined 40mg BID and 80 mg QD). A participant was considered to be in MMR at Week 48 if he/she met the MMR criterion (BCR::ABL1 ≤ 0.1% IS) at Week 48 while on study treatment. The primary estimand (the same as discussed for study J12301) was analyzed based on the data from FAS and according to the Intention to Treat (ITT) principle. Exact test for single proportion was used at the one- sided 2.5% level of significance. MMR rate and its 95% confidence interval were based on the Clopper-Pearson method. The null hypothesis was that the MMR rate at Week 48 is equal to 0.23, which is the upper limit of 95% exact binomial CI of the MMR rate at Week 48 in the bosutinib arm (11.1%, 95% CI: 4.2-22.6) from Study A2301. The alternative hypothesis is that the rate is greater than 0.23. The null hypothesis was to be rejected when the lower bound of the two-sided 95% CI is above 23%. Handling of missing data for the primary endpoint was done as for study J12301. In addition to the primary efficacy analysis, various subgroup and sensitivity analyses were performed to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics.

Propensity score weighting (post hoc)

As Study A2302 was not designed to compare the 2 dose groups and no baseline characteristics were stratified, propensity score weighting methodology was used to assess differences in MMR rates between the two dosing regimens, to correct potential imbalances and lack of stratification in baseline characteristics. The propensity score weighting method is a statistical technique that mitigates confounding by balancing dose groups and facilitates indirect comparisons when direct head-to-head comparisons are not possible.

Logistic regression accounting for gender, age (<65, >=65), reason for discontinuation of last prior TKI, number of prior TKI therapies, MR2 status at baseline and mutation type was used to assign

weights to patients which are then used to compare the 40mg BID and 80 mg QD within study A2302 as well as the 40mg BID arm from study A2302 with the 40mg BID arm from study A2301.

Analysis sets

FAS: includes participants resistant or intolerant to 2 or more prior TKI treatments without MMR at baseline to whom study treatment had been assigned by randomization.

Results

Conduct of the study

The study was initiated on 13 October 2021 and had a data cut-off for the week 48 analysis on 12 March 2024. The study enrolled 169 without MMR at baseline with 85 in asciminib 40 mg BID arm and 84 in asciminib 80 mg QD arm.

Protocol deviations

An overview about protocol deviations is given in *Table 38*.

Table 38 Protocol deviations (FAS)

Category Protocol deviation	Asciminib 40 mg b.i.d. N=85 n (%)	Asciminib 80 mg q.d. N=84 n (%)	All subjects N=169 n (%)
Any protocol deviation	48 (56.5)	49 (58.3)	97 (57.4)
Other deviation	40 (47.1)	46 (54.8)	86 (50.9)
KEY PROCEDURES TO ASSESS ELIGIBILITY, RANDOMIZE, REPORT SAFETY EVENTS AND ASSESS THE PRIMARY OR KEY SECONDARY OUTCOME, NOT PERFORMED AS PER PROTOCOL	28 (32.9)	31 (36.9)	59 (34.9)
STUDY PROCEDURES NOT PERFORMED AS PER PROTOCOL	11 (12.9)	17 (20.2)	28 (16.6)
WEEK 48 ASSESSMENTS/VISIT OUT OF WINDOW	5 (5.9)	3 (3.6)	8 (4.7)
MISSING ECG AT DOSE ESCALATION (PRE AND POST DOSE)	2 (2.4)	5 (6.0)	7 (4.1)
RANDOMIZATION GROUP IN IRT (BID/ QD REGIMEN) DIFFERS FROM GROUP REPORTED BY INVESTIGATOR ON CRF	1 (1.2)	0	1 (0.6)
SAE NOT REPORTED TO NOVARTIS WITHIN 24 HOURS OF LEARNING ABOUT THE EVENT	1 (1.2)	3 (3.6)	4 (2.4)
DOSE ESCALATION NOT PER PROTOCOL	0	2 (2.4)	2 (1.2)
Study treatment deviation	13 (15.3)	11 (13.1)	24 (14.2)
STUDY TREATMENT NOT REDUCED/INTERRUPTED/RESUMED AT LOWER DOSE LEVEL AS REQUESTED PER PROTOCOL	9 (10.6)	7 (8.3)	16 (9.5)
MORE THAN 7 DAYS OF CONSECUTIVE INSUFFICIENT TREATMENT OR CUMULATED INSUFFICIENT TREATMENT OVER A PERIOD OF 24 WEEKS IS OBSERVED.	3 (3.5)	3 (3.6)	6 (3.6)
DRUG SUPPLY METHOD CHANGED	2 (2.4)	0	2 (1.2)
PATIENT DID NOT RECEIVE STUDY TREATMENT	0	1 (1.2)	1 (0.6)
Exclusion criteria not met	7 (8.2)	4 (4.8)	11 (6.5)

Patient disposition

An overview about patient disposition is given in Table ***39***.

Table 39 Patient disposition (FAS) study A2302

	Asciminib 40 mg b.i.d. N=85 n (%)	Asciminib 80 mg q.d. N=84 n (%)	All participants N=169 n (%)
Participants randomized			
Treated	84 (98.8)	84 (100)	168 (99.4)
Not treated	1 (1.2)	0	1 (0.6)
Reason for not being treated			
Participant Decision	1 (1.2)	0	1 (0.6)
Treatment ongoing *	68 (80.0)	68 (81.0)	136 (80.5)
Discontinued from treatment	16 (18.8)	16 (19.0)	32 (18.9)
< Week 24	10 (11.8)	7 (8.3)	17 (10.1)
≥ Week 24 and < Week 48	4 (4.7)	3 (3.6)	7 (4.1)
≥ Week 48 and < Week 96	2 (2.4)	6 (7.1)	8 (4.7)
Reason for discontinuation			
Adverse Event	6 (7.1)	4 (4.8)	10 (5.9)
Unsatisfactory Therapeutic Effect	4 (4.7)	3 (3.6)	7 (4.1)
Progressive Disease	1 (1.2)	5 (6.0)	6 (3.6)
Physician Decision	2 (2.4)	2 (2.4)	4 (2.4)
Failure To Meet Continuation Criteria	2 (2.4)	1 (1.2)	3 (1.8)
Participant Decision	1 (1.2)	0	1 (0.6)
Protocol Deviation	0	1 (1.2)	1 (0.6)
< Week 24			
Adverse Event	4 (4.7)	3 (3.6)	7 (4.1)
Failure To Meet Continuation Criteria	2 (2.4)	0	2 (1.2)
Unsatisfactory Therapeutic Effect	2 (2.4)	0	2 (1.2)
Physician Decision	1 (1.2)	0	1 (0.6)
Participant Decision	1 (1.2)	0	1 (0.6)
Progressive Disease	0	3 (3.6)	3 (1.8)
Protocol Deviation	0	1 (1.2)	1 (0.6)
≥ Week 24 and < Week 48			
Adverse Event	2 (2.4)	1 (1.2)	3 (1.8)
Physician Decision	1 (1.2)	1 (1.2)	2 (1.2)
Progressive Disease	1 (1.2)	1 (1.2)	2 (1.2)

≥ Week 48 and < Week 96			
Unsatisfactory Therapeutic Effect	2 (2.4)	3 (3.6)	5 (3.0)
Failure To Meet Continuation Criteria	0	1 (1.2)	1 (0.6)
Physician Decision	0	1 (1.2)	1 (0.6)
Progressive Disease	0	1 (1.2)	1 (0.6)
Post-Treatment safety follow-up for participant who Discontinued			
Did not enter post-treatment safety follow-up	1 (1.2)	0	1 (0.6)
Completed post-treatment safety follow-up	9 (10.6)	11 (13.1)	20 (11.8)
Entered post-treatment safety follow-up, discontinued	6 (7.1)	5 (6.0)	11 (6.5)
Reason for Discontinuation			
Adverse Event	4 (4.7)	0	4 (2.4)
Physician Decision	1 (1.2)	1 (1.2)	2 (1.2)
Participant Decision	1 (1.2)	1 (1.2)	2 (1.2)
Death	0	1 (1.2)	1 (0.6)
Failure To Meet Continuation Criteria	0	1 (1.2)	1 (0.6)
Unsatisfactory Therapeutic Effect	0	1 (1.2)	1 (0.6)

Patient exposure

Table 40 ***Duration of exposure to study drug (Safety set) – Study A2302***

	Asciminib 40 mg b.i.d. N=84	**Asciminib 80 mg QD N=84**	**All participants N=168**
Duration of exposure (week)			
Mean (SD)	68.0 (30.93)	68.7 (27.38)	68.3 (29.12)
Median	67.3	68.6	67.8
Q1-Q3	51.7-92.4	53.1-90.4	52.2-91.5
Min-Max	2.6-116.1	1.3-118.7	1.3-118.7
Duration of exposure categories-n (%)			
Less than 24 weeks	10 (11.9)	8 (9.5)	18 (10.7)
At least 24 weeks	74 (88.1)	76 (90.5)	150 (89.3)
At least 48 weeks	70 (83.3)	73 (86.9)	143 (85.1)
At least 96 weeks	18 (21.4)	16 (19.0)	34 (20.2)
At least 144 weeks	0	0	0
Participant treatment time (year)	109.4	110.5	219.9

Participant treatment time is the sum of each participant's treatment exposure in year.

Information about patient exposure is provided in *Table 40*.

Baseline characteristics

Important baseline characteristics are provided in *Table 41*.

Table 41 Important patient-/ and disease baseline characteristics (Study A2302)

Demographic Variable	Study A2302 40 mg b.i.d. N=85 n (%)	Study A2302 80 mg QD N=84 n (%)
Age Group		
< 65 years	64 (75.3)	59 (70.2)
≥ 65 years	21 (24.7)	25 (29.8)
Sex		
Female	37 (43.5)	27 (32.1)
Male	48 (56.5)	57 (67.9)
Number of prior TKI therapies		
2	47 (55.3)	42 (50.0)
≥3	38 (44.7)	42 (50.0)
Reason for discontinuation of last prior TKI		
Failure	43 (50.6)	46 (54.8)
Intolerance	19 (22.4)	20 (23.8)
Unknown/Other	23 (27.1)	18 (21.4)
MR2 status at baseline		
0	55 (64.7)	58 (69.0)
1	30 (35.3)	26 (31.0)
Mutational status		
Mutation	5 (5.9)	11 (13.1)
Wild Type	68 (80)	63 (75.0)
Unknown	12 (14.1)	10 (11.9)

Outcomes and estimation

Primary endpoint:

The study met its primary endpoint. For participants without MMR at baseline, the overall rate of MMR at Week 48 in FAS was 38.5% (95% CI: 31.09, 46.24).

Objective of the post- hoc comparison

The rate of MMR at Week 48 for patients without MRR at baseline was 42.4% (95% CI: 31.70, 53.55) in the asciminib 40 mg BID group and was 34.5% (95% CI: 24.48, 45.69) in the asciminib 80 mg QD group. The numerical difference in MMR rate between 40 mg BID and 80 mg QD is 7.9%.

Mean exposure was comparable between the arms (68.0 vs. 68.7 weeks)

Baseline characteristics show marginal differences in age groups (≥ 65 years 24.7% vs. 29.8% in 40 mg BID vs 80 mg QD), sex (female 43.5 vs. 32.1), patients with previous treatment failure (50.6% vs. 54.8%) or mutations (5.9% vs. 13.1%). However, the study was 1:1 randomised, and residual imbalances do not justify post-hoc rebalancing for the primary endpoint.

The primary endpoint was met, due to the limitations in study design no comparison between 40 mg BID and 80 mg QD was predefined. The rate of MMR at Week 48 for patients without MRR at baseline was 42.4% (95% CI: 31.70, 53.55) in the asciminib 40 mg BID group and was 34.5% (95% CI: 24.48, 45.69) in the asciminib 80 mg QD group. The numerical difference in MMR rate between 40 mg BID and 80 mg QD is 7.9%, translating into a 23% higher change of achieving MMR at 48 weeks with 40 mg BID than with 80 mg QD without a predefined acceptable margin to claim equivalence.

The performed post-hoc propensity score weighting, which is not adequately justified and reliable, led to a reduced difference of 2.43 (95% CI: -12.71, 17.56).

Propensity score weighting

Some differences in distribution among some baseline demographic and disease characteristics (*Table 41*) were observed between the two dosing regimens. Baseline covariate differences were adjusted using propensity scores, and propensity score weighting was employed to compare the MMR rates at Week 48.

After propensity score weighting by the applicant, the difference in the MMR rates at Week 48 between the 40 mg BID and 80 mg QD dosing regimens was reduced. (MMR of 36.95% vs 34.52%, post- hoc p=0.753). The adjusted MMR rate at Week 48 in the 40 mg BID was 36.95% and the difference in MMR rate between the 40 mg BID and the 80 mg QD dose groups after post-hoc adjustment was 2.43 (95% CI: -12.71, 17.56, Table *42*).

Table 42 MMR rates at Week 48 for asciminib 80 mg QD vs. unadjusted/adjusted 40 mg BID dosing regimens - Study A2302

Study	N	MMR Week 48 (%)	Difference	95% CI	p-value
80 mg q.d.	84	34.52			
40 mg b.i.d. adjusted	71[a]	36.95	2.43	(-12.71, 17.56)	0.753[b]
40 mg b.i.d. unadjusted	85	42.35			

Cumulative MMR rate at scheduled timepoints is presented in *Table 43* and the cumulative incidence visualised in *Figure 34*. Risk difference at scheduled timepoints is 5.4% at week 12, 6.8% at week 24, 7.8% at week 36 and 5.4% at week 48 in favour of 40mg BID in comparison to 80 mg QD.

Table 43 MMR rate at scheduled timepoints (Full analysis set) – Study A2302

Table 3-11 MMR rate by scheduled timepoints (Full analysis set) – Study A2302

	Asciminib 40 mg b.i.d. N=85		Asciminib 80 mg q.d. N=84		All participants N=169	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
MMR (1)						
by Overall	37 (43.5)	(32.80, 54.72)	32 (38.1)	(27.71, 49.34)	69 (40.8)	(33.34, 48.64)
by Week 12	26 (30.6)	(21.05, 41.53)	20 (23.8)	(15.19, 34.35)	46 (27.2)	(20.67, 34.59)
by Week 24	31 (36.5)	(26.29, 47.62)	26 (31.0)	(21.31, 41.98)	57 (33.7)	(26.65, 41.39)
by Week 36	37 (43.5)	(32.80, 54.72)	30 (35.7)	(25.55, 46.92)	67 (39.6)	(32.22, 47.44)
by Week 48	37 (43.5)	(32.80, 54.72)	32 (38.1)	(27.71, 49.34)	69 (40.8)	(33.34, 48.64)

(1) Pearson-Clopper 95% 2-sided CI for response rate.
Source: Study A2302 W48 CSR - Table 14.2-1.2

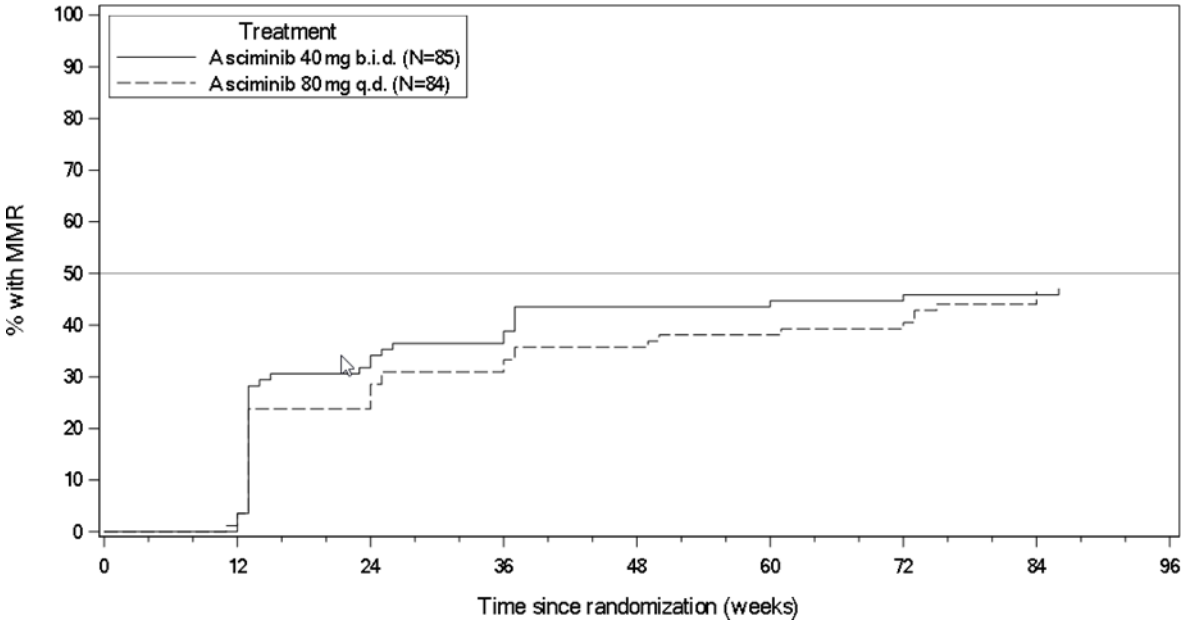


Figure 34: Cumulative incidence of MMR (Full analysis set) – Study A2302

The cumulative response plot of time to first MMR is shown below. The median time to response was 59.3 weeks (95% CI: 24.1, NE) vs 72.1 weeks (95% CI: 48.1, NE) for patients treated with 40 mg BID or 80 mg QD, respectively.

Table 44 Kaplan-Meier estimates of time to first MMR (Full analysis set) – Study A2302

	Asciminib 40 mg b.i.d. N=85	Asciminib 80 mg q.d. N=84	All participants N=169
Number of response (n)	40	39	79
Percentage of response (n/N) (%)	47.1	46.4	46.7
Time to response (week)			
K-M percentiles (95% CI)			
25th	12.4 (12.1, 22.7)	23.7 (12.1, 36.0)	12.4 (12.3, 23.7)
50th	59.3 (24.1, NE)	72.1 (48.1, NE)	72.1 (36.9, NE)
75th	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
K-M % in response (95% CI)			
24 weeks	62.7 (50.9, 72.4)	70.3 (59.0, 79.0)	66.6 (58.6, 73.3)
48 weeks	51.5 (39.7, 62.1)	62.6 (51.1, 72.2)	57.2 (49.1, 64.6)
72 weeks	46.5 (34.0, 58.1)	54.9 (42.4, 65.8)	50.8 (42.0, 58.9)
96 weeks	40.7 (25.7, 55.2)	39.5 (25.2, 53.4)	40.6 (30.4, 50.5)
144 weeks	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

CIs for K-M percentiles are based on Brookmeyer and Crowley (1982).
CIs for K-M estimates of % in response are based on Greenwood formula.
NE: Not estimable.
Source: Study A2302 W48 CSR - Table 14.2-1.18

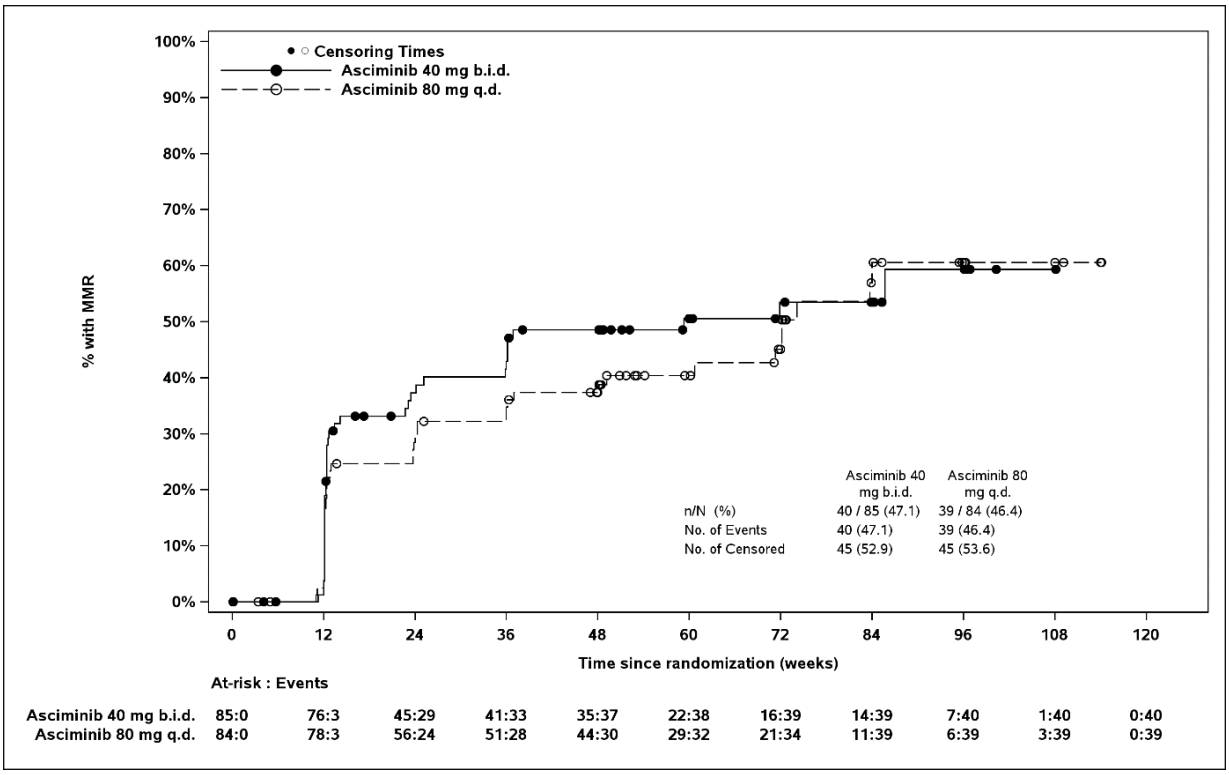


Figure 35 Cumulative response plot of time to first MMR (Full analysis set) – Study A2302

Secondary endpoints: other depth of response levels

BCR::ABL1 ≤ 10% rate

The BCR::ABL1 ≤ 10% rate for all participants at 12 weeks was 75.1%, at 24 weeks was 74.6%, at 36 weeks was 76.9% and at 48 weeks was 75.1%. The BCR::ABL1 ≤ 10% rate by scheduled timepoints showed overall (by 48 weeks) was 82.2%.

The comparison of responses between 40 mg BID and 80 mg QD doses is provided in *Table 45* and *Table 46*.

Table 45 BCR::ABL1 ≤ 10% rate at scheduled timepoints (Full analysis set) – Study A2302

	Asciminib 40 mg b.i.d. N=85		Asciminib 80 mg q.d. N=84		All participants N=169	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
BCR::ABL1 ≤ 10% (1)						
at Week 12	59 (69.4)	(58.47, 78.95)	68 (81.0)	(70.92, 88.70)	127 (75.1)	(67.93, 81.46)
at Week 24	62 (72.9)	(62.21, 82.01)	64 (76.2)	(65.65, 84.81)	126 (74.6)	(67.30, 80.93)
at Week 36	61 (71.8)	(60.96, 81.00)	69 (82.1)	(72.26, 89.65)	130 (76.9)	(69.83, 83.05)
at Week 48	61 (71.8)	(60.96, 81.00)	66 (78.6)	(68.26, 86.78)	127 (75.1)	(67.93, 81.46)

(1) Pearson-Clopper 95% 2-sided CI for response rate
Participants without PCR assessment at a time point are considered as non-responders at that time point.
Source: Study A2302 W48 CSR - Table 14.2-1.7

Table 46 BCR::ABL1 ≤ 10% rate by scheduled timepoints (Full analysis set) – Study A2302

	Asciminib 40 mg b.i.d. N=85		Asciminib 80 mg q.d. N=84		All participants N=169	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
BCR::ABL1 ≤ 10% (1)						
by overall	65 (76.5)	(66.03, 85.00)	74 (88.1)	(79.19, 94.14)	139 (82.2)	(75.64, 87.69)
by Week 12	59 (69.4)	(58.47, 78.95)	68 (81.0)	(70.92, 88.70)	127 (75.1)	(67.93, 81.46)
by Week 24	63 (74.1)	(63.48, 83.01)	72 (85.7)	(76.38, 92.39)	135 (79.9)	(73.04, 85.65)
by Week 36	65 (76.5)	(66.03, 85.00)	74 (88.1)	(79.19, 94.14)	139 (82.2)	(75.64, 87.69)
by Week 48	65 (76.5)	(66.03, 85.00)	74 (88.1)	(79.19, 94.14)	139 (82.2)	(75.64, 87.69)

(1) Pearson-Clopper 95% 2-sided CI for response rate.
Source: Study A2302 W48 CSR - Table 14.2-1.8

BCR::ABL1 ⩽ 1% level (MR2.0)

The comparison of responses between 40 mg BID and 80 mg QD doses is provided in *Table 47* and *Table 48*.

Table 47 BCR::ABL1 ⩽ 1% rate at scheduled timepoints (Full analysis set) – Study A2302

	Asciminib 40 mg b.i.d. N=85		Asciminib 80 mg q.d. N=84		All participants N=169	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
BCR::ABL1 ≤ 1% (1)						
at Week 12	52 (61.2)	(49.99, 71.56)	45 (53.6)	(42.35, 64.53)	97 (57.4)	(49.57, 64.96)
at Week 24	55 (64.7)	(53.59, 74.77)	49 (58.3)	(47.06, 69.00)	104 (61.5)	(53.76, 68.91)
at Week 36	54 (63.5)	(52.38, 73.71)	54 (64.3)	(53.08, 74.45)	108 (63.9)	(56.17, 71.14)
at Week 48	55 (64.7)	(53.59, 74.77)	50 (59.5)	(48.25, 70.10)	105 (62.1)	(54.36, 69.47)

(1) Pearson-Clopper 95% 2-sided CI for response rate
Participants without PCR assessment at a time point are considered as non-responders at that time point.
Source: Study A2302 W48 CSR - Table 14.2-1.9

Table 48 BCR::ABL1 ≤ 1% rate by scheduled timepoints (Full analysis set) Study A2302

	Asciminib 40 mg b.i.d. N=85		Asciminib 80 mg q.d. N=84		All participants N=169	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
BCR::ABL1 ≤ 1% (1)						
by overall	58 (68.2)	(57.24, 77.92)	56 (66.7)	(55.54, 76.58)	114 (67.5)	(59.83, 74.45)
by Week 12	52 (61.2)	(49.99, 71.56)	45 (53.6)	(42.35, 64.53)	97 (57.4)	(49.57, 64.96)
by Week 24	56 (65.9)	(54.80, 75.82)	51 (60.7)	(49.45, 71.20)	107 (63.3)	(55.57, 70.58)
by Week 36	57 (67.1)	(56.02, 76.87)	56 (66.7)	(55.54, 76.58)	113 (66.9)	(59.22, 73.90)
by Week 48	58 (68.2)	(57.24, 77.92)	56 (66.7)	(55.54, 76.58)	114 (67.5)	(59.83, 74.45)

(1) Pearson-Clopper 95% 2-sided CI for response rate.
Source: Study A2302 W48 CSR - Table 14.2-1.10

At the the BCR::ABL1 ≤ 1% level, at week 48, 64.7% vs. 59.5% of patients showed a response for the 40 mg BID arm vs 80 mg QD arm, respectively. The numerical trend is supported by assessments at different timepoints (week 12, 24) and an assessment by scheduled timepoints (week 12, 24, 36, 48).

BCR::ABL1 ≤ 0.1% level (MR3.0)

Responses at the MR3.0 level (MMR) were the primary objective of the study A2302 and described there.

Rate of MR4.0 and MR 4.5 (DMR)

At the MR4.0 level, at week 48, 20.0% vs. 13.0% of patients showed a response for the 40 mg BID arm vs 80 mg QD arm, respectively. The numerical trend is supported by assessments at different timepoints (week 12, 24, 36) and an assessment *by* scheduled timepoints (week 12, 24, 36, 48).

At the MR4.5 level, at week 48, 11.8% vs. 8.3% of patients showed a response for the 40 mg BID arm vs 80 mg QD arm, respectively. The numerical trend is supported by assessments at different timepoints (week 12, 24, 36) and an assessment by scheduled timepoints (week 24, 36, 48).

