NOVARTIS

Patient Safety & Pharmacovigilance

European Union Risk Management Plan (EU RMP)

Scemblix® (Asciminib)

ABL001

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Date of final sign off	19-Jan-2026

Rationale for submitting an updated RMP

This EU Risk Management Plan (EU-RMP) v7.0 is prepared in response to the EMA request dated 11-Dec-2025 (Procedure number: EMA/X/0000256688) to update the RMP in line with the indication for the treatment of adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP) (hereafter referred to as Ph + CML-CP) with the T315I mutation who are resistant to, intolerant to or ineligible for ponatinib and consolidates EU RMPs v3.0 and v3.1 with the effective EU RMP v6.0. All RMP changes submitted to EMA under this procedure have been incorporated into this consolidated version.

Summary of significant changes in this RMP

The below section provides a summary of updates made in RMP v3.0 and v3.1,, as compared to v6.0, along with inclusion of indication for the treatment of adult patients with Ph+ CML-CP with the T315I mutation who are resistant to, intolerant to or ineligible for ponatinib.

- Updated the proposed expanded indication of use of asciminib and dosage in adult patients with Ph + CML-CP with T315I mutation. Further, the indication wording has been aligned with the SmPC.
- Updated epidemiology details for Ph+ CML-CP with T315I mutation.
- Exposure and safety data from CABL001X2101 First-In-Human study (X2101, FIH) has been added to support the proposed expanded indication.
- Data across the sections of the document is aligned with the proposed Summary of Product Characteristics (SmPC).
- Included evaluation of the safety profile of the 200 mg b.i.d. dose within the PSURs as routine pharmacovigilance activities beyond ADRs reporting and signal detection.

Part	Major changes compared to RMP v 6.0
Part I	Product information has been updated to include the indication and dosage in adult patients with Ph+ CML-CP with T315I mutation who are resistant to, intolerant to or ineligible for ponatinib.
Part II	Module SI Updated epidemiology for Ph + CML-CP with T315I mutation. Module SII: Updated dose of 200 mg b.i.d. in non-clinical part of safety specification. Module SIII: Updated clinical trial exposure details X2101 study Module SIV: • Updated exclusion criteria for children and adolescents in pivotal studies within development program. • Updated exposure of special populations included or not in clinical trial development from X2101 study. Module SV: No change Module SVI: No change Module SVII: Updated data from X2101 study to support the indication expansion of asciminib in adult patients with Ph+CML-CP with the T315I mutation Module SVIII: No change.

Part	Major changes compared to RMP v 6.0
Part III	Inclusion of evaluation of the safety profile of the 200 mg b.i.d. dose within the PSURs as routine pharmacovigilance activities beyond ADRs reporting and signal detection.
Part IV	No change.
Part V	Aligned details as per current SmPC.
Part VI	Updated the text for adult patients with Ph+ CML-CP with the T315I mutation who are resistant to, intolerant to or ineligible for ponatinib.
Part VII	Annex 4: No change. Annex 6: No change.

Other RMP versions under evaluation

Not applicable.

Details of the currently approved RMP

Version number	6.0
Approved with procedure	EMA/VR/0000280241
Date of approval (opinion date)	27-Nov-2025

QPPV name: Dr. Justin Daniels PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of abbreviations

2G-TKI	Second-generation tyrosine kinase inhibitor
ABL1	Abelson oncogene
AE	Adverse event
AESI	Adverse event of special interest
aGFR	Absolute glomerular filtration rate
ALL	Acute lymphoblastic leukemia
Allo-SCT	Allogeneic stem cell transplantation
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute Myeloid Leukemia
AP	Accelerated phase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration versus time curve
AUCinf	AUC from time zero to infinity
BCR	Breakpoint cluster region
BCR::ABL1/BCR::ABL1	BCR-ABL fusion gene and encoded oncoprotein
b.i.d.	Twice a Day
BP	Blast phase
CDS	Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CML	Chronic myeloid leukemia
Cmax	Maximum (peak) concentration of drug
CNS	Central nervous system
CP	Chronic phase
CrCl	Creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CYP	Cytochrome P450
DCO	Data cut off
DNA	Deoxyribonucleic Acid
EAIR	Exposure-adjusted incidence rate
ECG	Electrocardiogram
EEA	European Economic Area
ELN	European LeukemiaNet
EMEA	European Medicines Evaluation Agency
EOT	End of Trial
EPAR	European Public Assessment Report
EU	European Union
FCT	Film-coated tablet
GBD	Global Burden of Disease