Table 49 MR4 rate at scheduled time points (Full analysis set) – Study A2302

	Asciminib 40 mg b.i.d. N=85		Asciminib 80 mg q.d. N=84		All participants N=169	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
MR4 (1)						
at Week 12	8 (9.4)	(4.15, 17.71)	3 (3.6)	(0.74, 10.08)	11 (6.5)	(3.29, 11.35)
at Week 24	19 (22.4)	(14.03, 32.69)	9 (10.7)	(5.02, 19.37)	28 (16.6)	(11.30, 23.05)
at Week 36	17 (20.0)	(12.10, 30.08)	10 (11.9)	(5.86, 20.81)	27 (16.0)	(10.80, 22.39)
at Week 48	17 (20.0)	(12.10, 30.08)	11 (13.1)	(6.72, 22.22)	28 (16.6)	(11.30, 23.05)

(1) Pearson-Clopper 95% 2-sided CI for response rate
Participants without PCR assessment at a time point are considered as non-responders at that time point.
Source: Study A2302 W48 CSR - Table 14.2-1.3

Table 50 MR4 rate by scheduled time points (Full analysis set) – Study A2302

	Asciminib 40 mg b.i.d. N=85		Asciminib 80 mg q.d. N=84		All participants N=169	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
MR4 (1)						
by Overall	19 (22.4)	(14.03, 32.69)	12 (14.3)	(7.61, 23.62)	31 (18.3)	(12.82, 25.01)
by Week 12	8 (9.4)	(4.15, 17.71)	3 (3.6)	(0.74, 10.08)	11 (6.5)	(3.29, 11.35)
by Week 24	19 (22.4)	(14.03, 32.69)	9 (10.7)	(5.02, 19.37)	28 (16.6)	(11.30, 23.05)
by Week 36	19 (22.4)	(14.03, 32.69)	11 (13.1)	(6.72, 22.22)	30 (17.8)	(12.31, 24.36)
by Week 48	19 (22.4)	(14.03, 32.69)	12 (14.3)	(7.61, 23.62)	31 (18.3)	(12.82, 25.01)

(1) Pearson-Clopper 95% 2-sided CI for response rate.
Source: Study A2302 W48 CSR - Table 14.2-1.4

Table 51 MR4.5 rate at scheduled time point (Full analysis set) – Study A2302

	Asciminib 40 mg b.i.d. N=85		Asciminib 80 mg q.d. N=84		All participants N=169	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
MR4.5 (1)						
at Week 12	1 (1.2)	(0.03, 6.38)	1 (1.2)	(0.03, 6.46)	2 (1.2)	(0.14, 4.21)
at Week 24	10 (11.8)	(5.79, 20.57)	4 (4.8)	(1.31, 11.75)	14 (8.3)	(4.60, 13.51)
at Week 36	12 (14.1)	(7.51, 23.36)	6 (7.1)	(2.67, 14.90)	18 (10.7)	(6.44, 16.31)
at Week 48	10 (11.8)	(5.79, 20.57)	7 (8.3)	(3.42, 16.42)	17 (10.1)	(5.97, 15.62)

(1) Pearson-Clopper 95% 2-sided CI for response rate
Participants without PCR assessment at a time point are considered as non-responders at that time point.
Source: Study A2302 W48 CSR - Table 14.2-1.5

Table 52 MR4.5 rate by scheduled time point (Full analysis set) – Study A2302

	Asciminib 40 mg b.i.d. N=85		Asciminib 80 mg q.d. N=84		All participants N=169	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
MR4.5 (1)						
by Overall	15 (17.6)	(10.23, 27.43)	7 (8.3)	(3.42, 16.42)	22 (13.0)	(8.34, 19.04)
by Week 12	1 (1.2)	(0.03, 6.38)	1 (1.2)	(0.03, 6.46)	2 (1.2)	(0.14, 4.21)
by Week 24	10 (11.8)	(5.79, 20.57)	4 (4.8)	(1.31, 11.75)	14 (8.3)	(4.60, 13.51)
by Week 36	14 (16.5)	(9.31, 26.09)	6 (7.1)	(2.67, 14.90)	20 (11.8)	(7.38, 17.68)
by Week 48	15 (17.6)	(10.23, 27.43)	7 (8.3)	(3.42, 16.42)	22 (13.0)	(8.34, 19.04)

(1) Pearson-Clopper 95% 2-sided CI for response rate.
Source: Study A2302 W48 CSR - Table 14.2-1.6

Duration of MMR (MR3.0) and MR4.0

The majority of participants who achieved MMR continued to have MMR; subsequent loss of response was reported in 3 participants (3.8%) at or before 72 weeks. One participant (80 mg QD) had loss of response by 24 weeks, one participant (40 mg b.i.d.) had loss of response by 48 weeks, and one participant (40 mg b.i.d.) had loss of response by 72 weeks.

MMR was lost in only 5% (2/40 patients, 40 mg BID) and 2.5% (1/39 patients, 80 mg QD) before week 72. MR4.0 was lost by 14.3% of patients in each arm (3/21 patients in 40 mg BID and 2/14 in 80 mg QD) before week 72.

Time to treatment failure

Treatment failure prior to 48 weeks was defined as participants who discontinued study treatment. Starting at 48 weeks, treatment failure included participants with BCR::ABL1 > 1%. For participants without MMR at baseline, the Kaplan-Meier plot of time to treatment failure is presented in Figure 36. After a median follow-up time of 1.0 year, 23.5% vs. 36.9% of patients had treatment failure in the 40 mg BID and 80 mg QD arm, respectively.

Table 53 Kaplan-Meier estimates of time to treatment failure (Full analysis set) – Study A2302

	Asciminib 40 mg b.i.d. N=85 n (%)	Asciminib 80 mg q.d. N=84 n (%)	All participants N=169 n (%)
Number of participants with event (n)	20	31	51
Percentage of participants with events (n/N) (%)	23.5	36.9	30.2
Maximum follow-up (year)	2.1	2.1	2.1
Median follow-up (year)	1.0	1.0	1.0
Time to event (year)			
K-M percentiles (95% CI)			
25th	0.9 (0.9, NE)	0.9 (0.9, 0.9)	0.9 (0.9, 0.9)
50th	NE (NE, NE)	NE (0.9, NE)	NE (NE, NE)
75th	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
K-M % event free (95% CI)			
1 Year	70.7 (58.1, 80.1)	58.9 (46.9, 69.1)	64.6 (56.1, 71.9)
2 Years	70.7 (58.1, 80.1)	58.9 (46.9, 69.1)	64.6 (56.1, 71.9)
3 Years	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

% Event free probability estimate is the estimated probability that a participant will not have an event prior to the specified time point. % Event free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups. Here event is defined by treatment failure.
CIs for K-M percentiles are based on Brookmeyer and Crowley (1982).
CIs for K-M estimates of % event free are based on Greenwood formula.
NE: Not estimable.
Source: Study A2302 W48 CSR - Table 14.2-3.1

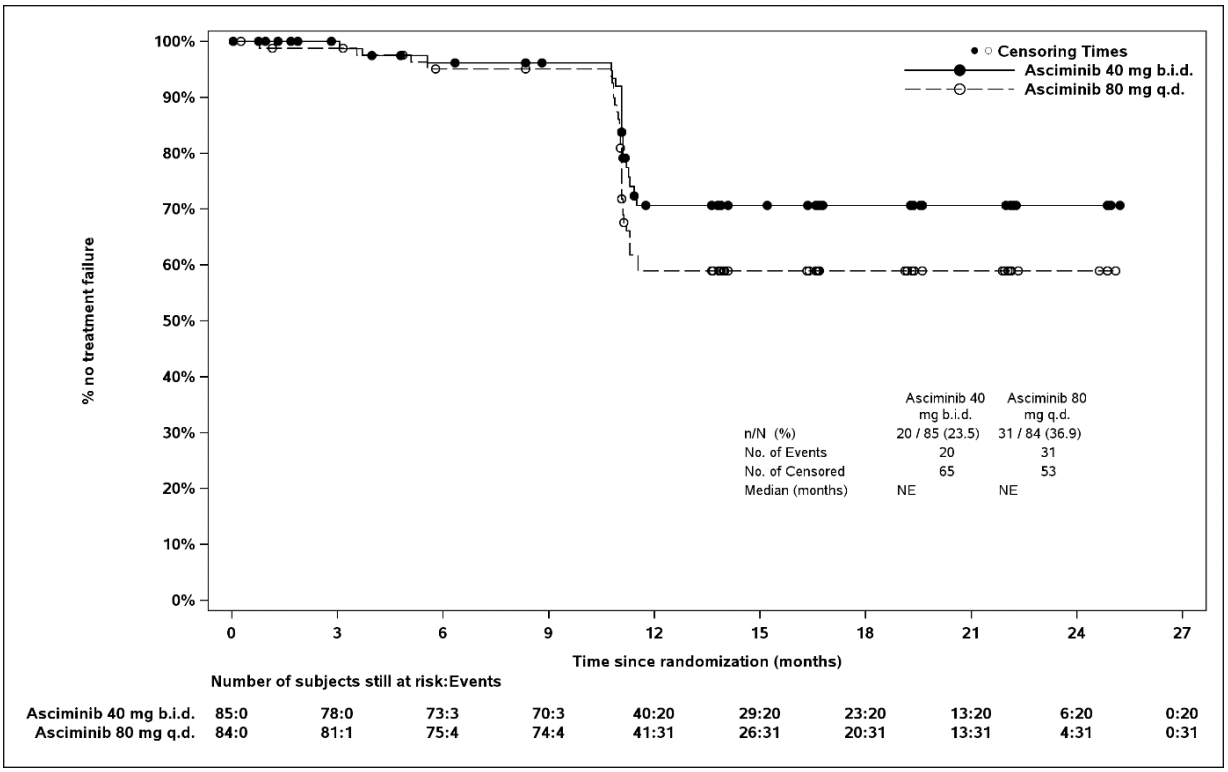


Figure 36: Kaplan-Meier plot of time to treatment failure (Full analysis set) – Study A2302

Progression-free survival

PFS data were immature at the time of DCO with 3.5% (3/85 patients) of participants and 4.8% (4/84) of participants with PFS events in the 40 mg BID and 80 mg QD groups respectively.

Overall survival

Overall survival data were immature at time of the Week 48 analysis. One participant (1.2%) in the 80 mg QD group died due to cerebrovascular accident. The cause of death was not suspected to be related to the study drug.

Supportive comparison of MMR rates in Study A2302 and Study A2301 at Week 48

Study A2301 was the pivotal phase 3 study confirming the efficacy and safety of asciminib in patients with CML-CP previously treated with at least 2 TKIs. The study met its primary objective, with superiority demonstrated for asciminib 40 mg BID (MRR rate at week 24: 25.5%) relative to bosutinib 500 mg (13.2%) QD for the primary endpoint of MMR at 24 weeks with a treatment difference of 12.2% % (95% CI: 2.19, 22.30, two-sided p-value: 0.029).

Table 54 Comparison of baseline characteristics between Study A2301 and Study A2302 that were adjusted using propensity scores

Demographic Variable	Study A2301* 40 mg b.i.d. N=157 n (%)	Study A2302 40 mg b.i.d. N=85 n (%)	Study A2302 80 mg q.d. N=84 n (%)
Age Group			
< 65 years	128 (81.5)	64 (75.3)	59 (70.2)
≥ 65 years	29 (18.5)	21 (24.7)	25 (29.8)
Sex			
Female	75 (47.8)	37 (43.5)	27 (32.1)
Male	82 (52.2)	48 (56.5)	57 (67.9)
Number of prior TKI therapies			
2	89 (56.7)	47 (55.3)	42 (50.0)
≥3	68 (43.3)	38 (44.7)	42 (50.0)
Reason for discontinuation of last prior TKI			
Failure	95 (60.5)	43 (50.6)	46 (54.8)
Intolerance	59 (37.6)	19 (22.4)	20 (23.8)
Unknown/Other	3 (1.9)	23 (27.1)	18 (21.4)
MR2 status at baseline			
0	142 (90.4)	55 (64.7)	58 (69.0)
1	15 (9.6)	30 (35.3)	26 (31.0)
Mutation			
Mutation	17 (10.8)	5 (5.9)	11 (13.1)
Wild Type	125 (79.6)	68 (80)	63 (75.0)
Unknown	15 (9.6)	12 (14.1)	10 (11.9)

*See 3L Original SCE – Section 3.1.1 for detailed demographic and baseline characteristics of the study population in A2301
Source: SCE Appendix 1-Table 1

A post-hoc propensity score analysis to, following the applicant, considering differences in baseline characteristics (*Table 54*), was performed to compare the following:

- MMR rate at Week 48 between Study A2302 40 mg BID vs. Study A2301 40 mg BID for asciminib
- MMR rate at Week 48 between Study A2302 80 mg QD vs. Study A2301 40 mg BID for Asciminib

The difference in MMR rate between Study A2301 40 mg BID and Study A2302 40 mg BID dose groups after adjustment for differences for baseline characteristics due to different study designs by the applicant is provided in *Table 55*.

Table 55 MMR at Week 48 for Study A2302 40 mg BID vs. unadjusted/adjusted Study A2301 40 mg BID

Study	N	MMR Week 48 (%)	Difference	95% CI	p-value
Study A2302 40 mg b.i.d.	62[a]	40.32	-2.45	(-18.96, 14.06)	0.771[c]
Study A2301 40 mg b.i.d. adjusted	73[b]	37.88			
Study A2301 40 mg b.i.d. unadjusted	154[a]	29.87			

[a]Including only failure and intolerance participants in the analysis to match Study A2301 design
[b]Effective sample size = square of the summed weights / sum of squared weights
[c]Nominal p-value computed only for post-hoc analysis for descriptive purposes
Source: SCE Appendix 1-Table 2

The difference in MMR rate at Week 48 for Study A2301 40 mg BID vs. Study A2302 80 mg QD dose groups after adjustment for differences for baseline characteristics due to different study designs by the applicant is provided in *Table 56*.

Table 56 MMR rate at Week 48 for Study A2301 40 mg BID vs. Study A2302 80 mg QD

Study	N	MMR Week 48 (%)	Difference	95% CI	p-value
Study A2302 80 mg q.d.	66[a]	33.33	0.74	(-14.32, 15.79)	0.923[c]
Study A2301 40 mg b.i.d. adjusted	89[b]	34.07			

Study	N	MMR Week 48 (%)	Difference	95% CI	p-value
Study A2301 40 mg b.i.d. unadjusted	154[a]	29.87			

[a]Including only failure and intolerance participants in the analysis to match Study A2301 design
[b]Effective sample size = square of the summed weights / sum of squared weights
[c]Nominal p-value, computed only for post-hoc analysis for descriptive purposes
Source: SCE Appendix 1-Table 3

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

I. Extension of indication to patients with newly diagnosed CML-CP

The applicant conducted one pivotal study for the extension of indication to CP-CML-CP 1st line treatment. Ongoing phase III, randomised (1:1)-controlled, open-label, multicentre, superiority trial J12301 (ASC4FIRST) comparing asciminib 80 mg QD monotherapy with investigator's selected TKI

(imatinib 400 mg QD, nilotinib 300 mg BID dasatinib 100 mg QD or bosutinib 400 mg QD) in estimated 402 patients with CML-CP.

Diagnosis of CML-CP was made following ELN 2020 criteria, thereby excluding CML-AP and CML-BP. Only patients with ECOG PS 0 and 1 were eligible for enrolment.

Protocol assistance was obtained before study start in March 2021. Regarding the study design, activity as an estimate to measure positive effects was accepted but should ideally be supported by estimates that reflects changes in clinical management and a favourable safety profile.

The proposed primary endpoint 'MMR (MR3.0) at 48 weeks' for the overall population was considered difficult for interpretation, regarding the heterogeneity of the multi -comparator control arm and that the effect may mainly be driven by imatinib. Furthermore, activity after one year was seen rather short for a reliable comparison, as the current EMA guidance recommends assessment after 18 months in this setting.

The applicant chose 'MMR at week 48' for asciminib vs. IS-TKI (FAS) as 'primary endpoint 1' and MMR at week 48 for asciminib^{IMA} vs. IS-TKI^{IMA}, in the imatinib-stratum, as 'primary endpoint 2', implying a positive study if *either* is positive. MMR at week 96 was planned as a key secondary endpoint in the corresponding populations.

The Applicant addressed the efficacy comparison between asciminib and 2G TKI by stratification and a secondary endpoint for MMR at weeks 48 and 96 for this subpopulation in the primary analysis. Further secondary objectives included different molecular levels and duration of the remission at different time points up to week 96 (CHR, MR2.0, MR3.0 (MMR), MR4.0 and MR4.5 by all scheduled data collection time points), time to treatment failure and event free survival.

The choice of primary endpoints can in principle be followed. Current (2020) ELN and NCCN (2025) guidelines highlight 'MMR at 48 weeks' as a so-called 'optimal' response to treatment. However, a grey zone exists (so called 'warning') of clinical decision making between MMR and MR2.0 after 48 weeks. Interpretability in terms of clinical meaningfulness of this landmark analysis for MMR is somewhat limited, as many of these patients may also deepen responses (potentially allowing for TFR) at a later time. Of note, not achieving MR2.0 is considered treatment failure with implication on survival rates, MR2.0 rate was implemented as a secondary endpoint. However, evidence of translation into clinically meaningful endpoints like number and duration of TFR and a more mature EFS analysis, a data update was requested, as PFS or even OS is unlikely to become mature. The MAH committed to provide an 8 year follow-up for study J12301 (Annex II condition).

The specified estimands combining treatment policy and composite strategy for relevant intercurrent events are overall agreed and considered relevant in this situation.

All four control arm TKIs were initially planned to be administered at the approved dosages.

Stratification was performed based on the ELTS risk score (low vs. intermediate vs. high) and the TKI selected prior to randomisation (imatinib vs. second-generation TKI). Unfortunately, geographic region was not included in the study design as a stratum. The effect of region on the outcome is at least partially addressed by the stratification due to respective TKI selection.

The open-label design was previously accepted in this setting because the use of different dosing regimens (QD, BID, food restrictions, etc.) and additional placebos would have made conducting the study extremely difficult.

Sample size (planned n=402) for the primary endpoints was calculated assuming MMR rates at week 48 to be 52.5% for asciminib, 28% for imatinib, and 45% for any 2G TKI. Based on a 1-sided 2.5%

level of significance, the study had 94.6% power to reject at least one of the null hypotheses (MRR at week 48 in the FAS and/or FAS^{IMA}).

The statistical analyses are overall considered appropriate and aligned to the targeted estimands. For multiplicity controlled primary and key secondary efficacy endpoints, sufficient sensitivity analyses evaluating alternative missing data handling were done and supportive estimands were addressed with results aligned to the primary evaluation.

While the SAP was only finalized after starting the study, which is less ideal for an open label study, this is not of further concern, as the protocol contained extensive and sufficient information on the statistical analyses in particular for the multiplicity-controlled endpoints.

The study was conducted between October 2021 and December 2022. The data cut-off for efficacy was on 28 November 2023. The study is planned to be terminated after five years from last patient first treatment. Overall, 405 patients were randomised in 116 centres in 29 countries worldwide. An Interactive Response Technology safeguarded equal distribution of enrolment in the strata of imatinib vs. 2G TKI. At the time of data cut-off, treatment was ongoing for 86.1% of patients in the ASC arm and 68.6% in the 2G- TKI arm. More patients in the control arm had a treatment failure compared to asciminib (ASC 5%; IS-TKI 11.8% (including TKI^{IMA} 15.7%/ TKI^{2G} 7.8%) until DCO. Confirmed loss of MRR (ASC 0.5%; IS-TKI 0%) or progressive disease (ASC 1%; IS-TKI 2%) were rare.

The two protocol amendments were minor without implications for the study interpretability.

Protocol deviations were generally seen in both arms (any deviation: ASC 54.2%; IS-TKI 51.5%) with a high rate of 'selection criteria not met' (ASC 14.4% vs. IS-TKI 12.3%) after randomisation.

Baseline characteristics were generally balanced between the ASC- and IS-TKI arm. This accounts especially for age, BMI and CVD risk categories. ELTS Risk Score was employed for stratification and balanced between ASC- and IS-TKI arm. As expected, patients in the imatinib – stratum had a higher age, and a higher CVD risk compared to patients from the 2G-TKi stratum. No difference in the ECOG-PS (0 vs. 1) was observed.

II. Extension of the indication to 2nd line CML-CP treatment

To close the gap between approved 3L or later line indication and the applied first line indication the applicant submitted data from 63 2L CML- CP patients treated with asciminib 80 mg QD monotherapy from an ongoing uncontrolled, single-arm, dose escalation, phase II trial CABL001AUS08. At the time of submission, the study had completed enrolment, with 101 participants in 2nd line treatment by 17-Sep-2024. Endpoints were, among others, BCR::ABL =< 10% rate, MR2-/ MMR-/ MR4- and MR4.5 rates.

Most evaluable patients were pretreated with dasatinib and imatinib, which is adequate. Mean time of exposure at DCO was 40.1 (SD 17.22) weeks. Overall, treatment discontinuation was reported for 8.9% of patients (4% due to AE).

III. New posology of 80 mg QD for the 3rd or later line, 40 mg BID in earlier lines

Besides available data of the effectiveness in the 1st and 2nd line of the 80 mg QD posology for potential extrapolation to the 3rd and later line, the applicant provided data from supportive study A2302.

In the initial MAA for Scemblix, conclusions on comparative efficacy and safety could not be reliably drawn for the 80 mg QD dose regimen in 3rd or later line CML-CP patients in comparison to 40 mg BID due to only 17 preliminary investigated subjects (in phase I study X2101) on that respective dose. At the time of the positive CHMP opinion in June 2022, the clinical study A2302 for this question was already initiated as a PASS supportive for the benefit and risk for the 80 mg QD posology.

Ongoing non- comparative, multicentre, randomised (1:1) controlled, open-label, phase IIIb treatment optimisation study A2302 (ASC4OPT) in patients who had prior treatment with at least two TKIs and who were either in warning, resistant (ELN 2020 recommendations) or intolerant to the last TKI treatment. Randomisation was between asciminib monotherapy 40 mg BID and 80 mg QD with MMR rate at week 48 as the primary endpoint, aiming at a statistically significant difference to MMR rate at week 48 of 23% in the overall population. No stratification was applied. However, the actual comparison between the established dosing regimen and the proposed alternative regimen was not adequately addressed in the study design. No direct comparison was planned or conducted between both groups and no margin for equivalence/non-inferiority was pre-specified. Extrapolation of efficacy of 40 mg BID dosing to earlier treatment lines can be accepted.

Efficacy data and additional analyses

I. Extension of indication to patients with newly diagnosed CML-CP

On 28 November 2023 DCO, the study was positive for the two primary endpoints and the two key secondary endpoints. The difference between MMR rates at week 48 was Δ 18.88% (95% CI: 9.59, 28.17; one sided p-value: <0.001) comparing the overall ASC arm (67.7%) to the overall IS-TKI arm (49.0%). The effect was more pronounced in the imatinib stratum, primary endpoint 2 showed a difference in the MMR rate of 29.55% 95% CI: 16.91, 42.18; one-sided adjusted p-value: < 0.001; ASC^{IMA} 74.1% vs. $IS\text{-}TKI^{IMA}$ 52.0%). For the key secondary endpoints, the difference in MMR rate at week 96 increased in the overall population (FAS) to Δ 22.4% (ASC 74.1% and 52.0% IS-TKI) and to 29.7% in the FAS^{IMA} population (ASC^{IMA} 76.2% $IS\text{-}TKI^{IMA}$ 47.1%). As a prespecified analysis in the 2G TKI stratum, MMR rate between ASC^{2G} and $IS\text{-}TKI^{2G}$ was numerically higher at 48 weeks (Δ 8.2%, 66.0 vs. 57.8%) and 96 weeks (Δ 15.1%, 72.0% vs. 56.9%).

Sensitivity analyses of MMR rate at week 48 without imputation and analyses for important subgroups (ELTS score, age) supported the result of the primary analysis.

Achieving MR2 (analogous to CCyR) within the 1st year of treatment has been considered to be prognostically relevant for long term survival in treatment guidelines for 1st and 2nd generation TKI. In the FAS^{IMA} numerical difference between arms is Δ 22.0% (91.1% vs. 69.6%) and for the FAS^{2G} Δ 9.67% (94.0% vs. 84.3%). The difference is maintained in the 2-year assessment.

Achieving DMR (MR4 or better) offers, among other necessary factors, the possibility for treatment discontinuation. MR4 rates are numerically higher in the ASC arm compared to IS-TKI. The effect is present in the different strata and at different timepoints (FAS^{IMA} 48 week: 37.0% vs. 10.0%; week 96: 56.0% vs. 27.2%; FAS^{2G} 48 week: 31.0% vs. 21.8%; week 96: 45.0% vs. 40.8%).

For MMR, a sustained effect was observed in the 1st two years of treatment, as 97% of patients who achieved MMR in both arms continued to remain in MMR at week 96.

Early molecular response (EMR; ≤10% BCR::ABL1 IS at 12 weeks) is, according to clinical guidelines (NCCN 2025), another response milestone predictive for long term PFS. Here asciminib treatment showed a numerical difference of Δ 28.3% (88.1% vs. 59.8%) and Δ 10.6% (91.0% vs. 80.4%) in the imatinib-/ and 2GTKI- stratum for asciminib vs. IS-TKI, respectively.

Rates of discontinuation due to treatment failure per ELN criteria was remarkably higher in patients receiving imatinib (18.6%) and 2G TKI (8.8%) than in patients receiving asciminib (5.0%). The probability of treatment failure was lower in the asciminib arm compared to IS TKI arm (HR=0.37; 95% CI: 0.25, 0.55). The effect was coherent in both strata (FAS^{IMA} and $FAS2^{GTKI}$).

EFS, including death, progression or treatment change at week 96 was numerically higher for the asciminib arm irrespective of the imatinib (16.8% vs. 35.3%) or 2G-TKI stratum (12.0% vs. 23.5%).

II. Extension of the indication to 2nd line CML-CP treatment

At six months, 82.5% (95%CI: 70.9%, 91.0%) of evaluable 2L patients achieved MR2 and 44.4% (95%CI: 31.9%, 57.5%) achieved MMR in the single – arm trial. Observed MMR rate at week 36 is 52.4 % (36.4, 68.0). Due to the uncontrolled nature of the data, interpretability of data is hampered. The observed activity lays within MMR rates of asciminib after 6 months in 1L (57.71%, study J12301, see above) and >=3L (25.5%, study A2301, initial MAA). The observed MR2.0 rate is promising in comparison to historical CCyR rates of TKI in the 2nd line (Jabbour et al.; 2024). In an update at IA5, median duration of exposure to study treatment was 51.3 weeks in the second-line cohort, 54.5% (55 patients) had a duration of exposure > 48 weeks. At IA5, MMR rate at week 48 in patients with adequate follow-up was 55.6% (40/72; 95% CI: 43.4; 67.3%). Supportive results come from MR2 rate at 48 weeks with 77.8% (56/72; 95% CI: 66.4; 86.7%) and DMR at 48 weeks with 25% (18/72; 95%CI: 15.5%, 36.6%).

III. New posology of 80 mg QD for the 3rd or later line and 40 mg BID to earlier lines

In study A2302, mean exposure was comparable between the arms (68.0 vs. 68.7 weeks). Baseline characteristics show marginal differences in age groups (≥ 65 years 24.7% vs. 29.8% in 40 mg BID vs 80 mg QD), sex (female 43.5 vs. 32.1), patients with previous treatment failure (50.6% vs. 54.8%) or mutations (5.9% vs. 13.1%).

The study met its primary endpoint, for participants without MMR at baseline, the overall rate of MMR at Week 48 in FAS was 38.5% (95% CI: 31.09, 46.24).

In a post- hoc comparison, the rate of MMR at Week 48 was 42.4% (95% CI: 31.70, 53.55) vs. 34.5% (95% CI: 24.48, 45.69) for the asciminib 40 mg BID group vs. asciminib 80 mg QD group, respectively. The numerical difference in MMR rate is 7.8% in favour of 40 mg BID.

Residual imbalances and lack of stratification do not justify post hoc rebalancing for the primary endpoint. The primary focus should be on the randomised comparison (even if not preplanned) considering that there are no extensive imbalances observed between randomised treatment arms.

The provided analyses are considered insufficient to alleviate the concern of a considerably higher MMR rate at week 48 for the 40mg BID group. Aside from this, selection of covariates included in the post-hoc analysis and robustness of results with respect to the selection of included covariates is unclear. Furthermore, neither based on the randomised nor the post-hoc comparison a non-inferiority claim with a reasonable margin (5-10%) can be made.

The primary endpoint (rejecting an MMR rate at week 48 of 23% in the overall population) was met, due to the limitations in study design no comparison between 40 mg BID and 80 mg QD was predefined. The rate of MMR at Week 48 for patients without MRR at baseline was 42.4% (95% CI: 31.70, 53.55) in the asciminib 40 mg BID group and was 34.5% (95% CI: 24.48, 45.69) in the asciminib 80 mg QD group. The numerical difference in MMR rate between 40 mg BID and 80 mg QD is 7.8%, without a predefined acceptable margin to claim equivalence.

The performed post-hoc propensity score weighting, which is not justified, adequate or reliable, led to a reduced difference of 2.43 (95% CI: -12.71, 17.56).

At the BCR::ABL1 ≤ 10% level, at week 48, 71.8% vs. 78.6% of patients showed a response for the 40 mg BID arm vs 80 mg QD arm. The numerical trend is supported by assessments at different timepoints (week 12, 24, 36) and an assessment *by* scheduled timepoints.

At the MR4.0 level, at week 48, 20.0% vs. 13.0% of patients showed a response for the 40 mg BID arm vs 80 mg QD arm, respectively. The numerical trend is supported by assessments at different timepoints (week 12, 24, 36) and an assessment by scheduled timepoints (week 12, 24, 36, 48).

At the MR4.5 level, at week 48, 11.8% vs. 8.3% of patients showed a response for the 40 mg BID arm vs 80 mg QD arm, respectively. The numerical trend is supported by assessments at different timepoints (week 12, 24, 36) and an assessment by scheduled timepoints (week 24, 36, 48).

The majority of response assessments at deeper response levels show numerical favourable effects of the 40 mg BID dose at scheduled timepoints from week 12 to week 36 with few exceptions.

After a median follow-up time of 1.0 year, 23.5% vs. 36.9% of patients had treatment failure in the 40 mg BID and 80 mg QD arm, respectively.

Further propensity score-weighted analyses were conducted to compare MMR rates at week 48 in the 40 mg BID and 80 mg QD arms with the responses of 40 mg BID patients in the pivotal phase III A2301 study for initial MAA. However, the post hoc analysis attempting to rebalance the 12.5% difference in MMR rates (42.4% vs. 29.9%) is problematic and not adequately justified, although the fact that to a certain extent, different populations were included in both studies (including patients with 'warning' according to ELN 2020 criteria only in study A2302) is acknowledged.

Of note, strong supportive evidence for efficacy of the 80 mg QD posology comes from the efficacy and activity data in the 1st and 2nd line of treatment, indicating a benefit for patients also in the 3rd line. Whether efficacy can be generally considered equipotent to the 40 mg BID posology or the once daily intake is only recommended to patients with problems following the twice daily intake in the fasting state, like some patients with diabetes mellitus, difficulties to swallow or low adherence, also depends on the outcome of the post-hoc comparison of the two study arms in study A2302.

In response to a request for additional information, the MAH confirmed the results of the post hoc comparison of the primary endpoint for the two dosing arms, showing a difference in MMR rate at week 48 of -7.8% (95% CI: -22.45, 6.79). This difference was clinically relevant in favour of the 40 mg BID dosing regimen, despite the confidence intervals overlapping. This potential for lower efficacy with the 80 mg QD regimen has been reflected in section 4.4 of the SmPC.

2.4.3. Conclusions on the clinical efficacy

Extension of indication to patients with newly diagnosed CML-CP

The pivotal RCT J12301 comparing asciminib monotherapy to imatinib or 2G-TKI was positive, as the primary endpoint, the difference between MMR rates at week 48 was 18.88% (95% CI: 9.59, 28.17; one sided p-value: <0.001) in the overall population. The effect was present in both, the imatinib stratum and the 2G- stratum, at different prescheduled timepoints (week 12-96), across different response levels (MR2.0, MMR/ MR3.0, DMR ink. MR4.0 and MR4.5) and for important subgroups (ELTS score, age). The effect is supported by numerically lower rates of discontinuation and higher EFS at week 96. Although no robust data on "hard" clinical endpoints like mature EFS/ PFS data, OS- data, number and duration of TFR is available yet, efficacy in newly diagnosed CML-CP patients has been demonstrated.

The results of the long-term (>96 weeks) outcomes of this potentially lifelong therapy are pending. The MAH should provide, via an Annex IID condition, long-term efficacy and safety data for the J12301 (ASC4FIRST) trial, including but not limited to treatment free intervals (TRI) and durations of TRI, OS, PFS, PFS2, resistance mechanisms, resistance mutations and response rates to subsequent TKIs for 8 years.

Extension of the indication to 2nd line CML-CP treatment

The provided uncontrolled response data in 101 2nd line CML-CP patients with an MMR rate at week 24 of 44.4% (95%CI: 31.9%, 57.5%), 52.4 % (36.4, 68.0) at week 36 and 55.6% (43.4; 67.3%) at week 48 are in between described responses in 1L treatment (Study J12301) and 3rd or later line treatment (study 2301). Despite the limitations of the data, evidence has been provided to support the claim of activity in 2L CML-CP.

New posology of 80 mg QD for the 3rd or later line, 40 mg BID in earlier lines

Results of Phase III RCT Study A2302 do not provide evidence for similar efficacy of the 80 mg QD dosing in comparison to 40 mg BID dosing. Extrapolation of efficacy of 40 mg BID dosing to earlier treatment lines can be accepted.

The following measures are considered necessary to address issues related to efficacy:

In order to further evaluate the long-term efficacy and safety of asciminib in patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP), the MAH should submit the final CSR of study CABL001J12301 (ASC4FIRST), by 30 September 2031.

2.5. Clinical safety

Introduction

The safety results in this application were not pooled as a whole but presented individually within the framework of the respective studies presented in this application, which is accepted.

Therefore the safety data in this assessment is presented in 3 parts: Extension of indication to patients with newly diagnosed CML-CP, Extension of the indication to 2nd line CML-CP treatment and New posology of 80 mg QD for the 3rd or later line.

2.5.1. Extension of indication to patients with newly diagnosed CML-CP

The evaluation for extension of indication to patients with newly diagnosed CML-CP is primary based on safety data from the Phase III registration Study CABL001J12301 (ASC4FIRST, hereafter referred to as Study J12301) up to the data cut-off date of 22-Oct-2024 at Week 96, with 201 patients exposed to a dose of 80 mg QD from studies and 204 patients exposed to IS-TKI (imatinib, dasatinib, bosutinib, nilotinib) along with supportive data from Study CABL001A2301 (hereafter referred to as Study A2301) and Study CABL001X2101 (hereafter referred to as Study X2101).

Table 57 ***Overview of clinical studies contributing to the All Asciminib Safety Pool***

Studies/Population/ Total no. of No. of participants included in the safety pool (n)	Study description	Dose schedule	Data Cut-off dates	Completion status
Registration study				
Study J12301 / Adult patients with newly diagnosed Ph+ CML-CP N= 405/ n=200	A Phase III, multi-center, open-label, randomised study of oral asciminib vs. Investigator selected TKI in patients with newly diagnosed Ph+ CML-CP	80 mg QD	22-Oct-2024 (Week 96 - Secondary analysis CSR) And 28-Nov-2023 (Week 48 - Primary analysis CSR)	Ongoing
Supportive studies				
Study A2301# / Adult patients with Ph+ CML-CP previously treated with ≥ 2 TKIs N=233/ n=156	A Phase III, multi-center, open-label, randomised study of oral ABL001 (asciminib) vs. bosutinib in patients with Ph+ CML-CP, previously treated with 2 or more TKIs	40 mg b.i.d.	22-Mar-2023 (End of Treatment CSR)	Ongoing
Study X2101 / Adult patients with Ph+ CML or ALL, relapsed, refractory to or intolerant of TKIs N=326/ n=200	A Phase I, multicenter, open-label study of oral ABL001 in patients with Ph+ CML or Ph+ALL	10, 20, 40, 80, 150, 160, 200, 280 mg b.i.d. and 40, 60 80, 120, 160 and 200 mg QD as single agent* or in combination with imatinib, nilotinib or dasatinib	14-Mar-2023 (Final CSR)	Completed

Study J12301- No crossover of study treatment was allowed.

#Excludes switched participants from Study A2301

*Includes only asciminib monotherapy participants (Arm 1) from Study X2101

Source: [Study J12301 W96 CSR], [Study J12301 W48 CSR], [Study A2301 EOT CSR], [Study X2101 Final CSR] and [Tabular Listing of All Clinical Studies]

Patient exposure

Study J12301: As of the Week 96 data cut-off, the median duration of exposure was marginally longer in the asciminib group (115.79 weeks) relative to the IS-TKI group (108.70 weeks). A higher proportion of participants had a duration of exposure of at least 96 weeks in the asciminib group (81.0%) compared to the IS−TKI group (61.2%). Total exposure in the asciminib group was 410.6 patient-treatment year (PTY) vs. 353.6 PTY in the IS-TKI group. Within the IS-TKI group, the median duration of exposure was 100.29 weeks for imatinib and 115.57 weeks for 2G TKI; and the total exposure was 151.1 PTY for imatinib and 202.5 PTY for 2G TKI, Table 1-4. The enrolment for 2G TKI group was completed on 22-Sep-2022, and between 22-Sep-2022 and 21-Dec-2022 and 48 participants were enrolled in imatinib group to complete enrolment of 405 participant in the study. The difference in the duration of exposure between imatinib and 2G TKI can be attributed in part to the

recruitment dynamics, the 2G TKI stratum was closed earlier by approximately 3 months than the imatinib stratum, as well as the higher proportion of treatment discontinuations in imatinib compared to the 2G TKI.

In the All Asciminib Safety Pool, the median (min-max) duration of exposure was 123.29 weeks (0.1 to 439.0 weeks) and the total exposure to asciminib was 1558.6 PTY.

Table 58 Duration of exposure to study drug - Safety set

	Study J12301						Safety Pool
	Asciminib			Investigator Selected TKI			
	Imatinib N=100	2G TKI N=100	All Asciminib N=200	Imatinib N=99	2G TKI N=102	All Comparators N=201	All Asciminib N=556
Duration of exposure - weeks							
Mean (SD)	100.6 (34.7)	113.6 (32.8)	107.1 (34.3)	79.7 (41.4)	103.6 (37.7)	91.8 (41.2)	146.3 (108.2)
Median	107.50	121.07	115.79	100.29	115.57	108.71	123.29
Q1-Q3	99.86-121.29	111.07-133.00	102.57-129.43	42.57-111.29	86.00-128.29	59.71-122.14	64.43-195.64
Min-Max	0.7-154.7	5.9-152.1	0.7-154.7	2.7-146.0	1.3-150.1	1.3-150.1	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	5 (5.0)	8 (8.0)	13 (6.5)	17 (17.2)	16 (15.7)	33 (16.4)	47 (8.5)
96 - < 144 weeks	82 (82.0)	80 (80.0)	162 (81.0)	54 (54.5)	69 (67.6)	123 (61.2)	183 (32.9)
144 - < 192 weeks	1 (1.0)	4 (4.0)	5 (2.5)	1 (1.0)	5 (4.9)	6 (3.0)	69 (12.4)
≥ 192 weeks	0	0	0	0	0	0	142 (25.5)
Patient-Treatment-Year	192.9	217.8	410.6	151.1	202.5	353.6	1558.6

PTY is the sum of each participant's treatment exposure in year.
Source: 1L SCS Appendix 2-Table 1-2

Relative dose intensity

In study J12301 the planned dose for asciminib group was 80 mg QD for the IS-TKI group, the planned doses were 400 mg QD for imatinib, 300 mg BID for nilotinib, 100 mg QD for dasatinib, and 400 mg QD for bosutinib. The median RDI was 100.0% (range: 49.9% - 100.4%) in the asciminib group and 99.3% (range: 24.3% - 100.1%) in the IS-TKI group. Overall, 87.0% of participants in the asciminib group had the RDI > 90 to 110% compared to 74.1% in the IS- TKI group (ranging from 45.5% to 79.8%); a smaller proportion of participants received treatment with bosutinib (11 participants for bosutinib vs. 42 for dasatinib vs. 49 for nilotinib, and 99 for imatinib).

Patient disposition

As of the Week 96 data cut-off (22-Oct-2024) in study J12301, a higher proportion of participants were still on treatment in the asciminib group (81.6%) compared to IS-TKI group (60.3%). The proportion of participants who discontinued study treatment was lower in the asciminib group compared to the IS−TKI group, overall (17.9% vs. 38.2%) as well as for individual reasons, including mainly unsatisfactory therapeutic effect (9.5% vs. 20.6%) and AEs (6.0% vs. 12.7%), other individual reasons for discontinuation were each reported in ≤ 2.0% of participants. Among the participants who discontinued treatment due to unsatisfactory therapeutic effect, the most frequent reasons were treatment failure per ELN criteria 2020 (5.0% vs 13.7%), followed by other (2.5% vs 5.4%) and confirmed loss of MMR (2.0% vs 1.5%).

Time to discontinuation of study treatment (TTDAE) due to AE was a secondary objective in study J12301 assessed by cause-specific hazard analysis. The risk of study treatment discontinuation due to AEs at week 96 was d statistically significantly lower in the asciminib group compared to 2G TKI

(TTDAE, HR = 0.463; 95% CI: 0.215, 0.997; adjusted one sided p-value: 0.0246) and numerically lower compared to the imatinib group (HR = 0.381; 95% CI: 0.178, 0.818).

Adverse events

Overall, the incidence of AEs was comparable between the asciminib and IS-TKI groups (95.5% vs. 98.0%). Grade ≥ 3 AEs occurred at a lower frequency in the asciminib group compared to the IS-TKI group (44.5% vs. 54.7%). SAEs and treatment-related AEs also occurred at a lower frequency in the asciminib group compared to the IS-TKI group, whereas and AEs requiring additional therapy occurred at a similar frequency in both groups (*Table 59*).

The incidence of AEs leading to study treatment discontinuation (5.0% vs. 13.1%) and AEs leading to dose adjustment and/or interruption (33.0% vs. 41.4%) was lower in the asciminib-/ compared to the imatinib group and to the 2G TKI group (discontinuation: 5.0 % vs. 12.7%; adjustment/interruption: 33.0% vs. 57.8%).

Table 59 Overview of adverse events - Safety set

Table 2-1 Overview of adverse events - Safety set

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib N=100		2G TKI N=100		All Asciminib N=200		Imatinib N=99		2G TKI N=102		All Comparators N=201		All Asciminib N=556	
Category	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 (%)
Adverse events	97 (97.0)	48 (48.0)	94 (94.0)	41 (41.0)	191 (95.5)	89 (44.5)	95 (96.0)	49 (49.5)	102 (100)	61 (59.8)	197 (98.0)	110 (54.7)	533 (95.9)	324 (58.3)
Treatment-related	77 (77.0)	29 (29.0)	79 (79.0)	27 (27.0)	156 (78.0)	56 (28.0)	84 (84.8)	35 (35.4)	98 (96.1)	46 (45.1)	182 (90.5)	81 (40.3)	440 (79.1)	207 (37.2)
SAEs	18 (18.0)	14 (14.0)	11 (11.0)	9 (9.0)	29 (14.5)	23 (11.5)	16 (16.2)	14 (14.1)	25 (24.5)	18 (17.6)	41 (20.4)	32 (15.9)	159 (28.6)	125 (22.5)
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)	9 (8.8)	7 (6.9)	13 (6.5)	10 (5.0)	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)	4 (4.0)	3 (3.0)	10 (5.0)	6 (3.0)	13 (13.1)	7 (7.1)	13 (12.7)	5 (4.9)	26 (12.9)	12 (6.0)	48 (8.6)	38 (6.8)
Treatment-related	5 (5.0)	3 (3.0)	3 (3.0)	2 (2.0)	8 (4.0)	5 (2.5)	11 (11.1)	6 (6.1)	13 (12.7)	5 (4.9)	24 (11.9)	11 (5.5)	32 (5.8)	26 (4.7)
AEs leading to dose adjustment/ interruption	33 (33.0)	28 (28.0)	33 (33.0)	27 (27.0)	66 (33.0)	55 (27.5)	41 (41.4)	25 (25.3)	59 (57.8)	39 (38.2)	100 (49.8)	64 (31.8)	241 (43.3)	198 (35.6)
AEs requiring additional therapy	83 (83.0)	26 (26.0)	85 (85.0)	25 (25.0)	168 (84.0)	51 (25.5)	83 (83.8)	20 (20.2)	93 (91.2)	33 (32.4)	176 (87.6)	53 (26.4)	460 (82.7)	214 (38.5)

A participant with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 27.1, CTCAE version 5.0.
Source: 1L SCS Appendix 2-Table 2-1

Exposure-adjusted incidence rate of AEs

The EAIR of AEs per 100 PTY in the asciminib treatment group was lower compared to the IS- TKI treatment group (484.6 vs.1106.6), including compared to imatinib (484.6 vs. 711.5) and compared to 2G TKI (484.6 vs. 2292.6).

Adverse events by system organ class (SOC)

SOC where events were reported less frequently in the asciminib group (and with a ≥ 10% difference compared to IS-TKI group) included blood and lymphatic system disorders (31.5% vs. 42.8%). Vascular disorders AEs were reported more frequently in the asciminib group and with a ≥ 5% difference compared to the IS-TKI group (16.5% vs. 8.5%), and the difference was mainly due to hypertension (21 participants, 10.5% vs. 10 participants, 5.0%). There was no SOC where grade ≥ 3 events were reported more frequently (with a ≥ 5% difference) in the asciminib group compared to the IS-TKI group. The SOCs where grade ≥ 3 events were reported less frequently in the asciminib group

compared to the IS-TKI group included blood and lymphatic system disorders (10.5% vs. 18.4%). In comparison to the imatinib group, in the asciminib group, general disorders and administration site conditions (33.5% vs. 46.5%) and eye disorders (15.5% vs. 34.3%) were reported less frequently, while grade ≥ 3 events vascular disorders were reported more frequently (7.0% vs. 2.0%). In comparison to 2G-TKI, the SOC vascular disorders was reported more frequently in the asciminib group (16.5% vs. 7.8%), with the difference mainly due to hypertension (10.5% vs. 4.9%). SOC events less frequently reported included infections and infestations (54.0% vs. 64.7%), investigations (47.0% vs. 66.7%), gastrointestinal disorders' (45.5% vs. 60.8%), skin and subcutaneous tissue disorders (39.5% vs. 52.9%), blood and lymphatic system disorders (31.5% vs. 48.0%), respiratory, thoracic and mediastinal disorders (18.0% vs. 31.4%) and cardiac disorders (4.5% vs. 15.7%). The SOCs where grade ≥ 3 events were reported less frequently (with a ≥ 5%) in the asciminib group difference compared to the 2G TKI group included blood and lymphatic system disorders (10.5% vs. 22.5%) and investigations (19.5% vs. 27.5%).

Table 60 Adverse events by system organ class- Safety set

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib N=100		2G TKI N=100		All Asciminib N=200		Imatinib N=99		2G TKI N=102		All Comparators N=201		All Asciminib 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
Primary system organ class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
At least one event	97 (97.0)	48 (48.0)	94 (94.0)	41 (41.0)	191 (95.5)	89 (44.5)	95 (96.0)	49 (49.5)	102 (100)	61 (59.8)	197 (98.0)	110 (54.7)	533 (95.9)	324 (58.3)
Infections and infestations	50 (50.0)	3 (3.0)	58 (58.0)	5 (5.0)	108 (54.0)	8 (4.0)	52 (52.5)	6 (6.1)	66 (64.7)	7 (6.9)	118 (58.7)	13 (6.5)	324 (58.3)	49 (8.8)
Gastrointestinal disorders	43 (43.0)	1 (1.0)	48 (48.0)	2 (2.0)	91 (45.5)	3 (1.5)	49 (49.5)	3 (3.0)	62 (60.8)	6 (5.9)	111 (55.2)	9 (4.5)	297 (53.4)	34 (6.1)
Investigations	47 (47.0)	20 (20.0)	47 (47.0)	19 (19.0)	94 (47.0)	39 (19.5)	45 (45.5)	19 (19.2)	68 (66.7)	28 (27.5)	113 (56.2)	47 (23.4)	284 (51.1)	131 (23.6)
Musculoskeletal and connective tissue disorders	42 (42.0)	7 (7.0)	34 (34.0)	3 (3.0)	76 (38.0)	10 (5.0)	46 (46.5)	3 (3.0)	45 (44.1)	1 (1.0)	91 (45.3)	4 (2.0)	266 (47.8)	35 (6.3)
Skin and subcutaneous tissue disorders	40 (40.0)	0	39 (39.0)	0	79 (39.5)	0	31 (31.3)	2 (2.0)	54 (52.9)	2 (2.0)	85 (42.3)	4 (2.0)	251 (45.1)	3 (0.5)
General disorders and administration site	30 (30.0)	1 (1.0)	37 (37.0)	1 (1.0)	67 (33.5)	2 (1.0)	46 (46.5)	3 (3.0)	41 (40.2)	1 (1.0)	87 (43.3)	4 (2.0)	235 (42.3)	25 (4.5)
Nervous system disorders	32 (32.0)	3 (3.0)	24 (24.0)	3 (3.0)	56 (28.0)	6 (3.0)	20 (20.2)	1 (1.0)	37 (36.3)	1 (1.0)	57 (28.4)	2 (1.0)	230 (41.4)	32 (5.8)
Blood and lymphatic system disorders	30 (30.0)	13 (13.0)	33 (33.0)	8 (8.0)	63 (31.5)	21 (10.5)	37 (37.4)	14 (14.1)	49 (48.0)	23 (22.5)	86 (42.8)	37 (18.4)	192 (34.5)	99 (17.8)

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib N=100		2G TKI N=100		All Asciminib N=200		Imatinib N=99		2G TKI N=102		All Comparators N=201		All Asciminib 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
Primary system organ class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Respiratory, thoracic and mediastinal disorders	17 (17.0)	1 (1.0)	19 (19.0)	0	36 (18.0)	1 (0.5)	15 (15.2)	1 (1.0)	32 (31.4)	3 (2.9)	47 (23.4)	4 (2.0)	177 (31.8)	17 (3.1)
Metabolism and nutrition disorders	30 (30.0)	4 (4.0)	27 (27.0)	2 (2.0)	57 (28.5)	6 (3.0)	26 (26.3)	4 (4.0)	32 (31.4)	2 (2.0)	58 (28.9)	6 (3.0)	182 (32.7)	45 (8.1)
Vascular disorders	19 (19.0)	8 (8.0)	14 (14.0)	6 (6.0)	33 (16.5)	14 (7.0)	9 (9.1)	2 (2.0)	8 (7.8)	5 (4.9)	17 (8.5)	7 (3.5)	138 (24.8)	68 (12.2)
Eye disorders	11 (11.0)	1 (1.0)	20 (20.0)	1 (1.0)	31 (15.5)	2 (1.0)	34 (34.3)	0	15 (14.7)	1 (1.0)	49 (24.4)	1 (0.5)	119 (21.4)	10 (1.8)
Injury, poisoning and procedural complications	6 (6.0)	1 (1.0)	14 (14.0)	2 (2.0)	20 (10.0)	3 (1.5)	5 (5.1)	0	12 (11.8)	0	17 (8.5)	0	108 (19.4)	17 (3.1)
Psychiatric disorders	11 (11.0)	1 (1.0)	11 (11.0)	0	22 (11.0)	1 (0.5)	7 (7.1)	0	11 (10.8)	0	18 (9.0)	0	101 (18.2)	9 (1.6)
Cardiac disorders	6 (6.0)	0	3 (3.0)	0	9 (4.5)	0	4 (4.0)	1 (1.0)	16 (15.7)	3 (2.9)	20 (10.0)	4 (2.0)	79 (14.2)	24 (4.3)
Reproductive system and breast disorders	9 (9.0)	0	10 (10.0)	0	19 (9.5)	0	4 (4.0)	0	12 (11.8)	2 (2.0)	16 (8.0)	2 (1.0)	59 (10.6)	0
Renal and urinary disorders	5 (5.0)	0	2 (2.0)	0	7 (3.5)	0	6 (6.1)	0	8 (7.8)	1 (1.0)	14 (7.0)	1 (0.5)	49 (8.8)	9 (1.6)
Ear and labyrinth disorders	4 (4.0)	0	1 (1.0)	0	5 (2.5)	0	7 (7.1)	1 (1.0)	9 (8.8)	0	16 (8.0)	1 (0.5)	39 (7.0)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.0)	0	4 (4.0)	1 (1.0)	6 (3.0)	1 (0.5)	7 (7.1)	2 (2.0)	8 (7.8)	2 (2.0)	15 (7.5)	4 (2.0)	32 (5.8)	9 (1.6)
Hepatobiliary disorders	8 (8.0)	2 (2.0)	7 (7.0)	1 (1.0)	15 (7.5)	3 (1.5)	3 (3.0)	1 (1.0)	5 (4.9)	1 (1.0)	8 (4.0)	2 (1.0)	34 (6.1)	8 (1.4)
Endocrine disorders	1 (1.0)	0	4 (4.0)	0	5 (2.5)	0	3 (3.0)	0	0	0	3 (1.5)	0	13 (2.3)	0
Immune system disorders	0	0	0	0	0	0	2 (2.0)	0	2 (2.0)	0	4 (2.0)	0	10 (1.8)	1 (0.2)
Pregnancy, puerperium and perinatal conditions	0	0	0	0	0	0	0	0	0	0	0	0	4 (0.7)	2 (0.4)
Product issues	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	0	0	0	0	0	0	4 (0.7)	2 (0.4)
Congenital, familial and genetic disorders	0	0	0	0	0	0	1 (1.0)	0	0	0	1 (0.5)	0	1 (0.2)	0

A participant with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 27.1, CTCAE version 5.0.

Source: 1L SCS Appendix 2-Table 2-2.1

Adverse events by preferred term (PT)

AEs that were reported more frequently (with ≥ 5% difference) in the asciminib group compared to imatinib included abdominal pain (11.0% vs. 3.0%) headache (16.5% vs. 9.1%) constipation (10.0% vs. 4.0%) and hypertension (10.5% vs. 5.1%) pruritus (9.5% vs. 4.0%) and dry skin (6.0% vs. 1.0%). Less frequently reported in the asciminib arm compared to imatinib was diarrhea (17.5% vs. 28.3%), anemia (12.5% vs. 26.3%), WBC count decreased (11.0% vs. 17.2%), neutropenia (10.5% vs. 16.2%), nausea (9.5% vs. 21.2%), Blood ALP increased (6.0% vs. 13.1%), vomiting (7.0% vs. 13.1%), back pain (6.0% vs. 12.1%), lymphocyte count decreased (5.0% vs. 13.1%), muscle spasms (3.0% vs. 19.2%), edema peripheral (1.5% vs. 7.1%), periorbital edema (1.0% vs. 11.1%), hypokalemia (0.5% vs. 6.1%), hypophosphatemia (0.5% vs. 9.1%), eyelid edema (0% vs. 8.1%) and face edema (0% vs. 10.1%). There were no grade ≥ 3 AEs reported more frequently (with a ≥ 5%

difference) in the asciminib group compared to the imatinib. Grade ≥ 3 AEs reported less frequently in asciminib group compared to imatinib included neutropenia (4.5% vs. 11.1%).

In comparison to 2G-TKI, AEs that were reported more frequently in the asciminib group compared to 2G TKI (with ≥ 5% difference) included hypertension (10.5% vs. 4.9%). AEs that were reported less frequently (with ≥ 5% difference) in the asciminib group compared to 2G TKI included diarrhoea (17.5% vs. 27.5%), neutrophil count decreased (15.0% vs. 20.6%), headache (16.5% vs. 23.5%), rash (14.5% vs. 23.5%), anaemia (12.5% vs. 25.5%), neutropenia (10.5% vs. 16.7%), nausea (9.5% vs. 18.6%), ALT increased (8.5% vs. 20.6%), AST increased (3.0% vs. 15.7%), blood bilirubin increased (4.0% vs. 10.8%), cough (6.0% vs. 12.7%), alopecia (2.5% vs. 8.8%), influenza like illness (2.5% vs. 9.8%), dyspnoea (1.0% vs. 6.9%) and pleural effusion (0% vs. 9.8%). There were no grade ≥ 3 AEs reported more frequently (with a ≥ 5% difference) in the asciminib group compared to the 2G-TKI. Grade ≥ 3 AEs reported less frequently in the asciminib group compared to the 2G-TKI included neutropenia (4.5% vs. 9.8%) and ALT increased (2.0% vs. 7.8%, *Table 61*).

Table 61 AEs by preferred term (≥ 10% in Safety Pool All asciminib) - Safety set

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib		2G TKI		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
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
At least one event	**97 (97.0)**	**48 (48.0)**	**94 (94.0)**	**41 (41.0)**	**191 (95.5)**	**89 (44.5)**	**95 (96.0)**	**49 (49.5)**	**102 (100)**	**61 (59.8)**	**197 (98.0)**	**110 (54.7)**	**533 (95.9)**	**324 (58.3)**
Headache	18 (18.0)	1 (1.0)	15 (15.0)	0	33 (16.5)	1 (0.5)	9 (9.1)	0	24 (23.5)	0	33 (16.4)	0	127 (22.8)	8 (1.4)
Fatigue	15 (15.0)	0	15 (15.0)	1 (1.0)	30 (15.0)	1 (0.5)	15 (15.2)	1 (1.0)	20 (19.6)	0	35 (17.4)	1 (0.5)	116 (20.9)	6 (1.1)
Arthralgia	16 (16.0)	3 (3.0)	10 (10.0)	1 (1.0)	26 (13.0)	4 (2.0)	10 (10.1)	1 (1.0)	9 (8.8)	0	19 (9.5)	1 (0.5)	115 (20.7)	9 (1.6)
Diarrhoea	14 (14.0)	0	21 (21.0)	0	35 (17.5)	0	28 (28.3)	0	28 (27.5)	2 (2.0)	56 (27.9)	2 (1.0)	115 (20.7)	2 (0.4)
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)
COVID-19	13 (13.0)	0	30 (30.0)	0	43 (21.5)	0	20 (20.2)	0	24 (23.5)	1 (1.0)	44 (21.9)	1 (0.5)	103 (18.5)	5 (0.9)
Lipase increased	20 (20.0)	6 (6.0)	7 (7.0)	0	27 (13.5)	6 (3.0)	15 (15.2)	2 (2.0)	15 (14.7)	5 (4.9)	30 (14.9)	7 (3.5)	96 (17.3)	48 (8.6)
Hypertension	14 (14.0)	8 (8.0)	7 (7.0)	3 (3.0)	21 (10.5)	11 (5.5)	5 (5.1)	2 (2.0)	5 (4.9)	5 (4.9)	10 (5.0)	7 (3.5)	94 (16.9)	51 (9.2)
Nausea	8 (8.0)	0	11 (11.0)	0	19 (9.5)	0	21 (21.2)	0	19 (18.6)	0	40 (19.9)	0	93 (16.7)	3 (0.5)

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib		2G TKI		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
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Rash	9 (9.0)	0	20 (20.0)	0	29 (14.5)	0	11 (11.1)	2 (2.0)	24 (23.5)	1 (1.0)	35 (17.4)	3 (1.5)	88 (15.8)	0
Vomiting	6 (6.0)	0	8 (8.0)	0	14 (7.0)	0	13 (13.1)	0	7 (6.9)	0	20 (10.0)	0	78 (14.0)	8 (1.4)
Neutropenia	12 (12.0)	5 (5.0)	9 (9.0)	4 (4.0)	21 (10.5)	9 (4.5)	16 (16.2)	11 (11.1)	17 (16.7)	10 (9.8)	33 (16.4)	21 (10.4)	77 (13.8)	51 (9.2)
Abdominal pain	11 (11.0)	0	11 (11.0)	1 (1.0)	22 (11.0)	1 (0.5)	3 (3.0)	0	11 (10.8)	1 (1.0)	14 (7.0)	1 (0.5)	76 (13.7)	6 (1.1)
Myalgia	15 (15.0)	0	16 (16.0)	1 (1.0)	31 (15.5)	1 (0.5)	18 (18.2)	0	17 (16.7)	0	35 (17.4)	0	75 (13.5)	5 (0.9)
Anaemia	11 (11.0)	1 (1.0)	14 (14.0)	3 (3.0)	25 (12.5)	4 (2.0)	26 (26.3)	5 (5.1)	26 (25.5)	7 (6.9)	52 (25.9)	12 (6.0)	70 (12.6)	23 (4.1)
Cough	4 (4.0)	0	8 (8.0)	0	12 (6.0)	0	7 (7.1)	0	13 (12.7)	0	20 (10.0)	0	67 (12.1)	0
Upper respiratory tract infection	9 (9.0)	0	8 (8.0)	0	17 (8.5)	0	12 (12.1)	1 (1.0)	11 (10.8)	0	23 (11.4)	1 (0.5)	67 (12.1)	2 (0.4)
Pruritus	9 (9.0)	0	10 (10.0)	0	19 (9.5)	0	4 (4.0)	0	5 (4.9)	0	9 (4.5)	0	64 (11.5)	1 (0.2)
Constipation	9 (9.0)	0	11 (11.0)	0	20 (10.0)	0	4 (4.0)	0	14 (13.7)	1 (1.0)	18 (9.0)	1 (0.5)	63 (11.3)	1 (0.2)
Dizziness	4 (4.0)	0	5 (5.0)	0	9 (4.5)	0	2 (2.0)	0	7 (6.9)	0	9 (4.5)	0	62 (11.2)	1 (0.2)
Pain in extremity	7 (7.0)	1 (1.0)	3 (3.0)	0	10 (5.0)	1 (0.5)	6 (6.1)	0	5 (4.9)	0	11 (5.5)	0	61 (11.0)	3 (0.5)
Back pain	5 (5.0)	0	7 (7.0)	0	12 (6.0)	0	12 (12.1)	1 (1.0)	10 (9.8)	0	22 (10.9)	1 (0.5)	58 (10.4)	5 (0.9)
Nasopharyngitis	11 (11.0)	0	4 (4.0)	0	15 (7.5)	0	7 (7.1)	0	8 (7.8)	0	15 (7.5)	0	58 (10.4)	0
Alanine aminotransferase increased	9 (9.0)	3 (3.0)	8 (8.0)	1 (1.0)	17 (8.5)	4 (2.0)	7 (7.1)	2 (2.0)	21 (20.6)	8 (7.8)	28 (13.9)	10 (5.0)	57 (10.3)	14 (2.5)

A participant with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 27.1, CTCAE version 5.0
Source: [1L SCS Appendix 2-Table 2-2.2]

Incidence of AE over time

The first occurrence of AEs was primarily observed within the first 3 months of therapy across treatment groups with few participants experiencing a new AE at later time points.