GI	Gastrointestinal
HBV	Hepatitis B virus
hERG	Human ether-a-go-go-related gene
IBD	International Birth Date
IC50	Half maximal inhibitory concentration
INN	International Non-proprietary Name
IP	Incidence proportion
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Major molecular response
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OR	Odds ratio
OS	Overall Survival
PACE	Ponatinib Ph+ ALL and CML Evaluation
PFS	Progression Free Survival
PTY	Patient-treatment years
PAES	Post Authorization Efficacy Study
PASS	Post Authorization Safety Study
Ph+	Philadelphia chromosome-positive
PK	Pharmacokinetics
PL	Package leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Product Safety Update Report
PSUSA	Periodic Safety Update Report Single Assessment
PT	Preferred Term
STY	Subject-treatment years
QPPV	Qualified Person Responsible for Pharmacovigilance
QTc	Corrected QT interval
QTcF	Corrected QT interval by Fridericia
RDE	Recommended dose for expansion
RMP	Risk Management Plan
ROW	Rest-Of-the-World
SAE	Serious adverse event
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardized MeDRA query
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
US	United States (of America)
VMAT	Vesicular Monoamine Transporter

1 Part I: Product(s) Overview

Table 1-1 Part I.1 – Product(s) Overview

Active substance (INN or common name)	Asciminib
Pharmacotherapeutic group (ATC Code)	Tyrosine kinase inhibitor (L01EA06)
Marketing Authorization Applicant	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Scemblix®
Marketing authorization procedure	Centralized Procedure
Brief description of the product	**Chemical class:** Tyrosine kinase inhibitor
	Summary of mode of action: Asciminib is an oral, potent inhibitor of the kinase activity of the protein *BCR::ABL1* oncogene, which results from the fusion of a fragment of the breakpoint cluster region (*BCR*) gene with a fragment of the Abelson (*ABL1*) gene. The BCR::ABL1 protein has a constitutively active ABL1 tyrosine kinase domain. Asciminib specifically targets the ABL myristoyl pocket, thereby inhibiting the ABL kinase activity of ABL1, ABL2 and the chimeric BCR::ABL1 oncoprotein. In vitro, asciminib inhibits the proliferation of BCR::ABL1 dependent cell lines. In murine xenograft models of chronic myeloid leukemia (CML), asciminib potently inhibited tumor growth.
	Important information about its composition: The film-coated tablet (FCT) formulation with the strengths of 20 mg, 40 mg and 100 mg is manufactured with asciminib hydrochloride salt drug substance. Each 20 mg FCT contains 21.62 mg asciminib hydrochloride equivalent to 20 mg asciminib. Each 40 mg FCT contains 43.24 mg asciminib hydrochloride equivalent to 40 mg asciminib. Each 100 mg FCT contains 108.10 mg asciminib hydrochloride, which is equivalent to 100 mg asciminib.
Hyperlink to the Product Information	[Proposed SmPC]
Indications in the EEA	**Current:** Asciminib is indicated for treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP).
	Proposed: Asciminib is indicated for treatment of adult patients with Ph+ CML-CP with the T315I mutation who are resistant to, intolerant to or ineligible for ponatinib.
Dosage in the EEA	**Current:** The recommended total daily dose of asciminib is 80 mg. Asciminib can be taken orally either as 80 mg once daily or as 40 mg twice daily at approximately 12-hour intervals.