Serious adverse events

Deaths

As of the Week 96 data cut-off, no on-treatment death (up to 30 days after end of treatment) was reported. Overall, 2 (1.0%) participants from the asciminib group and 4 participants (2.0%; all were in the imatinib group) from the IS-TKI group died during the survival follow-up (more than 30 days after study treatment discontinuation). Reasons for death were complications due to HSCT after progression, after HSCT for unknown reason, after HSCT due to study indication, due to metastatic bronchial carcinoma or congestive heart failure.

Serious adverse events

Overall, the incidence of SAEs was lower in the asciminib group (14.5%) compared to the IS-TKI group (20.4%) as well as to 2G TKI (24.5%) and was similar to imatinib (16.2%). The incidence of individual SAEs was low in both asciminib and IS-TKI groups. The SAEs that were reported in at least 2 participants included for the asciminib group: Cholecystitis acute, large intestine perforation, neuralgia, and osteoarthritis (2 participants each). For the IS-TKI group: pneumonia (6 participants overall; including 1 in imatinib group, and 5 in the 2G TKI group), pleural effusion (4 participants overall; all in 2G TKI group), COVID-19 (2 participants overall; both in 2G TKI group), colitis (2 participants overall; both in 2G TKI group), prostate cancer (2 participants overall; including 1 in imatinib group and 1 in 2G TKI group), URTI (2 participants overall; including 1 in imatinib group and 1 in 2G TKI group). All other SAEs were reported as single cases.

SAEs of grade ≥ 3 occurred in similar proportion of participants in the asciminib group compared to the IS-TKI group (11.5% vs. 15.9%). Grade ≥ 3 SAEs that occurred in more than 1 participant in the asciminib group included cholecystitis acute, neuralgia, and osteoarthritis (in 2 participants each). Grade ≥ 3 SAEs that occurred in more than 1 participant in the IS-TKI group included: pneumonia (5 participants overall, including 1 in imatinib group and 4 in 2G TKI group); and pleural effusion (2 participants, both in 2G TKI group).

Adverse events of special interest

The MedDRA grouping definitions used to define each AESI are presented in *Table 62*.

Table 62 Adverse events of special interest – MedDRA grouping definitions

Topic	Definition
Acute pancreatitis (including isolated pancreatic enzyme elevations)	Pancreatitis (including laboratory terms) (CMQ, Broad) Pancreatitis and Pancreatitis acute
Acute pancreatitis (clinical events)	Acute pancreatitis (SMQ, Narrow)
Arterial occlusive events (AOEs)	Embolic and thrombotic events, arterial (SMQ) Ischaemic central nervous system vascular conditions (SMQ) Ischaemic heart disease (SMQ, Narrow)
Cardiac failure (clinical events)	Cardiac failure (SMQ, Narrow)
Edema and fluid retention	Haemodynamic oedema, effusions and fluid overload (SMQ)
GI toxicity	Gastrointestinal nonspecific symptoms and therapeutic procedures (SMQ, Narrow)
Hemorrhage	Haemorrhages (SMQ, Narrow)
Hepatitis B virus reactivation	Hepatitis B virus reactivation (CMQ)
Hepatotoxicity (including laboratory terms)	Cholestasis and jaundice of hepatic origin (SMQ, Broad) Liver related investigations, signs and symptoms (SMQ, Broad) Hepatitis, non-infectious (SMQ, Broad) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ, Broad)
Hepatotoxicity (clinical events)	Hepatitis, non-infectious (SMQ, Broad) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ, Broad)
Hypersensitivity	Hypersensitivity (SMQ, Narrow)
Ischemic heart and CNS conditions	Ischaemic heart disease (SMQ, Broad) Ischaemic central nervous system vascular conditions (SMQ)
Myelosuppression	Haematopoietic cytopenias affecting more than one type of blood cell (SMQ, Narrow) Haematopoietic erythropenia (SMQ, Broad) Haematopoietic leukopenia (SMQ, Narrow) Haematopoietic thrombocytopenia (SMQ, Narrow)
Phototoxicity	Photosensitivity reactions (NMQ)
QTc prolongation	Torsade de pointes/QT prolongation (SMQ, Broad)
Reproductive toxicity	Pregnancy and neonatal topics (SMQ, Broad)

Note: the definitions of Arterial occlusive events (AOEs) and Ischemic heart and CNS conditions contain highly overlapping terms.
Source: 1L SCS Appendix 2-Listing 6-1

AESI all grades that were less frequent in the asciminib treatment group compared to the IS-TKI treatment group. In comparison with imatinib, none of the AESI was more often reported in the asciminib group. Exposure-adjusted incidence rates of AESI were lower in the asciminib group compared to the IS-TKI group (129.4 vs. 387.3- imatinib: 280.1, 2G-TKI 574.7).

Table 63 Overview of adverse events of special interest - Safety set

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib N=100		2G TKI N=100		All Asciminib N=200		Imatinib N=99		2G TKI N=102		All Comparators N=201		All Asciminib N=556	
Safety topic	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	34 (34.0)	0	44 (44.0)	1 (1.0)	78 (39.0)	1 (0.5)	43 (43.4)	0	53 (52.0)	5 (4.9)	96 (47.8)	5 (2.5)	259 (46.6)	19 (3.4)
Myelosuppression*	41 (41.0)	19 (19.0)	46 (46.0)	21 (21.0)	87 (43.5)	40 (20.0)	51 (51.5)	24 (24.2)	65 (63.7)	34 (33.3)	116 (57.7)	58 (28.9)	220 (39.6)	127 (22.8)
Myelosuppression (Erythropenia)	11 (11.0)	1 (1.0)	14 (14.0)	3 (3.0)	25 (12.5)	4 (2.0)	26 (26.3)	5 (5.1)	26 (25.5)	7 (6.9)	52 (25.9)	12 (6.0)	72 (12.9)	23 (4.1)
Myelosuppression (Leukopenia)	31 (31.0)	11 (11.0)	32 (32.0)	15 (15.0)	63 (31.5)	26 (13.0)	38 (38.4)	23 (23.2)	42 (41.2)	19 (18.6)	80 (39.8)	42 (20.9)	136 (24.5)	84 (15.1)
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 affecting more than one lineage)	0	0	0	0	0	0	0	0	0	0	0	0	2 (0.4)	1 (0.2)
Hypersensitivity	23 (23.0)	0	29 (29.0)	1 (1.0)	52 (26.0)	1 (0.5)	43 (43.4)	3 (3.0)	46 (45.1)	2 (2.0)	89 (44.3)	5 (2.5)	173 (31.1)	8 (1.4)
Hepatotoxicity (including laboratory terms)	21 (21.0)	3 (3.0)	19 (19.0)	2 (2.0)	40 (20.0)	5 (2.5)	21 (21.2)	4 (4.0)	37 (36.3)	8 (7.8)	58 (28.9)	12 (6.0)	120 (21.6)	23 (4.1)
Hepatotoxicity (clinical events)	3 (3.0)	0	4 (4.0)	1 (1.0)	7 (3.5)	1 (0.5)	1 (1.0)	1 (1.0)	3 (2.9)	0	4 (2.0)	1 (0.5)	12 (2.2)	2 (0.4)

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib N=100		2G TKI N=100		All Asciminib N=200		Imatinib N=99		2G TKI N=102		All Comparators N=201		All Asciminib N=556	
Safety topic	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 (%)
Acute pancreatitis (including isolated pancreatic enzyme elevations)	21 (21.0)	6 (6.0)	8 (8.0)	1 (1.0)	29 (14.5)	7 (3.5)	16 (16.2)	3 (3.0)	18 (17.6)	6 (5.9)	34 (16.9)	9 (4.5)	114 (20.5)	57 (10.3)
Acute pancreatitis (clinical events)	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	7 (7.0)	0	13 (6.5)	0	10 (10.1)	1 (1.0)	12 (11.8)	3 (2.9)	22 (10.9)	4 (2.0)	76 (13.7)	10 (1.8)
Edema and fluid retention	3 (3.0)	0	6 (6.0)	0	9 (4.5)	0	15 (15.2)	0	15 (14.7)	5 (4.9)	30 (14.9)	5 (2.5)	74 (13.3)	9 (1.6)
Ischemic heart and CNS conditions	7 (7.0)	2 (2.0)	8 (8.0)	4 (4.0)	15 (7.5)	6 (3.0)	7 (7.1)	0	11 (10.8)	4 (3.9)	18 (9.0)	4 (2.0)	58 (10.4)	26 (4.7)
Ischemic heart conditions	6 (6.0)	1 (1.0)	8 (8.0)	4 (4.0)	14 (7.0)	5 (2.5)	7 (7.1)	0	10 (9.8)	4 (3.9)	17 (8.5)	4 (2.0)	46 (8.3)	18 (3.2)
Ischemic CNS conditions	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)	0	0	2 (2.0)	0	2 (1.0)	0	16 (2.9)	9 (1.6)
Arterial-occlusive events (AOEs)	2 (2.0)	1 (1.0)	2 (2.0)	0	4 (2.0)	1 (0.5)	0	0	3 (2.9)	1 (1.0)	3 (1.5)	1 (0.5)	39 (7.0)	18 (3.2)
QTc prolongation	1 (1.0)	1 (1.0)	3 (3.0)	2 (2.0)	4 (2.0)	3 (1.5)	0	0	5 (4.9)	1 (1.0)	5 (2.5)	1 (0.5)	23 (4.1)	12 (2.2)
Phototoxicity	0	0	3 (3.0)	0	3 (1.5)	0	0	0	2 (2.0)	0	2 (1.0)	0	16 (2.9)	0
Cardiac failure	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)

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib N=100		2G TKI N=100		All Asciminib N=200		Imatinib N=99		2G TKI N=102		All Comparators N=201		All Asciminib N=556	
Safety topic	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 toxicity	1 (1.0)	0	2 (2.0)	1 (1.0)	3 (1.5)	1 (0.5)	1 (1.0)	0	1 (1.0)	0	2 (1.0)	0	9 (1.6)	4 (0.7)
Hepatitis B virus reactivation	0	0	0	0	0	0	1 (1.0)	0	0	0	1 (0.5)	0	1 (0.2)	0

MedDRA version 27.1, CTCAE version 5.0, Case Retrieval Strategy version released 28-Nov-2024.
*Myelosuppression includes Erythropenia, Leukopenia, Neutropenia, Thrombocytopenia, cytopenias affecting more than one lineage.
Source: 1L SCS Appendix 2-Table 2-13

An overview about the risk difference for TKI – class effects is provided in *Table 64*.

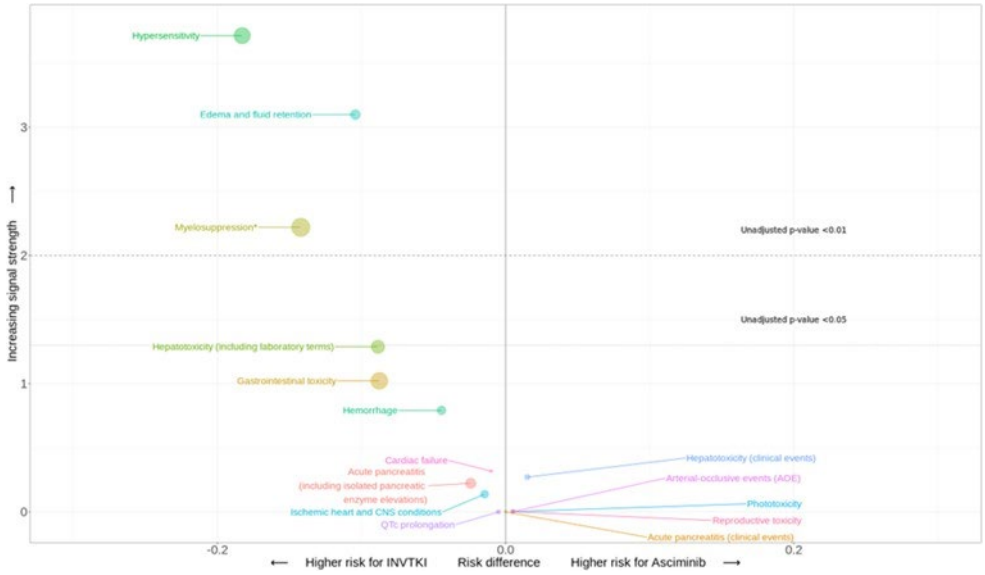


Table 64 Overview of AESI by risk difference between Asciminib and IS-TKI treatment groups - Safety Set
Source: SCS, figure 2-4

Gastrointestinal toxicity

Overall, 39.0% of participants in the asciminib treatment group had GI toxicity AESI vs. 47.8% in IS-TKI treatment group, including 43.4% in imatinib and 52.0% in 2G TKI. The effect was present according to diarrhoea, nausea and vomiting. Abdominal pain was reported more often in the asciminib arm (11%) in comparison to imatinib (3.0%), but not to 2G-TKI (10.8%), >=G3 events were overall rave, with 0.5% in the asciminib group, no events in the imatinib group and 4.9% in the 2G-group. However, the AE had not recovered in 9.0 % vs. 14.0% vs. 20.6% of patients having such an AE.

Table 65 Clinical impact of AESI Gastrointestinal toxicity - Safety set

	Study J12301						Safety Pool
	Asciminib			Investigator Selected TKI			
Gastrointestinal toxicity	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
At least one event	34 (34.0)	44 (44.0)	78 (39.0)	43 (43.4)	53 (52.0)	96 (47.8)	259 (46.6)
Diarrhoea	14 (14.0)	21 (21.0)	35 (17.5)	28 (28.3)	28 (27.5)	56 (27.9)	115 (20.7)
Nausea	8 (8.0)	11 (11.0)	19 (9.5)	21 (21.2)	19 (18.6)	40 (19.9)	93 (16.7)
Vomiting	6 (6.0)	8 (8.0)	14 (7.0)	13 (13.1)	7 (6.9)	20 (10.0)	78 (14.0)
Abdominal pain	11 (11.0)	11 (11.0)	22 (11.0)	3 (3.0)	11 (10.8)	14 (7.0)	76 (13.7)
Constipation	9 (9.0)	11 (11.0)	20 (10.0)	4 (4.0)	14 (13.7)	18 (9.0)	63 (11.3)
Abdominal pain upper	1 (1.0)	8 (8.0)	9 (4.5)	4 (4.0)	3 (2.9)	7 (3.5)	41 (7.4)
Non-cardiac chest pain	1 (1.0)	4 (4.0)	5 (2.5)	0	1 (1.0)	1 (0.5)	37 (6.7)
Abdominal distension	0	1 (1.0)	1 (0.5)	1 (1.0)	5 (4.9)	6 (3.0)	11 (2.0)
Abdominal discomfort	1 (1.0)	1 (1.0)	2 (1.0)	1 (1.0)	3 (2.9)	4 (2.0)	10 (1.8)
Flatulence	1 (1.0)	2 (2.0)	3 (1.5)	0	2 (2.0)	2 (1.0)	9 (1.6)
Abdominal pain lower	0	1 (1.0)	1 (0.5)	0	0	0	6 (1.1)
Gastrointestinal pain	1 (1.0)	0	1 (0.5)	0	0	0	3 (0.5)
Eructation	0	1 (1.0)	1 (0.5)	0	0	0	2 (0.4)
Bowel movement irregularity	0	0	0	0	1 (1.0)	1 (0.5)	0
Maximum grade							
Grade 3 AEs	0	1 (1.0)	1 (0.5)	0	5 (4.9)	5 (2.5)	19 (3.4)
Treatment-related AEs	17 (17.0)	18 (18.0)	35 (17.5)	37 (37.4)	33 (32.4)	70 (34.8)	133 (23.9)
SAEs	0	1 (1.0)	1 (0.5)	1 (1.0)	2 (2.0)	3 (1.5)	14 (2.5)

	Study J12301						Safety Pool
	Asciminib			Investigator Selected TKI			
Gastrointestinal toxicity	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
Action taken							
Drug withdrawn	0	0	0	3 (3.0)	0	3 (1.5)	1 (0.2)
Dose adjusted	0	0	0	4 (4.0)	2 (2.0)	6 (3.0)	11 (2.0)
Drug interrupted	2 (2.0)	4 (4.0)	6 (3.0)	4 (4.0)	4 (3.9)	8 (4.0)	27 (4.9)
Dose not changed/NA/Unknown	34 (34.0)	42 (42.0)	76 (38.0)	40 (40.4)	51 (50.0)	91 (45.3)	252 (45.3)
AE outcome							
Recovered/resolved	32 (32.0)	42 (42.0)	74 (37.0)	39 (39.4)	45 (44.1)	84 (41.8)	234 (42.1)
Recovering/resolving	3 (3.0)	3 (3.0)	6 (3.0)	2 (2.0)	8 (7.8)	10 (5.0)	22 (4.0)
Not recovered/not resolved	8 (8.0)	10 (10.0)	18 (9.0)	14 (14.1)	21 (20.6)	35 (17.4)	87 (15.6)

Participants/outcome with no events in Study J12301 are omitted from this in-text table. A participant may be counted in several rows for action taken and outcome.
MedDRA version 27.1, CTCAE version 5.0. Case Retrieval Strategy version released 28-Nov-2024.
Source: [1L SCS Appendix 2-Table 2-14.1]

Myelosuppression

Myelosuppression events all grades occurred less frequently in the asciminib group (43.5%) compared to the IS-TKI group overall (57.7%) as well as imatinib (51.5%) and 2G TKI (63.7%). Grade 3 and Grade 4 events occurred in 14.0% and 6.0% of participants in the asciminib group compared to 21.4% and 7.5% in the IS-TKI group overall (17.2% and 7.1% in the imatinib group; 25.5% and 7.8% in the 2G TKI group). For more details, see Table 66.

Table 66 Clinical impact of AESI Myelosuppression - Safety set

	Study J12301						Safety Pool
	Asciminib			Investigator Selected TKI			
Myelosuppression*	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
At least one event	41 (41.0)	46 (46.0)	87 (43.5)	51 (51.5)	65 (63.7)	116 (57.7)	220 (39.6)
Thrombocytopenia	15 (15.0)	12 (12.0)	27 (13.5)	14 (14.1)	17 (16.7)	31 (15.4)	109 (19.6)
Neutropenia	12 (12.0)	9 (9.0)	21 (10.5)	16 (16.2)	17 (16.7)	33 (16.4)	77 (13.8)
Anaemia	11 (11.0)	14 (14.0)	25 (12.5)	26 (26.3)	26 (25.5)	52 (25.9)	70 (12.6)
Platelet count decreased	11 (11.0)	18 (18.0)	29 (14.5)	14 (14.1)	19 (18.6)	33 (16.4)	52 (9.4)
Neutrophil count decreased	13 (13.0)	17 (17.0)	30 (15.0)	16 (16.2)	21 (20.6)	37 (18.4)	49 (8.8)
White blood cell count decreased	10 (10.0)	12 (12.0)	22 (11.0)	17 (17.2)	13 (12.7)	30 (14.9)	34 (6.1)
Leukopenia	7 (7.0)	10 (10.0)	17 (8.5)	12 (12.1)	8 (7.8)	20 (10.0)	24 (4.3)
Lymphocyte count decreased	6 (6.0)	4 (4.0)	10 (5.0)	13 (13.1)	3 (2.9)	16 (8.0)	10 (1.8)
Lymphopenia	3 (3.0)	0	3 (1.5)	4 (4.0)	4 (3.9)	8 (4.0)	7 (1.3)
Monocyte count decreased	2 (2.0)	3 (3.0)	5 (2.5)	3 (3.0)	2 (2.0)	5 (2.5)	5 (0.9)
Febrile neutropenia	0	1 (1.0)	1 (0.5)	0	0	0	4 (0.7)
Red blood cell count decreased	0	1 (1.0)	1 (0.5)	0	0	0	1 (0.2)
Erythropenia	0	0	0	1 (1.0)	0	1 (0.5)	0
Haematocrit decreased	0	0	0	1 (1.0)	0	1 (0.5)	0
Maximum grade							
Grade 3 AEs	16 (16.0)	12 (12.0)	28 (14.0)	17 (17.2)	26 (25.5)	43 (21.4)	60 (10.8)
Grade 4 AEs	3 (3.0)	9 (9.0)	12 (6.0)	7 (7.1)	8 (7.8)	15 (7.5)	67 (12.1)
Treatment-related AEs	37 (37.0)	42 (42.0)	79 (39.5)	47 (47.5)	59 (57.8)	106 (52.7)	178 (32.0)

	Study J12301						Safety Pool
	Asciminib			Investigator Selected TKI			
Myelosuppression*	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
SAEs	0	1 (1.0)	1 (0.5)	1 (1.0)	2 (2.0)	3 (1.5)	7 (1.3)
Action taken							
Drug withdrawn	1 (1.0)	1 (1.0)	2 (1.0)	3 (3.0)	1 (1.0)	4 (2.0)	12 (2.2)
Dose adjusted	5 (5.0)	2 (2.0)	7 (3.5)	6 (6.1)	15 (14.7)	21 (10.4)	31 (5.6)
Drug interrupted	14 (14.0)	19 (19.0)	33 (16.5)	19 (19.2)	21 (20.6)	40 (19.9)	85 (15.3)
Dose not changed/NA/Unknown	39 (39.0)	44 (44.0)	83 (41.5)	47 (47.5)	59 (57.8)	106 (52.7)	206 (37.1)
AE outcome							
Recovered/resolved	41 (41.0)	45 (45.0)	86 (43.0)	50 (50.5)	59 (57.8)	109 (54.2)	200 (36.0)
Recovering/resolving	17 (17.0)	22 (22.0)	39 (19.5)	20 (20.2)	25 (24.5)	45 (22.4)	104 (18.7)
Not recovered/not resolved	14 (14.0)	17 (17.0)	31 (15.5)	26 (26.3)	36 (35.3)	62 (30.8)	114 (20.5)

A participant may be counted in several rows for action taken and outcome. Participants/outcome with no events in Study J12301 are omitted from this in-text table.
MedDRA version 27.1, CTCAE version 5.0 case Retrieval Strategy version released 28-Nov-2024.
*Myelosuppression includes Erythropenia, Leukopenia, Neutropenia,Thrombocytopenia, Cytopenias affecting more than one lineage.
Source: I1L SCS Appendix 2-Table 2-14.1l

Hypersensivity

Hypersensitivity events (all grades) occurred markedly less frequently with asciminib as compared to IS-TKIs (26.0% vs. 44.3%) including as compared to imatinib (26.0% vs. 43.4%) and 2G TKI (26.0% vs. 45.1%).

Table 67 Clinical impact of AESI Hypersensitivity - Safety set

	Study J12301						Safety Pool
		Asciminib		Investigator Selected TKI			
Hypersensitivity	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
At least one event	23 (23.0)	29 (29.0)	52 (26.0)	43 (43.4)	46 (45.1)	89 (44.3)	173 (31.1)
Rash	9 (9.0)	20 (20.0)	29 (14.5)	11 (11.1)	24 (23.5)	35 (17.4)	88 (15.8)
Rash maculo-papular	1 (1.0)	2 (2.0)	3 (1.5)	0	3 (2.9)	3 (1.5)	22 (4.0)
Urticaria	4 (4.0)	2 (2.0)	6 (3.0)	0	5 (4.9)	5 (2.5)	19 (3.4)
Dermatitis acneiform	2 (2.0)	1 (1.0)	3 (1.5)	1 (1.0)	3 (2.9)	4 (2.0)	12 (2.2)
Eczema	2 (2.0)	2 (2.0)	4 (2.0)	3 (3.0)	6 (5.9)	9 (4.5)	11 (2.0)
Rhinitis allergic	1 (1.0)	1 (1.0)	2 (1.0)	0	1 (1.0)	1 (0.5)	9 (1.6)
Dermatitis allergic	2 (2.0)	1 (1.0)	3 (1.5)	0	3 (2.9)	3 (1.5)	5 (0.9)
Periorbital oedema	0	2 (2.0)	2 (1.0)	11 (11.1)	1 (1.0)	12 (6.0)	5 (0.9)
Rash pruritic	1 (1.0)	0	1 (0.5)	2 (2.0)	0	2 (1.0)	5 (0.9)
Rash pustular	0	0	0	0	1 (1.0)	1 (0.5)	4 (0.7)
Allergic transfusion reaction	0	1 (1.0)	1 (0.5)	0	0	0	2 (0.4)
Eye swelling	0	2 (2.0)	2 (1.0)	2 (2.0)	0	2 (1.0)	2 (0.4)
Face oedema	0	0	0	10 (10.1)	0	10 (5.0)	2 (0.4)
Contrast media reaction	0	0	0	1 (1.0)	0	1 (0.5)	1 (0.2)
Hypersensitivity	0	0	0	1 (1.0)	2 (2.0)	3 (1.5)	1 (0.2)
Infusion related reaction	0	1 (1.0)	1 (0.5)	0	0	0	1 (0.2)
Periorbital swelling	0	1 (1.0)	1 (0.5)	1 (1.0)	0	1 (0.5)	1 (0.2)
Rash macular	0	0	0	1 (1.0)	0	1 (0.5)	1 (0.2)
Rash vesicular	1 (1.0)	0	1 (0.5)	0	0	0	1 (0.2)
Vulval eczema	1 (1.0)	0	1 (0.5)	0	0	0	1 (0.2)
Dermatitis exfoliative	0	0	0	0	1 (1.0)	1 (0.5)	0
Drug eruption	0	0	0	1 (1.0)	0	1 (0.5)	0
Eyelid oedema	0	0	0	8 (8.1)	0	8 (4.0)	0
Solar urticaria	0	0	0	0	1 (1.0)	1 (0.5)	0
Swelling of eyelid	0	0	0	3 (3.0)	2 (2.0)	5 (2.5)	0
Maximum grade							
Grade 3 AEs	0	1 (1.0)	1 (0.5)	3 (3.0)	2 (2.0)	5 (2.5)	7 (1.3)
Treatment-related AEs	18 (18.0)	21 (21.0)	39 (19.5)	40 (40.4)	37 (36.3)	77 (38.3)	106 (19.1)
Action taken							
Drug withdrawn	0	0	0	1 (1.0)	3 (2.9)	4 (2.0)	2 (0.4)
Dose adjusted	0	0	0	4 (4.0)	4 (3.9)	8 (4.0)	2 (0.4)
Drug interrupted	1 (1.0)	1 (1.0)	2 (1.0)	3 (3.0)	4 (3.9)	7 (3.5)	6 (1.1)
Dose not changed/NA/Unknown	22 (22.0)	29 (29.0)	51 (25.5)	38 (38.4)	44 (43.1)	82 (40.8)	170 (30.6)
AE outcome							
Recovered/resolved	16 (16.0)	21 (21.0)	37 (18.5)	31 (31.3)	28 (27.5)	59 (29.4)	131 (23.6)
Recovering/resolving	2 (2.0)	1 (1.0)	3 (1.5)	3 (3.0)	5 (4.9)	8 (4.0)	9 (1.6)
Not recovered/not resolved	8 (8.0)	11 (11.0)	19 (9.5)	21 (21.2)	22 (21.6)	43 (21.4)	60 (10.8)

Participants/outcome with no events in Study J12301 are omitted from this in-text table. A participant may be counted in several rows for action taken and outcome.
MedDRA version 27.1, CTCAE version 5.0 Case Retrieval Strategy version released 28-Nov-2024.
Source: 1L SCS Appendix 2-Table 2-14.1

Hepatotoxicity

Detailed information about hepatotoxicity including laboratory terms is provided in Table 68. Following the applicant, no participant met Hy's law criteria after receiving the study treatment.

Table 68 Clinical impact of AESI Hepatotoxicity (including laboratory terms) - Safety set

	Study J12301						Safety Pool
	Asciminib			Investigator Selected TKI			
Hepatotoxicity (including laboratory terms)	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
At least one event	21 (21.0)	19 (19.0)	40 (20.0)	21 (21.2)	37 (36.3)	58 (28.9)	120 (21.6)
Alanine aminotransferase increased	9 (9.0)	8 (8.0)	17 (8.5)	7 (7.1)	21 (20.6)	28 (13.9)	57 (10.3)
Aspartate aminotransferase increased	2 (2.0)	4 (4.0)	6 (3.0)	7 (7.1)	16 (15.7)	23 (11.4)	42 (7.6)
Gamma-glutamyl transferase increased	7 (7.0))	7 (7.0)	14 (7.0)	4 (4.0)	9 (8.8)	13 (6.5)	36 (6.5)
Blood alkaline phosphatase increased	10 (10.0)	2 (2.0)	12 (6.0)	13 (13.1)	6 (5.9)	19 (9.5)	24 (4.3)
Blood bilirubin increased	2 (2.0)	6 (6.0)	8 (4.0)	2 (2.0)	11 (10.8)	13 (6.5)	24 (4.3)
Hyper transaminasaemia	1 (1.0)	0	1 (0.5)	0	0	0	7 (1.3)
Bilirubin conjugated increased	0	2 (2.0)	2 (1.0)	0	2 (2.0)	2 (1.0)	5 (0.9)
Hepatic steatosis	3 (3.0)	0	3 (1.5)	0	0	0	5 (0.9)
Liver disorder	1 (1.0)	2 (2.0)	3 (1.5)	0	1 (1.0)	1 (0.5)	4 (0.7)
Blood bilirubin unconjugated increased	0	2 (2.0)	2 (1.0)	0	0	0	3 (0.5)
Hyper bilirubinaemia	0	2 (2.0)	2 (1.0)	0	2 (2.0)	2 (1.0)	3 (0.5)
Hepatic function abnormal	1 (1.0)	0	1 (0.5)	2 (2.0)	0	2 (1.0)	2 (0.4)
Hepatobiliary disease	1 (1.0)	0	1 (0.5)	0	0	0	1 (0.2)
Hepatotoxicity	0	1 (1.0)	1 (0.5)	1 (1.0)	0	1 (0.5)	1 (0.2)
Liver injury	0	1 (1.0)	1 (0.5)	0	2 (2.0)	2 (1.0)	1 (0.2)
5'nucleotidase increased	0	0	0	0	1 (1.0)	1 (0.5)	0
Hepatic enzyme increased	0	0	0	0	2 (2.0)	2 (1.0)	0

	Study J12301						Safety Pool
	Asciminib			Investigator Selected TKI			
Hepatotoxicity (including laboratory terms)	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
Maximum grade							
Grade 3 AEs	3 (3.0)	0	3 (1.5)	3 (3.0)	8 (7.8)	11 (5.5)	18 (3.2)
Grade 4 AEs	0	2 (2.0)	2 (1.0)	1 (1.0)	0	1 (0.5)	5 (0.9)
Treatment-related AEs	14 (14.0)	14 (14.0)	28 (14.0)	16 (16.2)	31 (30.4)	47 (23.4)	65 (11.7)
SAEs	0	1 (1.0)	1 (0.5)	0	0	0	2 (0.4)
Action taken							
Drug withdrawn	0	1 (1.0)	1 (0.5)	2 (2.0)	0	2 (1.0)	1 (0.2)
Dose adjusted	1 (1.0)	0	1 (0.5)	1 (1.0)	3 (2.9)	4 (2.0)	4 (0.7)
Drug interrupted	6 (6.0)	1 (1.0)	7 (3.5)	3 (3.0)	9 (8.8)	12 (6.0)	18 (3.2)
Dose not changed/NA/Unknown	20 (20.0)	18 (18.0)	38 (19.0)	18 (18.2)	34 (33.3)	52 (25.9)	114 (20.5)
AE outcome							
Recovered/resolved	18 (18.0)	16 (16.0)	34 (17.0)	20 (20.2)	34 (33.3)	54 (26.9)	107 (19.2)
Recovering/resolving	5 (5.0)	2 (2.0)	7 (3.5)	5 (5.1)	10 (9.8)	15 (7.5)	26 (4.7)
Not recovered/not resolved	8 (8.0)	11 (11.0)	19 (9.5)	5 (5.1)	13 (12.7)	18 (9.0)	52 (9.4)

Participants/outcome with no events in Study J12301 are omitted from this in-text table. A participant may be counted in several rows for action taken and outcome.
MedDRA version 27.1, CTCAE version 5.0. Case Retrieval Strategy version released 28-Nov-2024.
Source: 1L SCS Appendix 2-Table 2-14.1

Acute pancreatitis

Overall, 14.5% of participants in the asciminib treatment group had acute pancreatitis (including isolated pancreatic enzyme elevations) AESI vs. 16.9% in IS-TKI treatment group, including 16.2% in imatinib and 17.6% in 2G TKI. The majority of patients were presenting with isolated laboratory abnormalities. Detailed information about acute pancreatitis including laboratory terms is provided in Table 69.

Table 69 Clinical impact of AESI Acute pancreatitis (including isolated pancreatic enzyme elevations) - Safety set

	Study J12301						Safety Pool
				Investigator Selected TKI			
Acute pancreatitis (including isolated pancreatic enzyme elevations)	**Imatinib N=100 n (%)**	**2G TKI N=100 n (%)**	**All Asciminib N=200 n (%)**	**Imatinib N=99 n (%)**	**2G TKI N=102 n (%)**	**All Comparators N=201 n (%)**	**All Asciminib N=556 n (%)**
At least one event	21 (21.0)	8 (8.0)	29 (14.5)	16 (16.2)	18 (17.6)	34 (16.9)	114 (20.5)
Lipase increased	20 (20.0)	7 (7.0)	27 (13.5)	15 (15.2)	15 (14.7)	30 (14.9)	96 (17.3)
Amylase increased	9 (9.0)	2 (2.0)	11 (5.5)	4 (4.0)	6 (5.9)	10 (5.0)	53 (9.5)
Pancreatitis	0	1 (1.0)	1 (0.5)	2 (2.0)	0	2 (1.0)	9 (1.6)
Pancreatitis acute	1 (1.0)	0	1 (0.5)	1 (1.0)	0	1 (0.5)	3 (0.5)
Pancreatic enzymes increased	0	0	0	0	1 (1.0)	1 (0.5)	0
Maximum grade							
Grade 3 AEs	4 (4.0)	1 (1.0)	5 (2.5)	3 (3.0)	5 (4.9)	8 (4.0)	46 (8.3)
Grade 4 AEs	2 (2.0)	0	2 (1.0)	0	1 (1.0)	1 (0.5)	11 (2.0)
Treatment-related AEs	16 (16.0)	7 (7.0)	23 (11.5)	14 (14.1)	14 (13.7)	28 (13.9)	89 (16.0)
SAEs	1 (1.0)	1 (1.0)	2 (1.0)	1 (1.0)	0	1 (0.5)	7 (1.3)
Action taken							
Drug withdrawn	3 (3.0)	0	3 (1.5)	1 (1.0)	0	1 (0.5)	13 (2.3)
Drug interrupted	4 (4.0)	3 (3.0)	7 (3.5)	2 (2.0)	3 (2.9)	5 (2.5)	42 (7.6)
Dose not changed/NA/Unknown	20 (20.0)	7 (7.0)	27 (13.5)	16 (16.2)	16 (15.7)	32 (15.9)	103 (18.5)

	Study J12301						Safety Pool
				Investigator Selected TKI			
Acute pancreatitis (including isolated pancreatic enzyme elevations)	**Imatinib N=100 n (%)**	**2G TKI N=100 n (%)**	**All Asciminib N=200 n (%)**	**Imatinib N=99 n (%)**	**2G TKI N=102 n (%)**	**All Comparators N=201 n (%)**	**All Asciminib N=556 n (%)**
AE outcome							
Recovered/resolved	20 (20.0)	8 (8.0)	28 (14.0)	16 (16.2)	17 (16.7)	33 (16.4)	111 (20.0)
Recovering/resolving	4 (4.0)	0	4 (2.0)	4 (4.0)	6 (5.9)	10 (5.0)	22 (4.0)
Not recovered/not resolved	5 (5.0)	2 (2.0)	7 (3.5)	5 (5.1)	5 (4.9)	10 (5.0)	28 (5.0)

A participant may be counted in several rows for action taken and outcome. Participants/outcome with no events in Study J12301 are omitted from this in-text table.
MedDRA version 27.1, CTCAE version 5.0. Case Retrieval Strategy version released 28-Nov-2024.
Source: 1L SCS Appendix 2-Table 2-14.1

Haemorrhage

Overall, 6.5% of participants in the asciminib treatment group had Hemorrhage AESI vs. 10.9% in IS-TKI treatment group, including 10.1% in imatinib and 11.8% in 2G TKI. All events were low grade (grade ≤ 2), except for one grade 3 in imatinib and three grade 3 events in 2G TKI. There was no permanent treatment discontinuation attributed to haemorrhage. Detailed information is provided in Table 70.

Table 70 Clinical impact of AESI Hemorrhage - Safety set

	Study J12301						Safety Pool
	Asciminib			Investigator Selected TKI			
Hemorrhage	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
At least one event	6 (6.0)	7 (7.0)	13 (6.5)	10 (10.1)	12 (11.8)	22 (10.9)	76 (13.7)
Contusion	2 (2.0)	2 (2.0)	4 (2.0)	0	3 (2.9)	3 (1.5)	18 (3.2)
Epistaxis	0	1 (1.0)	1 (0.5)	1 (1.0)	1 (1.0)	2 (1.0)	10 (1.8)
Haematoma	2 (2.0)	0	2 (1.0)	1 (1.0)	1 (1.0)	2 (1.0)	7 (1.3)
Haematuria	0	0	0	0	1 (1.0)	1 (0.5)	6 (1.1)
Heavy menstrual bleeding	0	2 (2.0)	2 (1.0)	1 (1.0)	2 (2.0)	3 (1.5)	6 (1.1)
Haematochezia	1 (1.0)	0	1 (0.5)	1 (1.0)	2 (2.0)	3 (1.5)	4 (0.7)
Mouth haemorrhage	0	1 (1.0)	1 (0.5)	0	0	0	4 (0.7)
Vaginal haemorrhage	2 (2.0)	0	2 (1.0)	0	0	0	4 (0.7)
Conjunctival haemorrhage	0	0	0	4 (4.0)	0	4 (2.0)	3 (0.5)
Bone contusion	0	0	0	0	1 (1.0)	1 (0.5)	2 (0.4)
Haemarthrosis	0	1 (1.0)	1 (0.5)	0	0	0	1 (0.2)
Haematospermia	0	1 (1.0)	1 (0.5)	0	0	0	1 (0.2)
Melaena	0	0	0	1 (1.0)	0	1 (0.5)	1 (0.2)
Purpura	0	0	0	1 (1.0)	0	1 (0.5)	1 (0.2)
Ecchymosis	0	0	0	1 (1.0)	0	1 (0.5)	0
Haemorrhage subcutaneous	0	0	0	0	1 (1.0)	1 (0.5)	0
Haemorrhagic diathesis	0	0	0	0	1 (1.0)	1 (0.5)	0
Intestinal haemorrhage	0	0	0	0	1 (1.0)	1 (0.5)	0

	Study J12301						Safety Pool
	Asciminib			Investigator Selected TKI			
Hemorrhage	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
Maximum grade							
Grade 3 AEs	0	0	0	1 (1.0)	3 (2.9)	4 (2.0)	9 (1.6)
Treatment-related AEs	1 (1.0)	0	1 (0.5)	4 (4.0)	3 (2.9)	7 (3.5)	17 (3.1)
SAEs	0	1 (1.0)	1 (0.5)	1 (1.0)	1 (1.0)	2 (1.0)	8 (1.4)
Action taken							
Dose adjusted	0	0	0	0	1 (1.0)	1 (0.5)	0
Drug interrupted	0	0	0	1 (1.0)	1 (1.0)	2 (1.0)	7 (1.3)
Dose not changed/NA/Unknown	6 (6.0)	7 (7.0)	13 (6.5)	9 (9.1)	10 (9.8)	19 (9.5)	71 (12.8)
AE outcome							
Recovered/resolved	5 (5.0)	7 (7.0)	12 (6.0)	8 (8.1)	10 (9.8)	18 (9.0)	71 (12.8)
Not recovered/not resolved	1 (1.0)	0	1 (0.5)	3 (3.0)	2 (2.0)	5 (2.5)	10 (1.8)

A participant may be counted in several rows for action taken and outcome. Participants/outcome with no events in Study J12301 are omitted from this in-text table.
MedDRA version 27.1, CTCAE version 5.0. Case Retrieval Strategy version released 28-Nov-2024.
Source: 1L SCS Appendix 2-Table 2-14.1

Ischemic heart and CNS conditions related AESI

Overall incidence of ischemic heart and CNS conditions related AESI were comparable across all treatment groups: 7.5% in the asciminib group vs. 9.0% in IS-TKI group, including 7.1% in imatinib and 10.8% in 2G TKI, the effect was mostly driven by reported blood CK elevations (5.5% in asciminib group, 7.5% in IS-TKI group, 6.1% in imatinib and 8.8% in 2G TKI) with Grade 3 or 4 and SAEs were rare events across all treatment groups (reported in ≤ 3%).

Table 71 Clinical impact of AESI Ischemic heart and CNS conditions - Safety set

	Study J12301						Safety Pool
	Asciminib			Investigator Selected TKI			
Ischemic heart and CNS conditions	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
At least one event	7 (7.0)	8 (8.0)	15 (7.5)	7 (7.1)	11 (10.8)	18 (9.0)	58 (10.4)
Blood creatine phosphokinase increased	5 (5.0)	6 (6.0)	11 (5.5)	6 (6.1)	9 (8.8)	15 (7.5)	24 (4.3)
Angina pectoris	1 (1.0)	0	1 (0.5)	0	0	0	10 (1.8)
Cerebrovascular accident	1 (1.0)	0	1 (0.5)	0	0	0	6 (1.1)
Myocardial infarction	0	0	0	0	1 (1.0)	1 (0.5)	4 (0.7)
Myocardial ischaemia	0	0	0	0	1 (1.0)	1 (0.5)	4 (0.7)
Arteriosclerosis coronary artery	0	2 (2.0)	2 (1.0)	0	0	0	2 (0.4)
Cerebral infarction	0	0	0	0	1 (1.0)	1 (0.5)	2 (0.4)
Electrocardiogram T wave abnormal	0	1 (1.0)	1 (0.5)	0	0	0	2 (0.4)
Electrocardiogram ST segment abnormal	0	1 (1.0)	1 (0.5)	1 (1.0)	0	1 (0.5)	1 (0.2)
Maximum grade							
Grade 3 AEs	0	3 (3.0)	3 (1.5)	0	2 (2.0)	2 (1.0)	16 (2.9)
Grade 4 AEs	2 (2.0)	1 (1.0)	3 (1.5)	0	2 (2.0)	2 (1.0)	8 (1.4)
Treatment-related AEs	2 (2.0)	4 (4.0)	6 (3.0)	4 (4.0)	7 (6.9)	11 (5.5)	20 (3.6)
SAEs	2 (2.0)	0	2 (1.0)	0	3 (2.9)	3 (1.5)	21 (3.8)
Action taken							
Drug withdrawn	1 (1.0)	0	1 (0.5)	0	0	0	3 (0.5)
Drug interrupted	0	2 (2.0)	2 (1.0)	0	3 (2.9)	3 (1.5)	14 (2.5)
Dose not changed/NA/Unknown	6 (6.0)	7 (7.0)	13 (6.5)	7 (7.1)	9 (8.8)	16 (8.0)	50 (9.0)

	Study J12301						Safety Pool
	Asciminib			Investigator Selected TKI			
Ischemic heart and CNS conditions	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
AE outcome							
Recovered/resolved	6 (6.0)	6 (6.0)	12 (6.0)	4 (4.0)	11 (10.8)	15 (7.5)	41 (7.4)
Recovering/resolving	1 (1.0)	1 (1.0)	2 (1.0)	1 (1.0)	0	1 (0.5)	7 (1.3)
Not recovered/not resolved	0	3 (3.0)	3 (1.5)	4 (4.0)	2 (2.0)	6 (3.0)	19 (3.4)

A participant may be counted in several rows for action taken and outcome. Participants/outcome with no events in Study J12301 are omitted from this in-text table.
MedDRA version 27.1, CTCAE version 5.0. Case Retrieval Strategy version released 28-Nov-2024.
Source: 1L SCS Appendix 2-Table 2-14.1

Arterial occlusive events (AOE)

AOE were sporadic events in all treatment groups (2.0% in asciminib compared to 1.5% in IS TKI, including none in imatinib and 2.9% in 2G TKI). In the asciminib group, one patient had a grade 4 cerebrovascular accident, however, resolving the next day without residues on the brain CT scan. Two more patients had grade 1 coronary artery disease and grade 1 angina pectoris.

Table 72 Clinical impact of AESI Arterial-occlusive events - Safety set

	Study J12301						Safety Pool
		Asciminib		Investigator Selected TKI			
AOEs	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
Participants with at least one event	2 (2.0)	2 (2.0)	4 (2.0)	0	3 (2.9)	3 (1.5)	39 (7.0)
Angina pectoris	1 (1.0)	0	1 (0.5)	0	0	0	10 (1.8)
Cerebrovascular accident	1 (1.0)	0	1 (0.5)	0	0	0	6 (1.1)
Peripheral arterial occlusive disease	0	1 (1.0)	1 (0.5)	0	0	0	5 (0.9)
Myocardial infarction	0	0	0	0	1 (1.0)	1 (0.5)	4 (0.7)
Myocardial ischaemia	0	0	0	0	1 (1.0)	1 (0.5)	4 (0.7)
Arteriosclerosis coronary artery	0	2 (2.0)	2 (1.0)	0	0	0	2 (0.4)
Cerebral infarction	0	0	0	0	1 (1.0)	1 (0.5)	2 (0.4)
Vertebral artery arteriosclerosis	0	0	0	0	1 (1.0)	1 (0.5)	0
Maximum grade							
Grade 4 AEs	1 (1.0)	0	1 (0.5)	0	1 (1.0)	1 (0.5)	3 (0.5)
Treatment-related AEs	1 (1.0)	2 (2.0)	3 (1.5)	0	2 (2.0)	2 (1.0)	14 (2.5)
SAEs	1 (1.0)	0	1 (0.5)	0	2 (2.0)	2 (1.0)	20 (3.6)
Action taken							
Drug withdrawn	1 (1.0)	0	1 (0.5)	0	0	0	3 (0.5)
Drug interrupted	0	0	0	0	2 (2.0)	2 (1.0)	10 (1.8)
Dose not changed/NA/Unknown	1 (1.0)	2 (2.0)	3 (1.5)	0	2 (2.0)	2 (1.0)	32 (5.8)

	Study J12301						Safety Pool
		Asciminib		Investigator Selected TKI			
AOEs	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
AE outcome							
Recovered/resolved	1 (1.0)	0	1 (0.5)	0	2 (2.0)	2 (1.0)	20 (3.6)
Recovering/resolving	1 (1.0)	0	1 (0.5)	0	0	0	7 (1.3)
Not recovered/not resolved	0	2 (2.0)	2 (1.0)	0	2 (2.0)	2 (1.0)	19 (3.4)

A participant may be counted in several rows for action taken and outcome. Participants/outcome with no events in Study J12301 are omitted from this in-text table.
MedDRA version 27.1, CTCAE version 5.0. Case Retrieval Strategy version released 28-Nov-2024.
Source: 1L SCS Appendix 2-Table 2-14.1

QTc prolongation

QTcF increase from baseline >30 to ≤ 60 ms occurred in a lower proportion of participants treated with asciminib (2.5%) compared to IS-TKIs (4.5%), as well as imatinib (4.0%) and 2G TKIs (4.9%). QTc prolongation related AESI were low across all treatment groups: asciminib treatment group (2.0%), IS-TKI treatment group (2.5%), imatinib (0%) and 2G TKI (4.9%). From the four patients in the asciminib group with an AESI, only one had a nonserious grad 3 prolongation by Δ 36 ms and a subsequent dose reduction to 40 mg QD.

Edema and fluid retention

AESI related to Edema and fluid retention occurred markedly less frequently with asciminib as compared to IS-TKIs (4.5% vs. 14.9%) including as compared to imatinib (4.5% vs. 15.2%) and to 2G TKI (4.5% vs. 14.7%), leading to no dose interruptions in the asciminib and imatinib group, but to 4.9% discontinuation, 1% dose reduction and 5.9% dose interruption of study treatment.

Table 73 Clinical impact of AESI QTc prolongation - Safety set

	Study J12301						Safety Pool
		Asciminib		Investigator Selected TKI			
QTc prolongation	Imatinib N=100 n (%)	2G TKI N=100 n (%)	All Asciminib N=200 n (%)	Imatinib N=99 n (%)	2G TKI N=102 n (%)	All Comparators N=201 n (%)	All Asciminib N=556 n (%)
At least one event	1 (1.0)	3 (3.0)	4 (2.0)	0	5 (4.9)	5 (2.5)	23 (4.1)
Syncope	0	3 (3.0)	3 (1.5)	0	2 (2.0)	2 (1.0)	11 (2.0)
Electrocardiogram QT prolonged	1 (1.0)	0	1 (0.5)	0	2 (2.0)	2 (1.0)	5 (0.9)
Long QT syndrome	0	0	0	0	1 (1.0)	1 (0.5)	0
Maximum grade							
Grade 3 AEs	1 (1.0)	2 (2.0)	3 (1.5)	0	1 (1.0)	1 (0.5)	10 (1.8)
Treatment-related AEs	1 (1.0)	0	1 (0.5)	0	2 (2.0)	2 (1.0)	3 (0.5)
SAEs	0	0	0	0	1 (1.0)	1 (0.5)	4 (0.7)
Action taken							
Drug withdrawn	0	0	0	0	1 (1.0)	1 (0.5)	1 (0.2)
Dose adjusted	1 (1.0)	0	1 (0.5)	0	0	0	1 (0.2)
Drug interrupted	1 (1.0)	0	1 (0.5)	0	0	0	3 (0.5)
Dose not changed/NA/Unknown	0	3 (3.0)	3 (1.5)	0	5 (4.9)	5 (2.5)	21 (3.8)
AE outcome							
Recovered/resolved	0	3 (3.0)	3 (1.5)	0	5 (4.9)	5 (2.5)	20 (3.6)
Recovering/resolving	1 (1.0)	0	1 (0.5)	0	0	0	2 (0.4)
Not recovered/not resolved	1 (1.0)	0	1 (0.5)	0	0	0	3 (0.5)

A participant may be counted in several rows for action taken and outcome. Participants/outcome with no events in Study J12301 are omitted from this in-text table.
MedDRA version 27.1, CTCAE version 5.0. Case Retrieval Strategy version released 28-Nov-2024.
Source: 1L SCS Appendix 2-Table 2-14.1

Cardiac failure

AEs pertaining to cardiac failures were reported not reported in the asciminib group in comparison to two participants 2G TKI group with grade 3 cardiac failure in a [18-86] year old participant on day 129 dasatinib treatment and a [18-86]-year-old participant with grade 3 pulmonary edema on day 161 under dasatinib treatment.

Phototoxicity

AEs regarding phototoxicity were rare and all events were low grade with 3 (1.5%) participants in asciminib treatment group and 2 (1.0%) participants in IS-TKI treatment group.

Hepatitis B virus infection reactivation

One participant was reported with an AE pertaining to Hepatitis B infection reactivation. This event was a grade 1 Hepatitis B reactivation (local laboratory test was positive for hepatitis B virus DNA) in imatinib-treated participant (IS-TKI treatment group). None was reported in an asciminib-treated participants.

Laboratory findings

An overview of post baseline abnormalities for haematology and for biochemistry is provided in the tables below.

Table 74 Haematology worst post-baseline abnormality based on CTC grades - Safety Set

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib N=100		2G TKI N=100		All Asciminib N=200		Imatinib N=99		2G TKI N=102		All 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 (%)
Hemoglobin (g/L), Blood decrease	69 (69.0)	2 (2.0)	78 (78.0)	5 (5.0)	147 (73.5)	7 (3.5)	85 (85.9)	5 (5.1)	93 (91.2)	9 (8.8)	178 (88.6)	14 (7.0)	384 (69.1)	26 (4.7)
Leukocytes (10^9/L), Blood decrease	58 (58.0)	4 (4.0)	59 (59.0)	6 (6.0)	117 (58.5)	10 (5.0)	72 (72.7)	15 (15.2)	69 (67.6)	12 (11.8)	141 (70.1)	27 (13.4)	294 (52.9)	46 (8.3)
Lymphocytes (10^9/L), Blood decrease	84 (84.0)	3 (3.0)	83 (83.0)	4 (4.0)	167 (83.5)	7 (3.5)	93 (93.9)	16 (16.2)	90 (88.2)	7 (6.9)	183 (91.0)	23 (11.4)	467 (84.0)	42 (7.6)
Neutrophils (10^9/L), Blood decrease	43 (43.0)	11 (11.0)	55 (55.0)	14 (14.0)	98 (49.0)	25 (12.5)	60 (60.6)	21 (21.2)	70 (68.6)	20 (19.6)	130 (64.7)	41 (20.4)	268 (48.2)	98 (17.6)
Platelets (10^9/L), Blood decrease	46 (46.0)	11 (11.0)	53 (53.0)	15 (15.0)	99 (49.5)	26 (13.0)	47 (47.5)	7 (7.1)	68 (66.7)	15 (14.7)	115 (57.2)	22 (10.9)	295 (53.1)	94 (16.9)
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)

Grades based on CTCAE version 5.0.
Source: 1L SCS Appendix 2-Table 3.3-3

Table 75 Biochemistry worst post-baseline abnormality based on CTC grades - Safety set

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib N=100		2G TKI N=100		All Asciminib N=200		Imatinib N=99		2G TKI N=102		All 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 (%)
Cholesterol (mmol/L), Serum - increase	63 (63.0)	0	52 (52.0)	0	115 (57.5)	0	34 (34.3)	0	69 (67.6)	0	103 (51.2)	0	230 (41.4)	1 (0.2)
Triglycerides (mmol/L), Plasma or Serum - increase	60 (60.0)	2 (2.0)	60 (60.0)	2 (2.0)	120 (60.0)	4 (2.0)	53 (53.5)	1 (1.0)	64 (62.7)	2 (2.0)	117 (58.2)	3 (1.5)	380 (68.3)	30 (5.4)
Alanine Aminotransferase (U/L), Serum - increase	40 (40.0)	4 (4.0)	40 (40.0)	1 (1.0)	80 (40.0)	5 (2.5)	32 (32.3)	3 (3.0)	67 (65.7)	8 (7.8)	99 (49.3)	11 (5.5)	254 (45.7)	15 (2.7)
Alkaline Phosphatase (U/L), Serum - increase	40 (40.0)	0	32 (32.0)	1 (1.0)	72 (36.0)	1 (0.5)	48 (48.5)	0	42 (41.2)	0	90 (44.8)	0	156 (28.1)	1 (0.2)
Aspartate Aminotransferase (U/L), Serum - increase	26 (26.0)	2 (2.0)	22 (22.0)	1 (1.0)	48 (24.0)	3 (1.5)	28 (28.3)	1 (1.0)	51 (50.0)	2 (2.0)	79 (39.3)	3 (1.5)	191 (34.4)	11 (2.0)
Creatinine (µmol/L), Plasma or Serum - increase	26 (26.0)	0	20 (20.0)	0	46 (23.0)	0	44 (44.4)	0	30 (29.4)	0	74 (36.8)	0	148 (26.6)	0
Lipase (U/L), Serum - increase	48 (48.0)	13 (13.0)	34 (34.0)	10 (10.0)	82 (41.0)	23 (11.5)	54 (54.5)	9 (9.1)	52 (51.0)	16 (15.7)	106 (52.7)	25 (12.4)	213 (38.3)	75 (13.5)
Amylase (U/L), Serum - increase	32 (32.0)	2 (2.0)	18 (18.0)	0	50 (25.0)	2 (1.0)	25 (25.3)	2 (2.0)	38 (37.3)	5 (4.9)	63 (31.3)	7 (3.5)	146 (26.3)	20 (3.6)
Bilirubin (µmol/L), Serum - increase	12 (12.0)	1 (1.0)	22 (22.0)	0	34 (17.0)	1 (0.5)	8 (8.1)	1 (1.0)	31 (30.4)	0	39 (19.4)	1 (0.5)	101 (18.2)	2 (0.4)
Albumin (g/L), Serum - decrease	2 (2.0)	0	3 (3.0)	0	5 (2.5)	0	4 (4.0)	0	3 (2.9)	0	7 (3.5)	0	58 (10.4)	3 (0.5)
Calcium Corrected (mmol/L), Plasma or Serum - decrease	50 (50.0)	1 (1.0)	54 (54.0)	0	104 (52.0)	1 (0.5)	77 (77.8)	1 (1.0)	84 (82.4)	3 (2.9)	161 (80.1)	4 (2.0)	228 (41.0)	4 (0.7)

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib N=100		2G TKI N=100		All Asciminib N=200		Imatinib N=99		2G TKI N=102		All 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 (%)
Calcium Corrected (mmol/L), Plasma or Serum - increase	0	0	1 (1.0)	0	1 (0.5)	0	0	0	1 (1.0)	0	1 (0.5)	0	22 (4.0)	1 (0.2)
Magnesium (mmol/L), Serum - decrease	5 (5.0)	0	1 (1.0)	0	6 (3.0)	0	5 (5.1)	0	1 (1.0)	0	6 (3.0)	0	62 (11.2)	2 (0.4)
Magnesium (mmol/L), Serum - increase	2 (2.0)	0	2 (2.0)	1 (1.0)	4 (2.0)	1 (0.5)	1 (1.0)	0	4 (3.9)	0	5 (2.5)	0	81 (14.6)	6 (1.1)
Potassium (mmol/L), Plasma or Serum - decrease	2 (2.0)	0	0	0	2 (1.0)	0	9 (9.1)	3 (3.0)	5 (4.9)	0	14 (7.0)	3 (1.5)	46 (8.3)	5 (0.9)
Potassium (mmol/L), Plasma or Serum - increase	16 (16.0)	1 (1.0)	9 (9.0)	0	25 (12.5)	1 (0.5)	4 (4.0)	0	8 (7.8)	0	12 (6.0)	0	128 (23.0)	7 (1.3)
Sodium (mmol/L), Plasma or Serum - decrease	9 (9.0)	0	5 (5.0)	0	14 (7.0)	0	10 (10.1)	0	14 (13.7)	0	24 (11.9)	0	75 (13.5)	3 (0.5)
Sodium (mmol/L), Plasma or Serum - increase	0	0	0	0	0	0	2 (2.0)	0	1 (1.0)	0	3 (1.5)	0	39 (7.0)	1 (0.2)

Grades based on CTCAE version 5.0.
Source: 1L SCS Appendix 2-Table 3.4-3

Safety by age category

The number of participants in the asciminib and IS-TKI treatment groups in each age category were: 154 and 153 participants 18 to < 65 year; 46 and 48 participants ≥ 65 year; 10 and 14 participants ≥ 75 year. An overview for patients treated with asciminib according to age group irrespective of stratum is provided Table *76*.