	Proposed: Ph+ CML-CP The recommended total daily dose of asciminib is 80 mg. Asciminib can be taken orally either as 80 mg once daily or as 40 mg twice daily at approximately 12-hour intervals. Ph+ CML-CP with the T315I mutation: The recommended dose of asciminib is 200 mg twice daily at approximately 12-hour intervals.
Pharmaceutical form(s) and strengths	**Current:** 20 mg and 40 mg FCT.
	Proposed: 100 mg FCT.
Is/will the product be subject to additional monitoring in the EU?	Yes

2 Part II: Safety specification

2.1 Part II: Module SI: Epidemiology of the indication(s) and target population

2.1.1 Indication: Chronic Myeloid Leukemia

Incidence

Chronic myeloid leukemia is the most common BCR::ABL1-positive myeloproliferative neoplasm (MPN), accounting for approximately 12-20% of all cases of leukemia in adults (Clarkson et al 2003, Siegel et al 2015, ACS 2024). Based on data from the Global Burden of Disease project of the Institute for Health Metrics and Evaluation, in the European Union (EU), the observed incidence of CML in 2022 was 1.55 cases per 100,000, being highest (1.63 per 100,000) in Western Europe and lowest (0.70 per 100,000) in Central Europe (GBD 2022). Assuming 15% of all new cases of leukemia are CML (ACS 2024), the incidence of 16.5 per 100,000 for leukemia in the EU in 2022, based on the European Cancer Information system (ECIS 2024) and Global Cancer Observatory (Ferlay et al 2024), the estimated incidence of CML is 2.5 per 100,000 in the EU. In the United States of America (US), the incidence is 1.9 per 100,000 persons (based on Surveillance, Epidemiology, and End Results [SEER] 21 data from 2016 to 2020, age-adjusted to the 2000 US standard population) and it is estimated that there would be 8,930 new patients with CML in 2023 (SEER 2024).

Table 2-1 Annual incidence of chronic myeloid leukemia in EU in the year 2022

Countries	Incidence of chronic myeloid leukemia					
	Male		Female		Male and Female	
	Rate*	Cases	Rate*	Cases	Rate*	Cases
France	2.15	693	1.62	554	1.88	1,248
Germany	2.34	996	1.99	852	2.16	1,848
Italy	2.29	665	1.78	544	2.03	1,209
Spain	1.34	297	1.12	259	1.23	556
United Kingdom	1.37	458	0.89	307	1.12	766
Central Europe	0.75	421	0.64	378	0.70	799
Eastern Europe	0.91	863	0.70	768	0.80	1,636
Western Europe	1.82	3,925	1.45	3,219	1.63	7,144
EU-28	1.71	3,733	1.39	3,164	1.55	6,897

Source: GBD 2022
* per 100,000, age-standardized to the Global Burden of Disease (GBD) world population.

In published studies, the proportion of patients with CML who received second-line therapy has been reported to range from 21.3% to 38.9% and the proportion of patients with CML who received 3L therapy was 5.2% to 14.4% (Henk et al 2015, Bosi et al 2019, Atallah et al 2022).

Prevalence

The prevalence of CML is steadily rising due to the substantially increased survival that has been achieved with targeted BCR::ABL1 kinase inhibitors (Bower et al 2016). In 2020, there were an estimated 66,366 people living with CML in the US (SEER 2024).

Data on the complete prevalence of CML in the overall EU region are limited. Based on the data from GBD, in the EU the observed prevalence of CML in 2022 was 15,818 persons (3.55 cases per 100,000) (GBD 2022). According to RARECARENet (2008), the complete prevalence of CML in Europe was 32,412 persons (6.3 per 100,000) in 2008. In a German study, the estimated complete prevalence for 2012 was 11.2 per 100,000 population (12.0 and 10.6 per 100,000 population in males and females, respectively) (Lauseker et al 2016). Another study in Germany reported an estimated prevalence of 14.0 per 100,000 population in 2012 in a population-based observational cohort study, based on an anonymized German health claim database (Saubele et al 2022). A study in France identified 10,789 prevalent CML patients in 2014, corresponding to a crude prevalence rate of 16.3 per 100,000 inhabitants (Foulon et al 2019). In a study in the United Kingdom, the complete prevalence was 14.7 per 100,000 population (17.1 and 12.5 in males and females, respectively) (Li et al 2016). A study conducted in Sweden (Gunnarsson et al 2016) reported that the complete prevalence of CML in 2012 was 11.9 per 100,000 population. The complete prevalence of CML in the Nordic countries collectively in 2021 was 16.7 per 100,000 (NORDCAN 2023). A study from Italy reported a prevalence of 23 per 100,000 in 2023 (Polverelli et al 2024).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease

According to SEER data from 2016 to 2020, the median age of diagnosis of CML is 66 years (SEER 2024). The age wise distribution of age at the time of diagnosis is as below:

- Approximately 2.1% of the patients diagnosed were under the age of 20 years.
- 7.1% between 20 and 34 years
- 8.3% between 35 and 44 years
- 11.9% between 45 and 54 years
- 18.4% between 55 and 64 years
- 22.7% between 65 and 74 years
- 20.1% between 75 and 84 years
- 9.5% over 84 years of age

The incidence of CML has been reported to be higher in males than in females (Table 2-1 and Table 2-2). Among men, the incidence is highest in Whites and Blacks, with the and lowest in the Asians/Pacific Islanders. Among women, the incidence was highest among Whites and Blacks, with the lowest incidence in Asians/Pacific Islanders.

Table 2-2 Incident rates by race/ethnicity and sex adjusted to the US population

Race/Ethnicity	Men (/100,000)	Women (/100,000)
All Races	2.5	1.5
White	2.6	1.6

Black	2.2	1.5
Asian/Pacific Islander	1.6	0.9
American Indian/Alaska Native	1.9	1.8
Hispanic	2.0	1.3
Source: SEER 2024		

Risk factors for the disease

Exposure to ionizing radiation is believed to be a risk factor for CML (ACS 2020).

Other associations have been suggested in published studies. In a case-control study in Minnesota (US) that compared 670 patients with myeloid leukemia (420 patients with acute myeloid leukemia [AML] and 186 patients with CML) and 701 population-based controls, a statistically significant association was observed between peptic ulcer and CML (Odds ratio [OR] 2.0; 95% Confidence interval [CI]: 1.1, 3.8). Another study using Swedish registry data reported that previous diagnoses of dyspepsia, gastritis or peptic ulcers, as well as previous proton pump inhibitor medication, were all associated with a significantly increased risk of CML and raised the potential role of previous *Helicobacter pylori* infection in the development of CML (Relative Risks, 1.5-2.0) (Larfors et al 2020).

A personal history of cancer also increased the risk for CML (OR 3.5; 95% CI: 2.0, 5.8) and this association remained significant after adjusting for previous radiation or chemotherapy treatment (OR 3.6; 95% CI: 1.9, 7.0) (Johnson et al 2012). In a study in Sweden, the prevalence of prior malignancies and autoimmune disease was elevated in CML patients compared with matched controls from the general population: OR 1.47 (95% CI: 1.20, 1.82) and 1.55 (95% CI: 1.21, 1.98), respectively (Gunnarsson et al 2016a).

While there is no known familial disposition to CML, rare families in which multiple members develop MPN, including CML, have been described. Studies of these families suggest that the presence of an autosomal dominant mutation may predispose to the acquisition of a secondary somatic mutation such as the Philadelphia chromosome translocation or Janus kinase 2 mutation (Van Etten 2019). A genome-wide association study of Korean and European cohorts suggested that people with genetic variants at 2 chromosomal loci, 6q25.1 and 17p11.1, may be more likely to develop CML (Kim et al 2011). Another study identified 5 single nucleotide polymorphisms belonging to the genes PSMB10, TNFRSF10D, PSMB2, PPARD and CYP26B1, which were associated with CML predisposition (Bruzzoni-Giovanelli et al 2015).

The main existing treatment options

Prior to 2001, hydroxyurea, busulphan or interferon-alpha based therapies were mostly used to keep the proliferative activity and the disease in control (Manley and Stiefl 2017). Since then, several BCR::ABL1 TKIs have been approved for the treatment of CML and TKI therapy has now become the standard treatment for most patients with CML. Imatinib was the first TKI authorized to treat CML, and inhibiting BCR::ABL1 kinase activity dramatically improved the prognosis such that targeted therapy with TKIs has become the gold standard treatment for CML. There are 4 TKIs approved for the treatment of newly diagnosed CML, imatinib and the second-generation TKIs (2GTKIs) nilotinib, dasatinib, and bosutinib, with imatinib being the most commonly used in clinical practice in CML-CP patients (Apperley 2015,