Table 76 Overview of adverse events in asciminib-treated participants by age groups in study J12301

Asciminib (N)	Age subgroup					
	18 – <65 yrs N (%)		≥65 – 74 yrs N (%)		≥75 yrs N (%)	
J12301 (200)	154		36		10	
Grades	All	≥G3	All	≥G3	All	≥G3
AEs	146 (94.8)	62 (40.3)	36 (100)	23 (63.9)	9 (90.0)	4 (40.0)
SAEs	16 (10.4)	11 (7.1)	10 (27.8)	9 (25.0)	3 (30.0)	3 (30.0)
Fatal SAEs	0	0	0	0	0	0
AEs leading to discontinuation	5 (3.2)	3 (1.9)	3 (8.3)	3 (8.3)	2 (20.0)	0
AEs leading to dose adjustment interruption	48 (31.2)	40 (26.0)	15 (41.7)	13 (36.1)	3 (30.0)	2 (20.0)
AEs requiring additional therapy	128 (83.1)	33 (21.4)	31 (86.1)	15 (41.7)	9 (90.0)	3 (30.0)

Most frequent PTs by age group were presented in *Table 77*, *Table 78*, *Table 79*.

Table 77 Most frequent PTs by age group - Safety set subgroup 18-64 years of age (reported in at least 15% of patients in the safety pool)

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib N=100		2G TKI N=100		All Asciminib N=200		Imatinib N=99		2G TKI N=102		All Comparators N=201		All Asciminib 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
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Subgroup: 18 - < 65 year (reported in at least 15.0% of participants in the Safety pool)													
	n=68		n=86		n=154		n=68		n=8		n=153		n=426	
At least one event	**66 (97.1)**	**29 (42.6)**	**80 (93.0)**	**33 (38.4)**	**146 (94.8)**	**62 (40.3)**	**65 (95.6)**	**32 (47.1)**	**85 (100)**	**48 (56.5)**	**150 (98.0)**	**80 (52.3)**	**405 (95.1)**	**233 (54.7)**
Headache	10 (14.7)	1 (1.5)	13 (15.1)	0	23 (14.9)	1 (0.6)	8 (11.8)	0	21 (24.7)	0	29 (19.0)	0	103 (24.2)	8 (1.9)
Fatigue	11 (16.2)	0	14 (16.3)	1 (1.2)	25 (16.2)	1 (0.6)	10 (14.7)	1 (1.5)	16 (18.8)	0	26 (17.0)	1 (0.7)	92 (21.6)	4 (0.9)
Diarrhoea	8 (11.8)	0	20 (23.3)	0	28 (18.2)	0	17 (25.0)	0	20 (23.5)	1 (1.2)	37 (24.2)	1 (0.7)	88 (20.7)	2 (0.5)
Arthralgia	10 (14.7)	1 (1.5)	9 (10.5)	1 (1.2)	19 (12.3)	2 (1.3)	8 (11.8)	0	7 (8.2)	0	15 (9.8)	0	85 (20.0)	5 (1.2)
COVID-19	9 (13.2)	0	24 (27.9)	0	33 (21.4)	0	17 (25.0)	0	19 (22.4)	0	36 (23.5)	0	84 (19.7)	3 (0.7)
Rash	9 (13.2)	0	17 (19.8)	0	26 (16.9)	0	6 (8.8)	1 (1.5)	20 (23.5)	1 (1.2)	26 (17.0)	2 (1.3)	78 (18.3)	0
Thrombocytopenia	10 (14.7)	6 (8.8)	10 (11.6)	5 (5.8)	20 (13.0)	11 (7.1)	10 (14.7)	3 (4.4)	15 (17.6)	7 (8.2)	25 (16.3)	10 (6.5)	78 (18.3)	51 (12.0)
Nausea	4 (5.9)	0	10 (11.6)	0	14 (9.1)	0	14 (20.6)	0	16 (18.8)	0	30 (19.6)	0	71 (16.7)	2 (0.5)

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib		2G TKI		All Asciminib		Imatinib		2G TKI		All Comparators		All Asciminib	
Lipase increased	12 (17.6)	5 (7.4)	7 (8.1)	0	19 (12.3)	5 (3.2)	9 (13.2)	1 (1.5)	11 (12.9)	4 (4.7)	20 (13.1)	5 (3.3)	68 (16.0)	37 (8.7)
Myalgia	12 (17.6)	0	13 (15.1)	1 (1.2)	25 (16.2)	1 (0.6)	18 (26.5)	0	15 (17.6)	0	33 (21.6)	0	65 (15.3)	5 (1.2)
Hypertension	9 (13.2)	4 (5.9)	5 (5.8)	2 (2.3)	14 (9.1)	6 (3.9)	3 (4.4)	0	4 (4.7)	4 (4.7)	7 (4.6)	4 (2.6)	64 (15.0)	29 (6.8)

Source: SOS, CML 1L, Table 5-1

Table 78 Most frequent PTs by age group - Safety set subgroup >=65 years of age

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib N=100		2G TKI N=100		All Asciminib N=200		Imatinib N=99		2G TKI N=102		All Comparators N=201		All Asciminib 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
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Subgroup: ≥ 65 year (reported in at least 15.0% of participants in the Safety pool)													
	n=32		n=14		n=46		n=31		n=17		n=48		n=130	
At least one event	**31 (96.9)**	**19 (59.4)**	**14 (100)**	**8 (57.1)**	**45 (97.8)**	**27 (58.7)**	**30 (96.8)**	**17 (54.8)**	**17 (100)**	**13 (76.5)**	**47 (97.9)**	**30 (62.5)**	**128 (98.5)**	**91 (70.0)**
Thrombocytopenia	5 (15.6)	3 (9.4)	2 (14.3)	2 (14.3)	7 (15.2)	5 (10.9)	4 (12.9)	1 (3.2)	2 (11.8)	0	6 (12.5)	1 (2.1)	31 (23.8)	19 (14.6)
Arthralgia	6 (18.8)	2 (6.3)	1 (7.1)	0	7 (15.2)	2 (4.3)	2 (6.5)	1 (3.2)	2 (11.8)	0	4 (8.3)	1 (2.1)	30 (23.1)	4 (3.1)
Hypertension	5 (15.6)	4 (12.5)	2 (14.3)	1 (7.1)	7 (15.2)	5 (10.9)	2 (6.5)	2 (6.5)	1 (5.9)	1 (5.9)	3 (6.3)	3 (6.3)	30 (23.1)	22 (16.9)
Lipase increased	8 (25.0)	1 (3.1)	0	0	8 (17.4)	1 (2.2)	6 (19.4)	1 (3.2)	4 (23.5)	1 (5.9)	10 (20.8)	2 (4.2)	28 (21.5)	11 (8.5)
Diarrhoea	6 (18.8)	0	1 (7.1)	0	7 (15.2)	0	11 (35.5)	0	8 (47.1)	1 (5.9)	19 (39.6)	1 (2.1)	27 (20.8)	0
Fatigue	4 (12.5)	0	1 (7.1)	0	5 (10.9)	0	5 (16.1)	0	4 (23.5)	0	9 (18.8)	0	24 (18.5)	2 (1.5)
Headache	8 (25.0)	0	2 (14.3)	0	10 (21.7)	0	1 (3.2)	0	3 (17.6)	0	4 (8.3)	0	24 (18.5)	0
Pain in extremity	3 (9.4)	1 (3.1)	1 (7.1)	0	4 (8.7)	1 (2.2)	0	0	0	0	0	0	23 (17.7)	2 (1.5)

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib		2G TKI		All Asciminib		Imatinib		2G TKI		All Comparators		All Asciminib	
Anaemia	4 (12.5)	0	1 (7.1)	1 (7.1)	5 (10.9)	1 (2.2)	9 (29.0)	0	7 (41.2)	2 (11.8)	16 (33.3)	2 (4.2)	22 (16.9)	9 (6.9)
Nausea	4 (12.5)	0	1 (7.1)	0	5 (10.9)	0	7 (22.6)	0	3 (17.6)	0	10 (20.8)	0	22 (16.9)	1 (0.8)
Constipation	5 (15.6)	0	4 (28.6)	0	9 (19.6)	0	0	0	5 (29.4)	1 (5.9)	5 (10.4)	1 (2.1)	20 (15.4)	0
Neutropenia	3 (9.4)	1 (3.1)	1 (7.1)	1 (7.1)	4 (8.7)	2 (4.3)	8 (25.8)	6 (19.4)	2 (11.8)	1 (5.9)	10 (20.8)	7 (14.6)	20 (15.4)	14 (10.8)

Table 79 Most frequent PTs by age group - Safety set subgroup >=75 years of age

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib N=100		2G TKI N=100		All Asciminib N=200		Imatinib N=99		2G TKI N=102		All Comparators N=201		All Asciminib N=556	
Preferred Term	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Subgroup: ≥ 75 year (reported in at least 15.0% of participants in the Safety pool)														
	n=8		n=2		n=10		n=9		n=5		n=14		n=31	
At least one event	**7 (87.5)**	**3 (37.5)**	**2 (100)**	**1 (50.0)**	**9 (90.0)**	**4 (40.0)**	**9 (100)**	**5 (55.6)**	**5 (100)**	**5 (100)**	**14 (100)**	**10 (71.4)**	**30 (96.8)**	**21 (67.7)**
Arthralgia	2 (25.0)	0	1 (50.0)	0	3 (30.0)	0	1 (11.1)	1 (11.1)	1 (20.0)	0	2 (14.3)	1 (7.1)	13 (41.9)	1 (3.2)
Nausea	2 (25.0)	0	1 (50.0)	0	3 (30.0)	0	4 (44.4)	0	0	0	4 (28.6)	0	11 (35.5)	0
Hypertension	2 (25.0)	2 (25.0)	0	0	2 (20.0)	2 (20.0)	0	0	1 (20.0)	1 (20.0)	1 (7.1)	1 (7.1)	9 (29.0)	8 (25.8)
Pain in extremity	2 (25.0)	1 (12.5)	1 (50.0)	0	3 (30.0)	1 (10.0)	0	0	0	0	0	0	9 (29.0)	1 (3.2)
Constipation	2 (25.0)	0	1 (50.0)	0	3 (30.0)	0	0	0	3 (60.0)	0	3 (21.4)	0	8 (25.8)	0
Diarrhoea	2 (25.0)	0	0	0	2 (20.0)	0	5 (55.6)	0	4 (80.0)	0	9 (64.3)	0	8 (25.8)	0
Fatigue	1 (12.5)	0	0	0	1 (10.0)	0	2 (22.2)	0	3 (60.0)	0	5 (35.7)	0	8 (25.8)	1 (3.2)
Headache	3 (37.5)	0	0	0	3 (30.0)	0	0	0	0	0	0	0	8 (25.8)	0
Pruritus	2 (25.0)	0	1 (50.0)	0	3 (30.0)	0	0	0	0	0	0	0	8 (25.8)	0
Back pain	1 (12.5)	0	0	0	1 (10.0)	0	2 (22.2)	0	1 (20.0)	0	3 (21.4)	0	6 (19.4)	0
COVID-19	2 (25.0)	0	1 (50.0)	0	3 (30.0)	0	0	0	1 (20.0)	0	1 (7.1)	0	6 (19.4)	0
Lipase increased	0	0	0	0	0	0	2 (22.2)	1 (11.1)	1 (20.0)	0	3 (21.4)	1 (7.1)	6 (19.4)	2 (6.5)
Platelet count decreased	1 (12.5)	0	1 (50.0)	0	2 (20.0)	0	1 (11.1)	0	1 (20.0)	0	2 (14.3)	0	6 (19.4)	3 (9.7)
Thrombocytopenia	0	0	0	0	0	0	1 (11.1)	0	1 (20.0)	0	2 (14.3)	0	6 (19.4)	5 (16.1)
Vomiting	1 (12.5)	0	0	0	1 (10.0)	0	3 (33.3)	0	1 (20.0)	0	4 (28.6)	0	6 (19.4)	1 (3.2)
Abdominal pain	0	0	1 (50.0)	1 (50.0)	1 (10.0)	1 (10.0)	0	0	0	0	0	0	5 (16.1)	2 (6.5)
Amylase increased	0	0	0	0	0	0	1 (11.1)	0	1 (20.0)	0	2 (14.3)	0	5 (16.1)	0
Anaemia	1 (12.5)	0	1 (50.0)	1 (50.0)	2 (20.0)	1 (10.0)	4 (44.4)	0	4 (80.0)	1 (20.0)	8 (57.1)	1 (7.1)	5 (16.1)	3 (9.7)
Insomnia	1 (12.5)	0	1 (50.0)	0	2 (20.0)	0	0	0	0	0	0	0	5 (16.1)	0
Myalgia	2 (25.0)	0	2 (100)	0	4 (40.0)	0	0	0	1 (20.0)	0	1 (7.1)	0	5 (16.1)	0

A participant with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 27.1, CTCAE version 5.0.
Source: 1L SCS Appendix 2-Table 6-3.1

The secondary endpoint of TTDAE was numerically in favour of asciminib in different age groups.

Table 80 Cause specific hazard ratios of TTDAE by age subgroups (Safety Set)

Age group	All asciminib m/N (%)	All controls m/N (%)	Hazard ratio (95% CI) *	Imatinib m/N (%)	Hazard ratio (95% CI) *	2G TKI m/N (%)	Hazard ratio (95% CI) *
All	12/200 (6.0)	26/201 (12.9)	0.419 (0.216, 0.814)	13/99 (13.1)	0.381 (0.178, 0.818)	13/102 (12.7)	0.463 (0.215, 0.997)
(18, 65]	7/154 (4.5)	16/153 (10.5)	0.400 (0.170, 0.944)	8/68 (11.8)	0.356 (0.134, 0.940)	8/85 (9.4)	0.468 (0.174, 1.261)
(65, 75]	3/36 (8.3)	4/34 (11.8)	0.664 (0.150, 2.937)	2/22 (9.1)	0.824 (0.138, 4.928)	2/12 (16.7)	0.484 (0.084, 2.791)
75 or older	2/10 (20.0)	6/14 (42.9)	0.136 (0.022, 0.852)	3/9 (33.3)	0.189 (0.024, 1.466)	3/5 (60.0)	0.076 (0.011, 0.516)

m: number of participants experienced TTDAE in each subgroup.
N: number of participants in each subgroup
* Hazard ratios are "All asciminib" vs "All controls", "Imatinib", and "2G TKI
Sources: Week 96 CSR Tables 14.3.1-30.2.1, 14.3.1-30.2.2, 14.3.1-30.2.3, Appendix Tables 14.3.1-30.2.1a, 14.3.1-30.2.2a, 14.3.1-30.2.3a

Safety related to drug-drug interactions and other interactions

Asciminib is a substrate of CYP3A4, UGT2B7 and UGT2B17, contributing with 36.0%, 13.3% and 7.8% to its clearance, respectively. It is estimated that the efflux transporter BCRP contributes to total systemic clearance by 31.1%. New DDI information from Study A2111 and Study A2110 has been provided as part of an ongoing procedure to update the prescribing information. Study A2111 demonstrated a small, but not clinically relevant increase in exposure of atorvastatin when co-administered with asciminib and no changes in CP-1 concentrations in coadministration with asciminib. Study A2111 also provided evidence that OATP1B is not inhibited by asciminib at 80 mg once daily dose. In addition, Study A2110 demonstrated no change in CP-1 concentrations following a single dose of 200 mg asciminib, providing further evidence that there is no clinically relevant interaction between asciminib and OATP1B substrates at all recommended doses (80 mg total daily dose and 200 mg twice daily).

Discontinuation, interruption and dose reduction due to adverse events

The cumulative incidences of AEs leading to treatment discontinuation were always lower at each time point (at Week 8, 24, 48, 96) in the asciminib treatment group compared to the IS- TKI treatment group, including compared to imatinib and 2G TKI (*Table 81*). The overall incidence of treatment-related AEs leading to dose interruption were lower in the asciminib group (22.5%) compared to the IS-TKI group (37.8%), including compared to imatinib (31.3%) and to 2G TKI (32.4%). The overall incidence of treatment-related AEs leading to dose reduction all grades was lower in the asciminib group (6.0%) compared to the IS-TKI group (20.4%), including compared to imatinib (16.2%) and to 2G TKI (24.5%).

Table 81 Cumulative incidences of AEs leading to study drug discontinuation - Safety set

	Study J12301												Safety Pool	
	Asciminib						Investigator Selected TKI							
	Imatinib		2G TKI		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 (%) cum. IP	Grade ≥ 3 n (%) cum. IP	All grades n (%) cum. IP	Grade ≥ 3 n (%) cum. IP	All grades n (%) cum. IP	Grade ≥ 3 n (%) cum. IP	All grades n (%) cum. IP	Grade ≥ 3 n (%) cum. IF	All grades n (%) cum. IP	Grade ≥ 3 n (%) cum. IP	All grades n (%) cum. IP	Grade ≥ 3 n (%) cum. IP	All grades n (%) cum. IP	Grade ≥ 3 n (%) cum. IP
At least one event at:														
Week 8 (Day 56)	3 (3.0)	2 (2.0)	0	0	3 (1.5)	2 (1.0)	4 (4.0)	2 (2.0)	3 (2.9)	1 (1.0)	7 (3.5)	3 (1.5)	16 (2.9)	14 (2.5)
Week 24 (Day 168)	5 (5.0)	3 (3.0)	1 (1.0)	1 (1.0)	6 (3.0)	4 (2.0)	6 (6.1)	3 (3.0)	4 (3.9)	2 (2.0)	10 (5.0)	5 (2.5)	27 (4.9)	23 (4.1)
Week 48 (Day 336)	5 (5.0)	3 (3.0)	2 (2.0)	2 (2.0)	7 (3.5)	5 (2.5)	12 (12.1)	6 (6.1)	5 (4.9)	3 (2.9)	17 (8.5)	9 (4.5)	30 (5.4)	25 (4.5)
Week 96 (Day 672)	6 (6.0)	3 (3.0)	3 (3.0)	3 (3.0)	9 (4.5)	6 (3.0)	13 (13.1)	7 (7.1)	13 (12.7)	5 (4.9)	26 (12.9)	12 (6.0)	36 (6.5)	29 (5.2)

Cum IP = cumulative incidence proportion up to Day x, considering competing risks (death, discontinuation due to any reason).
MedDRA version 27.1, CTCAE version 5.0.
Source: [1L SCS Appendix 2-Table 2.1-11]

Post marketing experience

The post-marketing experience with asciminib has been reviewed on an ongoing basis since the first registration in the United States on 29-Oct-2021. The most recent PSUR submitted to the EMA, covering the interval 29-Oct-2023 to 28-Apr-2024, presented post-marketing analyses representing an estimated cumulative post-marketing exposure of 7,601 PTY.

2.5.2. Extension of the indication to 2nd line CML-CP treatment

Listings were provided for the assessment of safety in 101 patients from ongoing study ABL001AUS08 2nd line safety cohort (n=101 patients). The median duration of exposure to study treatment was 26.1 weeks, with 58 patients having an exposure of more than 24 weeks, data cut-off was 15 November 2024.

Adverse events

An overview of adverse events is provided in *Table 82*. The most common adverse events reported in participants in the 2L cohort were headache (22.8%), nausea (20.8%), cough (15.8%), diarrhoea (15.8%), fatigue (15.8%) and hypertension (15.8%). The most common Grade >= 3 adverse event was hypertension, reported in 8.9% participants.

Table 82 Overview of adverse events for 2L Cohort (Safety Set)

	2L Cohort (N=101) n (%)
Any AEs	98 (97.0%)
Treatment-related	75 (74.3%)
Grade ≥ 3 AEs	36 (35.6%)
Treatment-related	15 (14.9%)
Serious AEs	10 (9.9%)
Treatment-related	1 (1.0%)
AEs leading to discontinuation	7 (6.9%)
Treatment-related	7 (6.9%)
AEs leading to dose reduction/ interruption	36 (35.6%)

Numbers (n) represent counts of participants.
AEs/SAEs occurring during treatment or within 30 days of the last study medication are summarized.

Information about SAE is shown in *Table 83*. No on-treatment deaths occurred in the 2nd line cohort. Narratives were provided for the three patients with SAE were provided. All patients restarted asciminib treatment after recovering.

Table 83 Serious adverse events, by system organ class and preferred term for 2L Cohort (IA 4, Safety Set)

Primary system organ class **Preferred term**	**2L Cohort** **N=101** **All grades** **n (%)**	 **Grade >=3** **n (%)**
Number of subjects with at least one event	3 (3.0)	3 (3.0)
Cardiac disorders	1 (1.0)	1 (1.0)
Aortic valve disease	1 (1.0)	1 (1.0)
Gastrointestinal disorders	1 (1.0)	1 (1.0)
Nausea	1 (1.0)	1 (1.0)
Vomiting	1 (1.0)	1 (1.0)
General disorders and administration site conditions	2 (2.0)	2 (2.0)
Catheter site pain	1 (1.0)	1 (1.0)
Chest pain	1 (1.0)	1 (1.0)
Non-cardiac chest pain	1 (1.0)	1 (1.0)

Numbers (n) represent counts of subjects.
SAEs occurring during treatment or within 30 days of the last study medication are summarized.
The primary SOC will be presented alphabetically, and the preferred terms will be sorted within primary SOC in descending frequency.
MedDRA version 27.1, CTCAE version 5.0.

Source: 6-Month Efficacy Key Outputs for 2L Cohort study CABL001AUS08, table 6-2

Adverse events of special interest

The most common adverse events of special interest for the 2L cohort were gastrointestinal toxicity (51.5%), hypersensitivity (21.8%) and acute pancreatitis (including isolated pancreatic enzyme

elevations) (16.8%). The most common Grade >=3 adverse events of special interest were thrombocytopenia (6.9%) and leukopenia (5.9%). No arterial occlusive events (AOEs) were reported. Haemorrhage was reported in 7.95% (G3-5: 1%). GI toxicity is higher in the AUS08 2nd line cohort (51.5%; G3-G5: 3%) compared to the newly diagnosed population of J12301 (39.0%, G3-5 0.5%) and in 3rd or later line study A2301 (31.4%, G3-5: 1.9%).Myelosuppression was reported in 11.9% of patients, 43.5% in the 1st line 37.8 % in 3rd or later line study A2301 with limited comparability due to different exposure in the respective lines, with otherwise comparable safety profiles. No new safety signal was detected.

Table 84 Overview of adverse events of special interest for 2L Cohort (Safety Set)

	2L Cohort N=101	
	All grades n (%)	Grade >=3 n (%)
Gastrointestinal toxicity	52 (51.5)	3 (3.0)
Hypersensitivity	22 (21.8)	0
Acute pancreatitis (including isolated pancreatic enzyme elevations)	17 (16.8)	2 (2.0)

	2L Cohort N=101	
	All grades n (%)	Grade >=3 n (%)
Acute pancreatitis (clinical events)	0	0
Myelosuppression*	12 (11.9)	8 (7.9)
Myelosuppression (Thrombocytopenia)	8 (7.9)	7 (6.9)
Myelosuppression (Leukopenia)	7 (6.9)	6 (5.9)
Myelosuppression (Erythropenia)	6 (5.9)	1 (1.0)
Myelosuppression (cytopenias affecting more than one lineage)	1 (1.0)	1 (1.0)
Hepatotoxicity (including laboratory terms)	9 (8.9)	1 (1.0)
Hepatotoxicity (clinical events)	1 (1.0)	0
Hemorrhage	8 (7.9)	1 (1.0)
Edema and fluid retention	7 (6.9)	1 (1.0)
Phototoxicity	3 (3.0)	0
Ischemic heart and CNS conditions	1 (1.0)	0
Ischemic heart conditions	1 (1.0)	0
Ischemic CNS conditions	0	0
Arterial-occlusive events (AOE)	0	0
Cardiac failure	0	0
Hepatitis B virus infection reactivation	0	0
QTc prolongation	0	0
Reproductive toxicity	0	0

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
*Myelosuppression includes erythropenia, leukopenia, thrombocytopenia, cytopenias affecting more than one lineage.
MedDRA version 27.1, CTCAE version 5.0, Case Retrieval Strategy version released 2025-01-14.

2.5.3. New posology of 80 mg QD for the 3rd or later line

The safety data submitted for the new posology includes safety results from the primary analysis of Study CABL001A2302 (ASC4OPT, hereafter referred to as Study A2302), a Phase IIIb, multi-center, non-comparative, open-label, treatment optimization study of oral asciminib (40 mg BID or 80 mg QD) in patients with CML-CP previously treated with 2 or more TKIs, additionally to data from the pivotal phase III Study CABL001A2301 (hereafter referred to as Study A2301) (using asciminib at a dose of 40 mg b.i.d.), the supplemental phase I Study CABL001X2101 (hereafter referred to as Study X2101) (studying various BID and QD dose regimens of asciminib) and exposure-response modelling served as the basis for the original asciminib approval for Ph+ CML-CP in the third line and beyond (3L+).

Table 85 ***Overview of clinical safety study and source of data***

Key features	Study A2302
Controlled study	No
Phase	IIIb
Study design	Non-comparative, treatment optimization study
Population	Adult participants previously treated with 2 or more TKIs
Treatment duration	144 weeks
No. participants (total)	169[1,2] (participants without MMR at baseline)
No. on Treatment(s)	Asciminib 80 mg q.d. (20 or 40 mg tablets): 84 Asciminib 40 mg b.i.d. (20 or 40 mg tablets): 84
Relevant entry criteria	
Age	≥ 18 years
Disease severity	Participants with CML-CP warning or resistant / intolerant to ≥ 2 prior TKIs
Completed/Ongoing	Ongoing (study was initiated on 13-Oct-2021 and had a data cut-off date for the last participant visit for the Week 48 analysis on 12-Mar-2024)

[1]An exploratory group of participants intolerant to their most recent TKI and in MMR at baseline was also enrolled (N=30); results from this exploratory cohort are not in scope of this document.
[2]1 participant was randomized to the 40 mg b.i.d. group but was not treated.
Source: Study A2302 W48 CSR-Section 9 and Study A2302 W48 CSR-Section 10

The safety analysis set (SAF) was defined as all participants who received at least one dose of study treatment except the additional participants who were intolerant to the last TKI and were in MMR at baseline. The SAF was used for baseline disease characteristics, exposure, and all safety analyses.

Patient exposure

The median exposure to asciminib 40 mg BID and 80 mg QD were 67.3 and 68.6 weeks, respectively.

Table 86 Duration of exposure to study drug (SAF)

	Asciminib 40 mg b.i.d. N=84	Asciminib 80 mg q.d. N=84	All participants N=168
Duration of exposure (week)			
Mean (SD)	68.0 (30.93)	68.7 (27.38)	68.3 (29.12)
Median	67.3	68.6	67.8
Q1-Q3	51.7-92.4	53.1-90.4	52.2-91.5
Min-Max	2.6-116.1	1.3-118.7	1.3-118.7
Duration of exposure categories-n (%)			
Less than 24 weeks	10 (11.9)	8 (9.5)	18 (10.7)
At least 24 weeks	74 (88.1)	76 (90.5)	150 (89.3)
At least 48 weeks	70 (83.3)	73 (86.9)	143 (85.1)
At least 96 weeks	18 (21.4)	16 (19.0)	34 (20.2)
At least 144 weeks	0	0	0
Participant treatment time (year)	109.4	110.5	219.9

Participant treatment time is the sum of each participant's treatment exposure in year.
The study is ongoing.
Source: Study A2302 W48 CSR-Table 14.3-1.1

Patient disposition

Of the 169 participants, 84 participants were treated with asciminib 40 mg b.i.d., 84 participants were treated with 80 mg QD and 1 participant was randomised to the 40 mg BID group but was not treated. Information on patient disposition is provided.

Table 87 Patient disposition (FAS)

	Asciminib 40 mg b.i.d. N=85 n (%)	Asciminib 80 mg q.d. N=84 n (%)	All participants N=169 n (%)
Participants randomized			
Treated	84 (98.8)	84 (100)	168 (99.4)
Not treated	1 (1.2)	0	1 (0.6)
Reason for not being treated			
Participant Decision	1 (1.2)	0	1 (0.6)
Treatment ongoing *	68 (80.0)	68 (81.0)	136 (80.5)
Discontinued from treatment	16 (18.8)	16 (19.0)	32 (18.9)
< Week 24	10 (11.8)	7 (8.3)	17 (10.1)
≥ Week 24 and < Week 48	4 (4.7)	3 (3.6)	7 (4.1)
≥ Week 48 and < Week 96	2 (2.4)	6 (7.1)	8 (4.7)
Reason for discontinuation			
Adverse Event	6 (7.1)	4 (4.8)	10 (5.9)
Unsatisfactory Therapeutic Effect	4 (4.7)	3 (3.6)	7 (4.1)
Progressive Disease	1 (1.2)	5 (6.0)	6 (3.6)
Physician Decision	2 (2.4)	2 (2.4)	4 (2.4)
Failure To Meet Continuation Criteria	2 (2.4)	1 (1.2)	3 (1.8)
Participant Decision	1 (1.2)	0	1 (0.6)
Protocol Deviation	0	1 (1.2)	1 (0.6)
< Week 24			
Adverse Event	4 (4.7)	3 (3.6)	7 (4.1)
Failure To Meet Continuation Criteria	2 (2.4)	0	2 (1.2)
Unsatisfactory Therapeutic Effect	2 (2.4)	0	2 (1.2)
Physician Decision	1 (1.2)	0	1 (0.6)
Participant Decision	1 (1.2)	0	1 (0.6)

	Asciminib 40 mg b.i.d. N=85 n (%)	Asciminib 80 mg q.d. N=84 n (%)	All participants N=169 n (%)
Progressive Disease	0	3 (3.6)	3 (1.8)
Protocol Deviation	0	1 (1.2)	1 (0.6)
≥ Week 24 and < Week 48			
Adverse Event	2 (2.4)	1 (1.2)	3 (1.8)
Physician Decision	1 (1.2)	1 (1.2)	2 (1.2)
Progressive Disease	1 (1.2)	1 (1.2)	2 (1.2)
≥ Week 48 and < Week 96			
Unsatisfactory Therapeutic Effect	2 (2.4)	3 (3.6)	5 (3.0)
Failure To Meet Continuation Criteria	0	1 (1.2)	1 (0.6)
Physician Decision	0	1 (1.2)	1 (0.6)
Progressive Disease	0	1 (1.2)	1 (0.6)
Post-Treatment safety follow-up for participant who Discontinued			
Did not enter post-treatment safety follow-up	1 (1.2)	0	1 (0.6)
Completed post-treatment safety follow-up	9 (10.6)	11 (13.1)	20 (11.8)
Entered post-treatment safety follow-up, discontinued	6 (7.1)	5 (6.0)	11 (6.5)
Reason for Discontinuation			
Adverse Event	4 (4.7)	0	4 (2.4)
Physician Decision	1 (1.2)	1 (1.2)	2 (1.2)
Participant Decision	1 (1.2)	1 (1.2)	2 (1.2)
Death	0	1 (1.2)	1 (0.6)
Failure To Meet Continuation Criteria	0	1 (1.2)	1 (0.6)
Unsatisfactory Therapeutic Effect	0	1 (1.2)	1 (0.6)

* Ongoing at the time of the data cut-off date 2024-03-12.
Source: Study A2302 W48 CSR-Table 14.1-1.1

Adverse events

A majority of participants treated in Study A2302 experienced at least 1 AE (76/84 (90.5%) participants in the asciminib 40 mg BID group and 74/84 (88.1%) participants in the asciminib 80 mg QD group). AEs considered to be treatment-related were reported in 46 (54.8%) participants in the asciminib 40 mg BID group and 53 (63.1%) participants in the asciminib 80 mg QD group. AEs ≥ grade 3 were reported in 21 (25.0%) participants in the asciminib 40 mg BID group and 29 (34.5%) participants in the asciminib 80 mg QD group.

Table 88 Overview of adverse events (SAF)

	Asciminib 40 mg b.i.d. N=84		Asciminib 80 mg QD N=84		All participants N=168	
Category	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Adverse events	76 (90.5)	21 (25.0)	74 (88.1)	29 (34.5)	150 (89.3)	50 (29.8)
Treatment-related	46 (54.8)	13 (15.5)	53 (63.1)	16 (19.0)	99 (58.9)	29 (17.3)
SAEs	9 (10.7)	6 (7.1)	9 (10.7)	8 (9.5)	18 (10.7)	14 (8.3)
Treatment-related	3 (3.6)	2 (2.4)	4 (4.8)	4 (4.8)	7 (4.2)	6 (3.6)
Fatal SAEs	0	0	1 (1.2)	1 (1.2)	1 (0.6)	1 (0.6)
Treatment-related	0	0	0	0	0	0
AEs leading to discontinuation	6 (7.1)	3 (3.6)	4 (4.8)	3 (3.6)	10 (6.0)	6 (3.6)
Treatment-related	4 (4.8)	2 (2.4)	3 (3.6)	2 (2.4)	7 (4.2)	4 (2.4)
AEs leading to dose adjustment/interruption	25 (29.8)	17 (20.2)	26 (31.0)	21 (25.0)	51 (30.4)	38 (22.6)
AEs requiring additional therapy	53 (63.1)	13 (15.5)	52 (61.9)	18 (21.4)	105 (62.5)	31 (18.5)

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: [Study A2302 W48 CSR-Table 14.3.1-17]

Adverse events by system organ class

AEs by SOCs occurred with ≥ 5% difference in 40 mg BID and 80 mg QD dose group included general disorders and administration site conditions (22.6% vs. 31.0%); injury, poisoning and procedural complications (8.3% vs. 2.4%) and psychiatric disorders (3.6% vs. 9.5%).

Table 89 Adverse events by system organ class and severity (SAF)

	Asciminib 40 mg b.i.d. N=84		Asciminib 80 mg q.d. N=84		All participants N=168	
Primary system organ class	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of participants with at least one event	76 (90.5)	21 (25.0)	74 (88.1)	29 (34.5)	150 (89.3)	50 (29.8)
Blood and lymphatic system disorders	15 (17.9)	8 (9.5)	17 (20.2)	12 (14.3)	32 (19.0)	20 (11.9)
Cardiac disorders	9 (10.7)	1 (1.2)	7 (8.3)	1 (1.2)	16 (9.5)	2 (1.2)
Ear and labyrinth disorders	0	0	3 (3.6)	1 (1.2)	3 (1.8)	1 (0.6)
Endocrine disorders	0	0	1 (1.2)	0	1 (0.6)	0
Eye disorders	5 (6.0)	0	5 (6.0)	0	10 (6.0)	0
Gastrointestinal disorders	24 (28.6)	1 (1.2)	27 (32.1)	2 (2.4)	51 (30.4)	3 (1.8)
General disorders and administration site conditions	19 (22.6)	0	26 (31.0)	1 (1.2)	45 (26.8)	1 (0.6)
Hepatobiliary disorders	0	0	1 (1.2)	0	1 (0.6)	0
Immune system disorders	1 (1.2)	0	0	0	1 (0.6)	0
Infections and infestations	27 (32.1)	1 (1.2)	27 (32.1)	3 (3.6)	54 (32.1)	4 (2.4)
Injury, poisoning and procedural complications	7 (8.3)	1 (1.2)	2 (2.4)	0	9 (5.4)	1 (0.6)
Investigations	28 (33.3)	7 (8.3)	30 (35.7)	7 (8.3)	58 (34.5)	14 (8.3)
Metabolism and nutrition disorders	10 (11.9)	2 (2.4)	9 (10.7)	3 (3.6)	19 (11.3)	5 (3.0)
Musculoskeletal and connective tissue disorders	25 (29.8)	2 (2.4)	25 (29.8)	1 (1.2)	50 (29.8)	3 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (1.2)	0	1 (0.6)	0
Nervous system disorders	17 (20.2)	3 (3.6)	18 (21.4)	1 (1.2)	35 (20.8)	4 (2.4)
Psychiatric disorders	3 (3.6)	0	8 (9.5)	0	11 (6.5)	0
Renal and urinary disorders	3 (3.6)	0	5 (6.0)	2 (2.4)	8 (4.8)	2 (1.2)
Reproductive system and breast disorders	4 (4.8)	0	5 (6.0)	0	9 (5.4)	0
Respiratory, thoracic and mediastinal disorders	8 (9.5)	2 (2.4)	10 (11.9)	1 (1.2)	18 (10.7)	3 (1.8)
Skin and subcutaneous tissue disorders	22 (26.2)	0	22 (26.2)	1 (1.2)	44 (26.2)	1 (0.6)
Vascular disorders	9 (10.7)	0	7 (8.3)	2 (2.4)	16 (9.5)	2 (1.2)

Numbers (n) represent counts of participants.
A participant with multiple severity grades for an AE is only counted under the maximum grade.
AEs occurring during treatment or within 30 days of last study medication are summarized.
MedDRA version 26.1, CTCAE version 5.0
Source: Study A2302 W48 CSR-Table 14.3.1-1

Adverse events by preferred term

Adverse events by preferred term were presented. No major imbalance was observed between the arms.

Table 90 Adverse events by preferred term (> 5% in all participants) (SAF)

	Asciminib 40 mg b.i.d. N=84		Asciminib 80 mg q.d. N=84		All participants N=168	
Preferred term	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of participants with at least one event	76 (90.5)	21 (25.0)	74 (88.1)	29 (34.5)	150 (89.3)	50 (29.8)
Arthralgia	10 (11.9)	2 (2.4)	13 (15.5)	0	23 (13.7)	2 (1.2)
COVID-19	11 (13.1)	0	9 (10.7)	0	20 (11.9)	0
Pruritus	12 (14.3)	0	5 (6.0)	0	17 (10.1)	0
Headache	8 (9.5)	0	8 (9.5)	0	16 (9.5)	0
Thrombocytopenia	7 (8.3)	4 (4.8)	9 (10.7)	6 (7.1)	16 (9.5)	10 (6.0)
Fatigue	3 (3.6)	0	12 (14.3)	1 (1.2)	15 (8.9)	1 (0.6)
Nausea	6 (7.1)	0	8 (9.5)	0	14 (8.3)	0
Neutropenia	7 (8.3)	6 (7.1)	7 (8.3)	5 (6.0)	14 (8.3)	11 (6.5)
Diarrhea	7 (8.3)	0	6 (7.1)	0	13 (7.7)	0
Lipase increased	6 (7.1)	1 (1.2)	7 (8.3)	0	13 (7.7)	1 (0.6)
Alanine aminotransferase increased	9 (10.7)	2 (2.4)	2 (2.4)	0	11 (6.5)	2 (1.2)
Back pain	4 (4.8)	0	7 (8.3)	0	11 (6.5)	0
Hypertension	6 (7.1)	0	5 (6.0)	2 (2.4)	11 (6.5)	2 (1.2)
Platelet count decreased	4 (4.8)	3 (3.6)	7 (8.3)	4 (4.8)	11 (6.5)	7 (4.2)
Abdominal pain	5 (6.0)	0	5 (6.0)	1 (1.2)	10 (6.0)	1 (0.6)
Aspartate aminotransferase increased	8 (9.5)	1 (1.2)	2 (2.4)	0	10 (6.0)	1 (0.6)
Dry skin	3 (3.6)	0	7 (8.3)	1 (1.2)	10 (6.0)	1 (0.6)
Myalgia	5 (6.0)	0	4 (4.8)	0	9 (5.4)	0

Numbers (n) represent counts of participants.
A participant with multiple severity grades for an AE is only counted under the maximum grade.
AEs occurring during treatment or within 30 days of last study medication are summarized.
MedDRA version 26.1, CTCAE version 5.0
Source: Study A2302 W48 CSR-Table 14.3.1-1b

Serious adverse events

Overall, SAEs regardless of study treatment relationship were reported in 10.7% of patients. SAEs ≥ grade 3 were reported in 8.3% of patients. The incidence of individual SAEs was low. The most frequently reported SAEs, regardless of relationship to study drug were febrile neutropenia, neutropenia, atrial fibrillation, and hypertriglyceridemia (2 (1.2%) patients, each). The most frequently reported SAEs ≥ grade 3 were febrile neutropenia, neutropenia, and hypertriglyceridemia (2 (1.2%) patients, each).

The number of patients reporting AEs irrespective of grade is equal (88 vs. 90%), while for >= G3 events, numerically more patients from the 80 mg QD arm report events (25.0 vs. 34.5%, Δ 8 patients).

Table 91 Serious adverse events by system organ class and preferred term in more than 1 participant (SAF)

	Asciminib 40 mg b.i.d. N=84		Asciminib 80 mg q.d. N=84		All participant N=168	
Primary system organ class	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of participants with at least one event	9 (10.7)	6 (7.1)	9 (10.7)	8 (9.5)	18 (10.7)	14 (8.3)
Blood and lymphatic system disorders	2 (2.4)	2 (2.4)	4 (4.8)	4 (4.8)	6 (3.6)	6 (3.6)
Febrile neutropenia	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	2 (1.2)	2 (1.2)
Neutropenia	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	2 (1.2)	2 (1.2)
Cardiac disorders	2 (2.4)	1 (1.2)	3 (3.6)	1 (1.2)	5 (3.0)	2 (1.2)
Atrial fibrillation	1 (1.2)	0	1 (1.2)	0	2 (1.2)	0
Infections and infestations	3 (3.6)	1 (1.2)	0	0	3 (1.8)	1 (0.6)
Metabolism and nutrition disorders	0	0	3 (3.6)	3 (3.6)	3 (1.8)	3 (1.8)
Hypertriglyceridemia	0	0	2 (2.4)	2 (2.4)	2 (1.2)	2 (1.2)
Nervous system disorders	2 (2.4)	2 (2.4)	1 (1.2)	1 (1.2)	3 (1.8)	3 (1.8)

Numbers (n) represent counts of participants.
A participant with multiple severity grades for an AE is only counted under the maximum grade.
AEs occurring during treatment or within 30 days of last study medication are summarized.
MedDRA version 26.1, CTCAE version 5.0
Source: Study A2302 W48 CSR-Table 14.3.1-6

Adverse events leading to discontinuation, dose adjustment and/ or interruption

The occurrence of AEs leading to discontinuation of study treatment was low and comparable between participants receiving 40 mg BID and 80 mg QD dose regimens (6 (7.1%) participants and 4 (4.8%) participants) in terms of all grades and ≥ grade 3 events. The most frequently reported AE leading to dose adjustment and/or interruption were neutropenia (40 mg BID 8.3% vs. 80 mg QD 3.6%) and thrombocytopenia (4.8% vs. 7.1%).

Deaths

No deaths were reported in asciminib 40 mg BID group; one death was reported in 80 mg QD group. One (0.6%) participant in the 80 mg QD group died on treatment. The primary reason of death was stroke (cerebrovascular accident). The participant had a history of stroke, treated with acetylsalicylic acid as prevention.

On Day 10, the participant had stroke (grade 4) with hemiparesis and coma. CT angiography revealed occlusion of the middle cerebral artery left and haemorrhage into the basal ganglia area right and increasing infarction demarcation. Participant received the last dose of the study drug on Day 9. On Day 11, CT revealed progressive cerebral edema, and, on the same day, the participant died. Autopsy was not performed. The event cerebrovascular accident was assessed as not suspected to be related with the study drug by the investigator.

Adverse events of special interest (AESI)

An overview of AESI is provided in Table 92.

Table 92 Overview of AESI (SAF)

Safety topic	Asciminib 40 mg b.i.d. N=84		Asciminib 80 mg q.d. N=84		All participants N=168	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
GI toxicity	20 (23.8)	0	25 (29.8)	1 (1.2)	45 (26.8)	1 (0.6)
Myelosuppression*	15 (17.9)	11 (13.1)	22 (26.2)	15 (17.9)	37 (22.0)	26 (15.5)
Myelosuppression (Thrombocytopenia)	11 (13.1)	7 (8.3)	15 (17.9)	10 (11.9)	26 (15.5)	17 (10.1)
Myelosuppression (Leukopenia)	9 (10.7)	7 (8.3)	10 (11.9)	6 (7.1)	19 (11.3)	13 (7.7)
Myelosuppression (Erythropenia)	3 (3.6)	1 (1.2)	4 (4.8)	3 (3.6)	7 (4.2)	4 (2.4)
Hypersensitivity	8 (9.5)	0	11 (13.1)	0	19 (11.3)	0
Acute pancreatitis (including isolated pancreatic enzyme elevations)	9 (10.7)	2 (2.4)	7 (8.3)	0	16 (9.5)	2 (1.2)
Hepatotoxicity (including laboratory terms)	11 (13.1)	2 (2.4)	4 (4.8)	0	15 (8.9)	2 (1.2)
Edema and fluid retention	8 (9.5)	1 (1.2)	6 (7.1)	0	14 (8.3)	1 (0.6)
Ischemic heart and CNS conditions	3 (3.6)	2 (2.4)	8 (9.5)	3 (3.6)	11 (6.5)	5 (3.0)
Ischemic heart conditions	2 (2.4)	1 (1.2)	8 (9.5)	2 (2.4)	10 (6.0)	3 (1.8)
Ischemic CNS conditions	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	2 (1.2)	2 (1.2)
Hemorrhage	4 (4.8)	0	3 (3.6)	0	7 (4.2)	0
Arterial-occlusive events (AOEs)	3 (3.6)	2 (2.4)	3 (3.6)	1 (1.2)	6 (3.6)	3 (1.8)
Cardiac failure (clinical events)	2 (2.4)	0	1 (1.2)	0	3 (1.8)	0
Phototoxicity	1 (1.2)	0	0	0	1 (0.6)	0
QTc prolongation	1 (1.2)	1 (1.2)	0	0	1 (0.6)	1 (0.6)

Numbers (n) represent counts of participants.
A participant with multiple severity grades for an AE is only counted under the maximum grade.
AESI occurring during treatment or within 30 days of last study medication are summarized.
*Myelosuppression includes erythropenia, leucopenia, thrombocytopenia, cytopenias affecting more than one lineage.
MedDRA version 26.1., CTCAE version 5.0, Case Retrieval Strategy version released 27-Feb-2024.
Source: Study A2302 W48 CSR-Table 14.3.1-13

Some AESI were numerically less often reported in 40-mg-BID than in 80-mg-QD patients: GI toxicity (23.8 vs. 29.8%); myelosuppression (13.1 vs. 17.9%) and hypersensivity (9.5 vs. 13.1%), ischaemic conditions (3.6 vs. 9.5%), other AESI were numerically more often observed as acute pancreatitis (including isolated enzyme elevations 10.7 vs. 8.3%) and haemorrhage (4.8 vs. 3.6%).

Haematology

The haematological worst post-baseline value shifts to grade 3/4 events included haemoglobin decrease (grade 3: 0.6%), leukocytes decreased (grade 3: 3.0%), leukocytes increase (grade 3:1.8%), neutrophils decrease (grade 3: 4.2%; grade 4: 2.4%) and platelet decrease (grade 3: 3.6%; grade 4: 4.8%) without a clear trend between the arms.

Clinical chemistry

The biochemistry worst post-baseline value shifts to Grade 3/4 events were alanine aminotransferase increase (grade 3: 1.2%), amylase increase (grade 3: 1.8%), aspartate aminotransferase increase (grade 3: 0.6%), creatine kinase increase (grade 3: 3.0%), glucose decrease (grade 3: 0.6%, grade 4: 1.8%), magnesium increase (grade 3: 0.6%), potassium decrease (grade 3: 0.6%), triglycerides (fasting) increase (grade 3: 1.2%, grade 4: 0.6%), and triglycerides increase (grade 3: 2.4%, grade 4: 0.6%) without a clear trend between the arms.

Electrocardiograms

Most common notable ECG findings were QT increase > 30 ms to ≤ 60 ms (28.3%) and QTcF increase > 30 ms to ≤ 60 ms (18.6%) without a clear trend between the arms.

2.5.1. Discussion on clinical safety

Extension of indication to patients with newly diagnosed CML-CP

At data cut-off 22 October 2024, the median duration of exposure was marginally longer in the asciminib group (115.79 weeks) relative to the IS-TKI group (108.70 weeks, FASIMA 100.29; FAS2G 116 weeks). The safety pool hereby presented has a total exposure period of 1.557 patient-treatment - years, pivotal study J12301 contributes with 411 years. A higher proportion of participants were still on treatment in the asciminib group (ASC 81.6% vs. IS-TKI 60.3%), as the predefined secondary endpoint TTDAE was positive in favour of asciminib.

The overall incidence of AEs was comparable (>95% in both arms), however, adjusted for exposure, AEs per PTY were reported less frequently (485 vs. 1107). Furthermore, the incidence of Grade ≥ 3 AEs (44.5% vs. 54.7%), SAE (14.5% vs. 20.4%) AE leading to dose adjustment and/or interruption (33.0% vs. 41.4%) or treatment discontinuation (5.0% vs. 13.1%) was lower in the asciminib group. The effect was found in comparison to imatinib and to 2G TKI.

Concerning AE by organ class and preferred term, vascular disorders, including hypertension were reported more frequently in the asciminib group (16.5% vs. 8.5%). Systolic blood pressure increase was seen more often at all grades of hypertension (from ≥ 140 mmHg ASC 33.5% vs. IS-TKI 23.9% until ≥180 mmHg 2.0% vs. 0.5%) highlighting the importance for asciminib safety. An increase in body weight≥ 10%) was often and more frequently reported in the asciminib group (32.0% to 20.4%).

Regarding myelosuppression, the picture is inconsistent with remarkably less anaemia (all grades 12.5% vs. 25.9%) and neutropenia (10.5% vs. 16.4%) with asciminib treatment, but more thrombocytopenia (13.5 vs. 15.4% G3/4: 8.0 vs. 5.5%).

For other non-haematologic AE, diarrhoea (17.5% vs. 27.9%), nausea (9.5% vs. 19.9%), peripheral oedema (1.5% vs. 6.5%) or AST increased (3.0% vs. 11.4%) was reported less frequently in the asciminib group. SAE were rare events, with no apparent pattern in the asciminib group with mostly single cases. Until DCO, no on treatment death had occurred.

The cumulative incidences of AEs leading to treatment discontinuation were always lower at each time point (at Week 8, 24, 48, 96) in the asciminib treatment group (week 96: 4.5% vs. 12.9% - imatinib 13.1%; 2G TKI 12.7%), whereas 3 patients from the asciminib group were reported to have 'lipase increased' and two thrombocytopenia. In the IS-TKI group, pleural effusion, diarrhoea and asthenia led to discontinuation for at least two patients. This tendency is present in lower rates of treatment interruptions and dose reductions due to AE. This favourable effect of lower rates of dose reductions and interruptions is acknowledged. However, the applied (and approved) TKI doses in study J12301 are high, given the clinical knowledge of lower, equally effective dosages for 2G- TKI.

The high granularity of data workup for 14 predefined AESI by the Applicant is appreciated. AESI were less frequently found in the asciminib treatment group compared to the IS-TKI treatment group (≥ 5.0% difference). In study J12301 asciminib showed lower rates for myelosuppression (43.5% vs. 51.5%), hypersensitivity (26.0% vs. 43.4%) and edema/fluid retention (4.5% vs. 15.2%) in comparison to imatinib and lower rates for myelosuppression (43.5% vs. 63.7%), GI toxicity (39.0% vs. 52.0%) hypersensitivity (26.0% vs. 45.1%) hepatotoxicity (20.0% vs. 36.3%), haemorrhage (potential sequala of thrombocytopenia, 6.5% vs. 11.8%) and edema/ fluid retention (4.5% vs. 14.7%) in comparison to 2G-TKI.

Across all age group categories, most of the AESI in the asciminib treatment group occurred at lower incidence relative to the IS-TKI treatment group. A higher incidence was observed for AE leading to discontinuation, dose adjustment and requiring additional therapy in some categories in the elderly age groups (≥ 65 and ≥ 75 year) compared to < 65 year across all treatment groups. This aspect should be further addressed in comparison to IS-TKI in the follow-up with more data in older patients (long term safety data in the elderly population will be provided as part of the Annex II condition).

Extension of indication to 2nd line CML-CP

In the 2nd line cohort of uncontrolled study CABL001AUS08, occurrence of AEs (95.0%, G3-5: 31.7%), SAEs (3.0%, G3-5: 3.0%) and the incidence of AE leading to dose adjustment (26.7%) is considered to be comparable to results from studies in other lines of therapy. No on-treatment death occurred.

The most common adverse events of special interest for the 2L cohort were gastrointestinal toxicity (51.5%), hypersensitivity (21.8%) and acute pancreatitis (including isolated pancreatic enzyme elevations) (16.8%). The most common Grade >=3 adverse events of special interest were thrombocytopenia (6.9%) and leukopenia (5.9%). No arterial occlusive events (AOEs) were reported. Haemorrhage was reported in 7.95% (G3-5: 1%). GI toxicity is higher in the AUS08 2nd line cohort (51.5%; G3-G5: 3%) compared to the newly diagnosed population of J12301 (39.0%, G3-5 0.5%) and in 3rd or later line study A2301 (31.4%, G3-5: 1.9%). Myelosuppression was reported in 11.9% of patients, 43.5% in the 1st line 37.8 % in 3rd or later line study A2301 with limited comparability due to different exposure in the respective lines, with otherwise comparable safety profiles. No new safety signal was detected.

New posology of 80 mg QD for the 3rd or later line

Study A2302 is a randomised open- label trial, including 84 patients with asciminib 40mg BID and 80mg QD each, data cut-off 12 March 2024 after a mean exposure of 68.3 weeks.

Patient exposure was comparable with median 67.3 (40 mg BID) vs. 68.6 (80 mg QD) weeks. The treatment was ongoing for 80 vs. 81% of patients. The number of patients reporting AEs irrespective of grade is equal (88 vs. 90%), while for >= G3 events, numerically more patients from the 80 mg QD arm report events (25.0 vs. 34.5%, Δ 8 patients from various PT). The occurrence of AEs leading to discontinuation of study treatment was low and numerically higher in the 40 mg BID arm (7.1% vs. 4.8%) The most frequently reported AE leading to dose adjustment and/or interruption were neutropenia (8.3% vs. 3.6%) and thrombocytopenia (4.8% vs. 7.1%). One death occurred on treatment in the 80 mg QD arm by stroke in a patient who already had a history of stroke. The event was not suspected to be related to the study drug.

Some AESI were numerically less often reported in 40-mg-BID than in 80-mg-QD patients: GI toxicity (23.8 vs. 29.8%); myelosuppression (13.1 vs. 17.9%) and hypersensivity (9.5 vs. 13.1%), ischaemic conditions (3.6 vs. 9.5%), other AESI were numerically more often observed as acute pancreatitis (including isolated enzyme elevations 10.7 vs. 8.3%) and haemorrhage (4.8 vs. 3.6%). Further

comparison of haematology, clinical chemistry including liver enzymes and ECG leads for QTcF comparison did not show major imbalances comparing the two dosing regimens in study A2302.

The comparison of safety in 168 patients with either 40 mg BID or 80 mg QD did not show any further safety signal.

2.5.2. Conclusions on clinical safety

Extension of indication to patients with newly diagnosed CML-CP

Regarding study J12301 for the use of asciminib in newly diagnosed CP-CML patients, no new safety concerns arose until DCO. The reported events suggest a manageable safety profile for CML-CP first-line treatment, consistent with previous descriptions. Thrombocytopenia was more common in patients treated with asciminib; however, this did not result in a higher bleeding rate. Instead, the haemorrhage rate was higher in the IS-TKI group. Hypertension and weight gain were observed more frequently with asciminib. Compared to imatinib, the safety profile shows more vascular events, including hypertension, as well as more constipation and abdominal pain. However, there are fewer cases of diarrhoea, anaemia, leukopenia, muscle spasms and oedema. Compared to 2G-TKIs, asciminib shows more vascular events, including hypertension, but fewer events are reported for cardiac disorders, anaemia, neutropenia, oedema, pleural effusions and hepatic toxicity, as well as nausea and diarrhoea.

In conclusion, the safety profile in newly diagnosed patients was generally consistent with that previously described, with no new safety concerns identified.

Long-term safety data will be provided with the final CSR of study CABL001J12301 (ASC4FIRST) as committed by the MAH in an Annex II condition.

Extension of indication to 2nd line CML-CP

Patients in study AUS08 demonstrated a safety that was generally comparable to the previously described safety profile of asciminib.

New posology of 80 mg QD for the 3rd or later line

Numerically more patients from the 80 mg QD arm reported G3-5 events (25.0 vs. 34.5%). Discontinuation rate due to AE was higher in the 40 mg BID arm. One death occurred on treatment in the 80 mg QD arm by stroke who already had a history of stroke.

In conclusion, the safety of the two regimens is generally comparable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 4.2 with the following content:

Safety concerns

Table Error! No text of specified style in document.**-93 Part II SVIII.1: Summary of safety concerns**

Important identified risks	• Acute pancreatitis (including isolated pancreatic enzyme elevations) • Myelosuppression • QTc prolongation
Important potential risks	• Hepatotoxicity • Hepatitis B virus infection reactivation • Reproductive toxicity
Missing information	• Long-term safety • Use in patients with renal impairment • Use in patients with hepatic impairment

Pharmacovigilance plan

Routine pharmacovigilance activities

Specific adverse reaction follow-up checklists:

Targeted follow-up checklist will be used to collect further data to help further characterize and/or closely monitor the safety concern specified below:

- Reproductive toxicity

Other forms of routine pharmacovigilance activities for risks

No other forms of routine PhV activities for important risks are proposed.

Other routine pharmacovigilance activities related to any safety topics for which a specific activity is required

The following safety topic will be closely monitored and reported in the Periodic Safety Update Reports:

- Arterial occlusive events (including ischemic heart and CNS conditions plus arterial embolic and thrombotic events).

Additional pharmacovigilance activities

Table Error! No text of specified style in document.**-94 Part III.1: Ongoing and planned additional pharmacovigilance activities**

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CABL001A2301 A Phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated	To compare the efficacy of asciminib with that of bosutinib in the treatment of patients with CML-CP having previously been treated with a minimum of 2 prior ATP-binding site TKIs with BCR::ABL1 ratios ≥ 1% IS at screening	Long-term safety, acute pancreatitis (including isolated pancreatic enzyme elevations), myelosuppression, QTc prolongation, hepatotoxicity	Final report submission	31-Jul-2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
with 2 or more tyrosine kinase inhibitors. Ongoing				
CABL001A2302 A Phase 3b, multi-center, open-label, treatment optimization study of oral asciminib in patients with chronic myelogenous leukemia in chronic phase (CMLCP) previously treated with 2 or more tyrosine kinase inhibitors. Ongoing	To optimize the treatment of asciminib in patients with chronic myelogenous leukemia in chronic phase (CML-CP) previously treated with 2 or more Tyrosine Kinase Inhibitors (TKIs).	Long-term safety, acute pancreatitis (including isolated pancreatic enzyme elevations), myelosuppression, QTc prolongation, hepatotoxicity. hepatitis B virus infection reactivation, use in patients with renal impairment, use in patients with hepatic impairment.	Final report submission	11-Mar-2027
CABL001A2001B An open label, multi-center asciminib roll-over study to assess long-term safety in patients who have completed a Novartis sponsored asciminib study and are judged by the investigator to benefit from continued treatment. Ongoing	To assess long-term safety and provide continued treatment with asciminib for patients with CML-CP who have participated in a Novartis sponsored asciminib clinical study (parent study) and, in the opinion of the investigator, would benefit from continuing treatment.	Long-term safety, acute pancreatitis (including isolated pancreatic enzyme elevations), myelosuppression, QTc prolongation, hepatotoxicity, hepatitis B virus infection reactivation.	Final report submission	31-Dec-2028

Table -95 Part IV.1: Planned and ongoing post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations

Study, Status	Summary of Objectives	Efficacy uncertainties addressed	Safety concerns addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization					
CABL001J12301 A phase III, multi-center, open-label, randomized study of oral asciminib versus Investigator selected TKI in patients with newly diagnosed Philadelphia Chromosome Positive Chronic Myelogenous Leukemia in Chronic Phase Ongoing	To compare the efficacy of asciminib versus Investigator selected TKI, with respect to the proportion of participants that are in Major Molecular Response (MMR) at Week 48 and Week 96 To compare the efficacy of asciminib versus Investigator selected TKI, within the stratum of participants with imatinib as the pre-randomization selected TKI, with	Long-term efficacy, including long-term response rates, progression-free survival, and overall survival.	Further characterizatio n of the safety and tolerability profile of asciminib [acute pancreatitis (including isolated pancreatic enzyme elevations), myelosuppress ion, QTc prolongation, hepatotoxicity, hepatitis B virus infection reactivation],	Final report submission	30-Sep-2031

Study, Status	Summary of Objectives	Efficacy uncertainties addressed	Safety concerns addressed	Milestones	Due Date
	respect to the proportion of participants that are in MMR at Week 48 and Week 96 To characterize the safety and tolerability profile of asciminib versus 2G TKIs (nilotinib, dasatinib, or bosutinib) during the course of study treatment.		Long-term Safety]		
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances					
None					

Risk minimisation measures

Table Error! No text of specified style in document.**-96 Summary of pharmacovigilance activities and risk minimization activities by safety concerns**

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Acute pancreatitis (including isolated pancreatic enzyme elevations)	**Routine risk minimization measures** SmPC Section 4.2 where posology and method of administration are described. SmPC Section 4.4 where description of the risk along with monitoring and treatment guidance are added. SmPC Section 4.8 where the adverse reactions related to acute pancreatitis (including isolated pancreatic enzyme elevations) are listed. PL Section 2 where precautions, monitoring and treatment are described. PL Section 4 where possible side effects of asciminib are described. Legal status: Medical prescription only product **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** Evaluation of data from studies CABL001A2301 (Final report submission: 31-Jul-2025), CABL001A2302 (Final report submission: 11-Mar-2027), and CABL001A2001B (Final report submission: 31-Dec-2028)
Myelosuppression	**Routine risk minimization measures** SmPC Section 4.2 where posology and method of administration are described. SmPC Section 4.4 where description of the risk along with monitoring and treatment guidance are added. SmPC Section 4.8 where the adverse reactions related to myelosuppression are listed. PL Section 2 where precautions, monitoring and treatment are described. PL Section 4 where possible side effects of asciminib are described. Legal status: Medical prescription only product	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** Evaluation of data from studies CABL001A2301 (Final report submission: 31-Jul-2025), CABL001A2302 (Final report submission: 11-Mar-2027), and CABL001A2001B (Final report submission: 31-Dec-2028)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures None	
QTc prolongation	**Routine risk minimization measures** SmPC Section 4.2 where posology and method of administration are described. SmPC Section 4.4 where description of the risk along with monitoring and treatment guidance are added. SmPC Section 4.5 where precaution while administrating asciminib with medicinal products with known risk of torsades de pointes is added. SmPC Section 4.8 where adverse reactions related to QTc prolongation are listed. SmPC Section 5.1 where effect of asciminib in cardiac electrophysiology is described. PL Section 2 where precautions, monitoring and treatment are described. PL Section 4 where possible side effects of asciminib are described. Legal status: Medical prescription only product **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** Evaluation of data from studies CABL001A2301 (Final report submission: 31-Jul-2025), CABL001A2302 (Final report submission: 11-Mar-2027), and CABL001A2001B (Final report submission: 31-Dec-2028)
Important potential risks		
Hepatotoxicity	**Routine risk minimization measures** SmPC Section 4.2 where posology and method of administration are described. SmPC Section 4.8 where the adverse reactions related to hepatotoxicity are listed. SmPC Section 5.2 where PK of asciminib in patients with hepatic impairment is described. PL Section 4 where possible side effects of asciminib are described. Legal status: Medical prescription only product **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** Evaluation of data from studies CABL001A2301 (Final report submission: 31-Jul-2025), CABL001A2302 (Final report submission: 11-Mar-2027), and CABL001A2001B (Final report submission: 31-Dec-2028)
Hepatitis B virus infection reactivation	**Routine risk minimization measures** SmPC Section 4.4 where description of the risk along with monitoring and treatment guidance are added. PL Section 2 where precautions, monitoring and treatment are described. Legal status: Medical prescription only product **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** Evaluation of data from studies CABL001A2302 (Final report submission: 11-Mar-2027), and CABL001A2001B (Final report submission: 31-Dec-2028)
Reproductive toxicity	**Routine risk minimization measures** SmPC Section 4.6 where effects of asciminib in fertility, pregnancy and lactation are described.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Follow-up using a targeted checklist. **Additional pharmacovigilance activities**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	PL Section 2 where precautions, monitoring and treatment are described. Legal status: Medical prescription only product **Additional risk minimization measures** None	None
Missing information		
Long-term safety	**Routine risk minimization measures** SmPC: None PL: None **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** Evaluation of data from studies CABL001A2301 (Final report submission: 31-Jul-2025), CABL001A2302 (Final report submission: 11-Mar-2027), and CABL001A2001B (Final report submission: 31-Dec-2028)
Use in patients with renal impairment	**Routine risk minimization measures** SmPC Section 4.2 where posology and method of administration are described. SmPC Section 5.2 where PK of asciminib in patients with renal impairment is described. **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** Evaluation of data from Study CABL001A2302 (Final report submission: 11-Mar-2027)
Use in patients with hepatic impairment	**Routine risk minimization measures** SmPC Section 4.2 where posology and method of administration are described. SmPC Section 5.2 where PK of asciminib in patients with hepatic impairment is described. **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** Evaluation of data from Study CABL001A2302 (Final report submission: 11-Mar-2027)

2.7. Update of the Product information

As a consequence of this new indication and posology, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Compared to the already approved PIL submitted with the MAA which underwent user testing, there are only limited updates in the currently proposed PIL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP).

3.1.2. Available therapies and unmet medical need

The two main goals of CML-CP treatment are to normalise survival and to achieve durable deep molecular remissions (DMR, including MR4 and MR4.5 lasting for 2-5+ years) allowing for treatment-free remission (TFR).

There are four TKIs approved in the EU for the treatment of newly diagnosed CML-CP (1st generation: imatinib; 2nd generation: nilotinib, dasatinib, bosutinib).

Asciminib (ABL001), administered orally, is a potent allosteric inhibitor of ABL/BCR-ABL1 tyrosine kinase by specifically targeting the ABL myristoyl pocket (STAMP). Asciminib was approved in the EU for adults after treatment with two or more TKIs on 25 August 2022.

The choice of the TKI depends on 1) the patient's age and comorbidities 2) the CML risk profile 3) the cost and affordability of the TKI and 4) the treatment goal, as imatinib is considered to be equally effective for prolongation of survival to 2nd generation TKI. Achievement of deep molecular remissions is potentially faster with 2nd generation TKI, possibly reaching the criteria for a discontinuation attempt in a TFR faster.

A respectable number of patients fail to reach or maintain deep remissions due to primary or secondary resistance or have difficulties in the tolerability of the drug.

3.1.3. Main clinical studies

Three clinical studies were presented in this application.

I. Study CABL001J12301 (ASC4FIRST):

Ongoing pivotal randomised-controlled phase III clinical trial comparing asciminib 80 mg QD monotherapy with investigator's selected TKI (imatinib 400 mg QD, nilotinib 300 mg BID, dasatinib 100 mg QD or bosutinib 400 mg QD) in 405 patients with CML-CP. Stratification was applied according to ELTS score (low vs. intermediate vs. high) and PRS-IKI (imatinib vs. 2G TKI). Primary endpoints were a comparison of MMR rates at week 48 for the overall population (FAS) and for the imatinib stratum (FAS_{IMA}); key secondary endpoints were a comparison of MMR rate at week 96 for the overall population (FAS) and for the imatinib stratum (FAS_{IMA}). The efficacy comparison between asciminib and 2G TKI was addressed by a secondary endpoint. Further secondary endpoints included different molecular levels and duration of the response at different time points up to week 96 (CHR, MR2.0, MR3.0 (MMR), MR4.0 and MR4.5 at all scheduled data collection time points), time to treatment failure and event free survival.

II. Study CABL001AUS08 / ASC2ESCALATE:

Supportive evidence for the 2nd line efficacy of asciminib in CML-CP comes from the 2nd line cohort of the ongoing, uncontrolled, open-label, single-arm, dose escalation, multicentre phase II study AUS08 in participants with CML-CP receiving asciminib 80 mg QD monotherapy with response levels as

endpoints. The study has completed enrolment with 101 2nd line patients, of which 63 were efficacy evaluable with MMR rates at week 24 at DCO 15 November 2024. After a request for supplementary information, results with data-cut off of 16 May 2025 were provided.

III. Study CABL001A2302 (ASC4OPT):

Supportive clinical evidence for the new posology of 80 mg QD for the 3rd or later line comes from an ongoing phase III, non-comparative, open-label, multi-centre, treatment optimisation study with 168 patients 1:1 randomised to asciminib 40 mg BID or asciminib 80 mg QD in CML-CP patients after two or more lines of therapy. MMR rate at week 48 is the primary endpoint, aiming at a statistically significant difference to MMR rate at week 48 of 23% in the overall population. No stratification was applied. No direct comparison was planned or conducted between both groups and no margin for equivalence/non-inferiority was pre-specified.

3.2. Favourable effects

I. Extension of indication to patients with newly diagnosed CML-CP

MMR rate at week 48 (co-primary endpoints 1+2): The differences in MMR rates at week 48 are

- in the overall population (FAS) Δ 18.9 % (95% CI: 9.59, 28.17; one sided p <0.001) with 67.7% vs. 49.0% MMR rate at week 48 in the ASC arm vs. IS-TKI arm, respectively.
- in the imatinib stratum (FAS^{IMA}) Δ 29.6% (95% CI: 16.9, 42.2; one-sided p < 0.001) with 69.3% vs. 40.2% MMR rate at week 48 in the ASC^{IMA} population vs. IS-TKI^{IMA} population, respectively.

MMR rate at week 96 (key secondary endpoints 1+2): The differences in MMR rates *at* week 96 are

- in the overall population (FAS) Δ 22.4% (95% CI: 13.6, 31.3; one sided p <0.001) with 74.1% vs 52.0% MMR rate at week 96 in the ASC arm vs. IS-TKI arm.
- in the imatinib stratum (FAS^{IMA}) Δ 29.7% (95% CI, 17.6, 41.8; one sided p<0.001) with 76.2% vs 47.1% MMR rate at week 96 in the ASC^{IMA} population vs. IS-TKI^{IMA} population.

Regarding MR2.0 rate, the numerical difference between arms by week 48 was 22.0% (95% CI: 11.95, 32.06; 91.1% vs. 69.6%) for the FAS^{IMA} and 9.67% (95% CI: 1.45, 17.89; 94.0% vs. 84.3%) for the FAS^{2G} in favour of asciminib.

Regarding MR4.0 rate, the numerical difference between arms by week 48 was 30.2% (95% CI: 18.61, 41.83; 56.4% vs. 28.4%) for the FAS^{IMA} and 7.54% (95% CI; -4.77, 19.86; 36.0% vs. 28.4%) for the FAS^{2G} in favour of asciminib.

Regarding MR4.5 rate, the numerical difference between arms by week 48 was 16.2% (95% CI: 7.01, 25.29; 21.8% vs. 5.9%) for the FAS^{IMA} and 0.33% (95% CI; -10.03, 10.69; 18.0% vs. 17.7%) for the FAS^{2G} in favour of asciminib.

The KM probability of treatment failure was numerically lower in the asciminib arm compared to the IS-TKI arm (HR=0.37; 95% CI: 0.25, 0.55), by one year the KM estimated probability of being treatment failure-free is higher in the asciminib arm (88.0%, 95% CI: 82.6, 91.8) compared to the IS-TKI arm (74.1%, 95% CI: 67.5, 79.6).

II. Extension of the indication to 2nd line CML-CP treatment

Responses at week 24: BCR::ABL1<=10% rate was 90.5% (95%CI: 80.4%, 96.4%) MR2 rate 82.5% (95%CI: 70.9%, 91.0%), MMR (MR3) rate 44.4% (95%CI: 31.9%, 57.5%), MR4.0 rate 25.4%

(95%CI: 15.3%, 37.9%) and MR4.5 rate 9.5% (95% CI: 3.6%, 19.6%). MMR rate at week 36 is 52.4% (36.4, 68.0). MMR rate at week 48: 55.6% (40/72; 95% CI: 43.4; 67.3%).

III. New posology of 80 mg QD for the 3rd or later line, 40 mg BID in earlier lines

The study met its primary endpoint, for participants without MMR at baseline, the overall rate of MMR at Week 48 in FAS was 38.5% (95% CI: 31.09, 46.24).

Post- hoc comparison: The rate of MMR at Week 48 was 42.4% (95% CI: 31.70, 53.55) vs. 34.5% (95% CI: 24.48, 45.69) for the asciminib 40 mg BID group vs. asciminib 80 mg QD group, respectively. The numerical difference in MMR rate is 7.8% in favour of 40 mg BID.

The performed post-hoc propensity score weighting according to baseline characteristics led to a reduced difference of 2.43 (95% CI: -12.71, 17.56) in favour of asciminib 40 mg BID.

Supportive evidence comes from efficacy and activity with 80 mg QD dosing in newly diagnosed CML-CP (study J12301) and 2nd line CML-CP (study AUS08).

3.3. Uncertainties and limitations about favourable effects

I. Extension of indication to patients with newly diagnosed CML-CP

The results of the long-term (>96 weeks) outcomes of this potentially lifelong therapy are pending. The MAH committed to provide (Annex IID condition) a follow up of 8 years to judge the durability of responses, particularly in terms of the number of TFRs achieved, the duration of TFI, and more mature EFS data, since PFS and OS data are unlikely to mature. As the predictiveness of responses for clinical endpoints has been established for CML based on ATP-binding site-targeting TKIs, the translation of responses to clinical endpoints for the myristoyl pocket-targeting agent while be further confirmed with the long term results (see Annex II).

II. Extension of the indication to 2nd line CML-CP treatment

The interpretability of the data is hampered due to the uncontrolled nature of the trial, however taken altogether the results support the efficacy in 2nd line treatment of CML-CP.

III. New posology of 80 mg QD for the 3rd or later line, 40 mg BID in earlier lines

The study design implemented a 1:1 randomisation between the two regimens of 40 mg BID and 80 mg QD, as the study was planned as a post-authorisation study for treatment optimisation. The objectives, however, were formally not aligned for a comparison between the two arms. The post-hoc defined propensity score weighting addressing putative imbalances in baseline characteristics for studies A2301 and A2302 is not justified, adequate or reliable. Following a request for supplementary information the applicant conducted the requested analyses. The difference in MMR rate at week 48 of -7.8% (95% CI: -22.45, 6.79) in the unadjusted analysis is considered clinically relevant. It is not possible to conclude on the equivalence/similarity of the two posologies based on overlapping confidence intervals, nor on superiority of one of the dosing regimen in the absence of statistical significant superiority of 40 mg BID dosing in comparison to 80 mg QD. The potential lower efficacy with 80 mg QD is reflected in section 4.4 of the SmPC.

3.4. Unfavourable effects

I. Extension of indication to newly diagnosed Ph+ CML-CP

The safety profile of asciminib in CML -CP 1st line is based on data (DCO 22 October 2024) from RCT J12301 in 200 asciminib–exposed patients with a median exposure of 115.8 weeks. Overall, estimated cumulative post-marketing exposure of asciminib contains 7601 patient treatment years (PTY).

The risk of study treatment discontinuation due to AEs at week 96 was a predefined endpoint and statistically significantly lower in the asciminib group compared to 2G TKI (TTDAE, HR = 0.463; 95% CI: 0.215, 0.997; adjusted one sided p-value: 0.0246) and numerically lower compared to the imatinib group (HR = 0.381; 95% CI: 0.178, 0.818). Most common reasons for discontinuation of asciminib (for more than two patients) by PT were 'lipase increased' or 'thrombocytopenia'.

The overall incidence of AE was comparable to IS-TKI (>95%), however, after adjustment for exposure numerically favourable for asciminib. Furthermore, the incidence of Grade ≥ 3 AEs (44.5% vs. 54.7%), SAE (14.5% vs. 20.4%) AE leading to dose adjustment and/or interruption (33.0% vs. 41.4%) or treatment discontinuation (5.0% vs. 13.1%) was numerically lower in the asciminib group. The effect was found in comparison to imatinib and to 2G TKI. Until DCO, no on treatment death had occurred.

The applicant defined 14 AESI derived from the current safety profile. Asciminib showed lower rates for myelosuppression, hypersensitivity and edema/fluid retention in comparison to imatinib and lower rates for myelosuppression, GI toxicity hypersensitivity hepatotoxicity, haemorrhage (potential sequala of thrombocytopenia, 6.5% vs. 11.8%) and edema/ fluid retention in comparison to 2G-TKI.

However, vascular disorders, including hypertension (16.5% vs. 8.5%), increase in body weight ≥ 10% (32.0% vs. 20.4%) and thrombocytopenia (13.5 vs. 15.4% G3/4: 8.0 vs. 5.5%) were reported more frequently in the asciminib group (16.5% vs. 8.5%).

II. Extension of indication to 2nd line CML-CP

Incidence of AEs in the SAT is 95.0% (G3-5: 31.7%), SAEs 3.0% (G3-5: 3.0%) and AE leading to dose adjustment 26.7% in 2L cohort of study AUS08. No on-treatment death occurred. Common AESI were GI toxicity (51.5%), hypersensitivity (21.8%), acute pancreatitis (ink. isolated enzyme elevations) with 16.8%. No AOE events occurred. No new safety signal was detected.

III. New posology of 80 mg QD for the 3rd or later line, 40 mg BID in earlier lines

Study A2302 is a randomised (1:1) open- label phase IIIB trial, including 168 patients with asciminib either 40mg BID or 80mg QD, data cut-off was 12 March 2024 after a mean exposure of 68.3 weeks.

Patient exposure was comparable with median 67.3 (40 mg BID) vs. 68.6 (80 mg QD) weeks. The treatment was ongoing for 80 vs. 81% of patients. The number of patients reporting AEs irrespective of grade is equal (88 vs. 90%), while for >= G3 events, numerically more patients from the 80 mg QD arm report events (25.0 vs. 34.5%, Δ 8 patients from various PT). The occurrence of AEs leading to discontinuation of study treatment was low and numerically higher in the 40 mg BID arm (7.1% vs. 4.8%). The most frequently reported AE leading to dose adjustment and/or interruption were neutropenia (8.3% vs. 3.6%) and thrombocytopenia (4.8% vs. 7.1%) for the 40 mg BID vs. 80 mg QD arm, respectively. One death occurred on treatment in the 80 mg QD arm by stroke who already had a history of stroke. The event was not suspected to be related to the study drug.

Some AESI were numerically less often reported in 40-mg-BID than in 80-mg-QD patients: GI toxicity (23.8 vs. 29.8%); myelosuppression (13.1 vs. 17.9%) and hypersensivity (9.5 vs. 13.1%), ischaemic conditions (3.6 vs. 9.5%), other AESI were numerically more often observed in the 40 mg -BID patients as acute pancreatitis (including isolated enzyme elevations 10.7 vs. 8.3%) and haemorrhage (4.8 vs. 3.6%). Further comparison of haematology, clinical chemistry including liver enzymes and ECG leads for QTcF interval prolongation did not show major imbalances between the two dosing regimens in study A2302.

The treatment of 168 patients with either 40 mg BID or 80 mg QD did not show any further safety signal.

3.5. Uncertainties and limitations about unfavourable effects

I. Extension of indication to newly diagnosed Ph+ CML-CP

From 200 asciminib exposed patients, only 10 patients were older than 74 years of age. In this age group, rates for AE by PT hypertension, constipation, diarrhoea, nausea, arthralgia, pain in extremities, pruritus and headache are higher compared to younger patients. Further follow- up is required to assess the safety profile in the older population.

For a potentially lifelong therapy, exposure and follow-up is still considered limited, especially regarding the experience with serious emerging safety signals in later follow up of other BCR-ABL targeting agents (esp. AOE). Long-term safety (including in the elderly population) will be collected and reported in the final CSR for study J12301 (see Annex II)

II. Extension of indication to 2nd line CML-CP

The median duration of exposure at DCO is only 26.1 weeks. Furthermore, no clear comparability is given due to a lack of a control arm, cross – study comparisons are difficult.

III. New posology of 80 mg QD for the 3rd or later line, 40 mg BID in earlier lines

N/A.

3.6. Effects Table

Table 97: Effects Table for asciminib in study J12301, data cut-off 28 November 2023

Effect	Short description	Population	Treatment	Control		Strength of evidence/ Uncertainties (95% CI)
Favourable Effects						
			Asciminib 80 mg QD	**IS-TKI**		
Major molecular response (MMR)	MMR rate at week 48 (vs IS-TKIs)	FAS	67.66%	All: 49.02%		18.88% 95% CI (9.59, 28.17); p<0.001
MMR	MMR rate at week 48 (vs imatinib)	FAS_{IMA}	69.31%	Imatinib: 40.2%		29.55% 95% CI (16.91, 42.18); p< 0.001.
MMR	MMR rate at week 96 (va IS-TKIs)	FAS	74.13%	51.96%		22.42% 95%CI (13.6, 31.3); p< 0.001
MMR	MMR rate at week 96 (vs imatinib)	FAS_{IMA}	76.24%	47.06%		29.76% 95% CI (17.6, 41.8); p<0.001
Unfavourable Effects						
Study J12301			**Asciminib** n=200	**2G TKI** n=102	**Imatinib** n=99	

Effect	Short description	Population	Treatment	Control		Strength of evidence/ Uncertainties (95% CI)
AE	All grade% Grade ≥3%		95.5 44.5	100 59.8	97 49.5	
SAE	All grade% Grade ≥3%		14.5 11.5	14.5 11.5	16.2 14.1	
Myelosuppression	All grade% Grade ≥3%		43.5 20.0	63.7 33.3	51.5 24.2	
GI toxicity	All grade% Grade ≥3%		39.0 0.5	52.0 4.9	43.4 0	
Acute pancreatitis (ink. isolated enzyme elevations)	All grade% Grade ≥3%		14.5 3.5	17.6 5.9	16.2 3.0	
Haemorrhage	All grade% Grade ≥3%		6.5 0	11.8 2.9	10.1 1.0	
Arterial-occlusive events	All grade% Grade ≥3%		2.0 0.5	2.9 1.0	0 0	

Abbreviations: AE=adverse events, GI=gastrointestinal, SAE=serious adverse event,. MMR=major molecular response, defined as BCR-ABL1 > 0.1%

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

I. Extension of indication to patients with newly diagnosed CML-CP

The phase III study J12301 demonstrated a statistically significant superiority for asciminib monotherapy compared to investigator's selected TKI in newly diagnosed CML–CP patients. The primary endpoint, MMR rate after 48 weeks resembling an 'optimal response' milestone according to current guidelines (NCCN, ELN) showed a 18.9% (95% CI: 9.59, 28.17) improvement for the overall population. The effect was conclusively present against the imatinib stratum too and, although in a lower extent, the 2G-TKI stratum as well and supported by statistical superior results at week 96, numerically higher rates of response for EMR, MR2.0, DMR. Subgroup analyses according to risk profile and age group support the effect. The results of the long-term (>96 weeks) outcomes of this potentially lifelong therapy are pending (the MAH has committed to provide them via an Annex IID condition).

No new safety concerns arose until the data cut-off. The reported events suggest a manageable safety profile for CML-CP first-line treatment, consistent with previous descriptions. Thrombocytopenia was more common in patients treated with asciminib; however, this did not result in a higher bleeding rate. Hypertension and weight gain were observed more frequently with asciminib.

Compared to imatinib, the safety profile shows more vascular events, including hypertension, as well as more constipation and abdominal pain. However, there are fewer cases of diarrhoea, anaemia, leukopenia, muscle spasms and oedema.

Compared to 2G-TKIs, asciminib shows more vascular events, including hypertension, but fewer events are reported for cardiac disorders, anaemia, neutropenia, oedema, pleural effusions and hepatic toxicity, as well as nausea and diarrhoea.

II. Extension of the indication to 2nd line CML-CP treatment

Results from the SAT in 2nd line CML-CP patients provide reasonable evidence for activity of asciminib after one previous TKI therapy. MMR rate achieved in this population lays in between rates in newly diagnosed or >= third line patients with asciminib monotherapy.

The safety of asciminib after one line of therapy is also consistent with the so far established safety profile. No new safety signals were detected.

III. New posology of 80 mg QD for the 3rd or later line, 40 mg BID in earlier lines

In general, evidence for the new posology comes from demonstrated activity and efficacy of asciminib 80 mg QD in CML-CP 1st and 2nd line patients. Of note, adherence/ relative dose intensity might be worse for the 40 mg BID in daily practice due to food restrictions compared to the study.

Supportive clinical evidence, RCT A2302 (ASC4OPT) in 169 patients, for the evaluation of efficacy of the two dosing regimens in 3rd line treatment was provided. The difference in MMR rate at week 48 was 7.83% (95% CI: -22.45, 6.79) in favour of 40 mg BID. No equivalence margin was predefined, however, the difference of 7.8% is considered to be clinically relevant. This potential for lower efficacy of the 80 mg QD posology is addressed in Section 4.4 of the SmPC.

Safety of the two posologies appears comparable in RCT A2102 (ASC4OPT), hence both regimen are recommended in section 4.2 thus providing different options to the patient.

Notably, the proposed posology of 80 mg QD is useful for patients with impaired adherence or for whom a twice daily intake in fasting conditions is not feasible (such as patients with food restrictions like diabetes mellitus, with difficulties to swallow or patients in need of care who only have nursing aid once a day). In order to make an informed treatment decision, prescribers should be able to base their decision on the information available. The results of study A2302 (ASC4OPT) have therefore been added to the SmPC (results are reported in section 5.1 and a warning has been added to section 4.4).

3.7.2. Balance of benefits and risks

I. Extension of indication to patients with newly diagnosed CML-CP

The efficacy of asciminib monotherapy compared with investigator's selected TKI has been demonstrated in the pivotal RCT J12301. The safety profile was generally consistent with that previously described, with no new safety concerns identified.

II. Extension of the indication to 2nd line CML-CP treatment

The benefit-risk balance for patients with CML-CP in the second-line treatment setting is considered to be similar to that in the first- and third/later-line disease settings.

III. New posology of 80 mg QD for the 3rd or later line, 40 mg BID in earlier lines

Efficacy of 80 mg QD has been shown in newly diagnosed CML-CP compared to investigator's selected TKI and activity was demonstrated with 80 mg QD in CML-CP 2nd line treatment.

However, clinical data provided from the ASC4OPT study does not support the equivalence of different regimens in the 3rd or later-line treatment of chronic myeloid leukaemia (CML), with clinically relevant lower major molecular response (MMR) rates at week 48 with the 80 mg once-daily (QD) dosing regimen.

The proposed posology of 80 mg QD is however considered useful for patients with impaired adherence or for whom a twice daily intake in fasting conditions is not feasible (i.e. patients with food restrictions

such as diabetes mellitus, with difficulties to swallow or patients in need of care who only have nursing aid once a day). In order to make an informed treatment decision, the results of study A2302 (ASC4OPT) have been added to the SmPC (section 5.1 and a warning has been added to section 4.4).

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Scemblix is positive.

The following measures are considered necessary to address remaining uncertainties related to long term efficacy and safety:

In order to further evaluate the long-term efficacy and safety of asciminib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP), the MAH should submit the final CSR of study CABL001J12301 (ASC4FIRST), see Annex II.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

A grouped application consisting of:

C.I.6.a: Extension of indication to include treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase (CP) for SCEMBLIX.
As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. RMP version 4.2 has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection.

C.I.4: Update of sections 4.2, 4.5, 5.1, 5.2 and 5.3 of the SmPC in order to introduction of a new posology regimen of 80 mg QD. The Package Leaflet is updated accordingly. RMP version 4.2 has also been submitted.

The group of variations leads to amendments to the annexes I, II and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

This recommendation is subject to the following new condition:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further evaluate the long-term efficacy and safety of asciminib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP), the MAH should submit the final CSR of study CABL001J12301 (ASC4FIRST).	30-Sep-2031

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

5. EPAR changes

The EPAR will be updated following Commission Decision for this <group of variations><variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Scemblix-H-C-5605-II-VR/0000265010.