Banegas et al 2019, and Hochhaus et al 2020a). Despite excellent outcomes, approximately 40% of patients by 5 years discontinue first-line TKI treatment due to either tolerability challenges or lack of efficacy (Druker et al 2006, Cortes et al 2016, Hochhaus et al 2016). In the second-line setting, the use of 2GTKIs is associated with an increased discontinuation rate, ranging between 60%-72% within 4-6 years after treatment initiation (Giles et al 2013, Shah et al 2014, Gambacorti-Passerini et al 2018). Asciminib is also approved in various countries for treatment of newly diagnosed and previously treated patients with CML-CP.

Available therapeutic options become more limited as CML patients experience disease resistance or intolerance to prior TKIs especially those who fail 2 or more previous TKIs. In these patients, any remaining TKI may be used; however, treatment selection is complex and it becomes limited by patient's comorbidities, age, emergence of mutations and the safety profile of each TKI (Hochhaus et al 2020a, Hochhaus et al 2017, NCCN Guidelines v3 2021). The use of 2G-TKI dasatinib or nilotinib in third and further lines of therapy may not result in a durable response (Hochhaus et al 2020b). Bosutinib, a 2G-TKI, was initially studied in patients who were resistant or intolerant to 2 or more prior TKIs (Khoury et al 2012). Ponatinib, a third-generation TKI (3G-TKI), is currently the only TKI approved for patients with the *BCR::ABL1* T315I mutation. In patients who have failed 2G-TKIs, ponatinib may be the preferred option. However, previous or concomitant arteriovascular disease represents a strong contraindication to ponatinib (Hochhaus et al 2020a).

Allogeneic stem cell transplantation (allo-SCT) may be considered for patients with resistance or intolerance to 2 or more TKIs (Hochhaus et al 2020b), but it carries a risk of morbidity and mortality. Further, allo-SCT is an option available only to patients with good performance status and normal organ functions, and for whom an appropriate donor is available (Jabbour and Kantarjian 2018). Although it can be curative, allo-SCT is generally not recommended as an upfront treatment for CML-CP, given the outcomes and long-term survival achievable with TKIs.

For patients progressing to CML blast phase (BP), the only option remains either allo-SCT or regimens as used to treat AML and acute lymphoblastic leukemia (ALL) in combination with TKIs, aiming to achieve a second CML-CP before allo-SCT, as a transplant in a full blastic patient is a compassionate procedure with high failure rate (Baccarani et al 2016). Patients progressing to CML-accelerated phase (AP) while on TKI, have a high rate of progression to BP with a poor survival. In these patients, an alternative TKI (not received before), as a bridge to allo-SCT, is beneficial (Baccarani et al 2016, Hochhaus et al 2017, NCCN 2024).

Natural history of the indicated condition in the population, including mortality and morbidity

Nearly 90% of patients with CML are diagnosed in CP. After a median of 3 to 5 years, untreated patients with CML-CP inevitably progress to CML-BP. Chronic myeloid leukemia accelerated phase (CML-AP) is characterized by an increasing arrest of maturation that usually heralds transformation to CML-BP. The median survival of patients with CML-AP is 1 to 2 years. Most patients with CML will remain in AP for 4-6 months before progressing to CML-BP (Quintás-Cardama et al 2006). Chronic myeloid leukemia-BP defined as 20% or more blasts in the peripheral blood or bone marrow or the presence of extra medullary blastic foci has a median

survival of 3 to 12 months (Quintás-Cardama et al 2006, Cortes 2004). In a recent study using data of the European LeukemiaNet Blast Phase Registry, a median overall survival (OS) of 23.8 months was reported (Brioli et al 2024). Prior to the molecularly targeted TKI treatments, median 5 year survival in patients with CML-CP was ~ 70%. With the introduction of imatinib in 2001 followed by other 2G- and 3GTKIs, the prognosis of patients with CML has improved dramatically, such that the life expectancy now approaches that of the general population (Van Etten 2019). Newly diagnosed CML patients treated with imatinib showed high rates of complete hematologic and cytogenetic response, low rates of progression to AP/BP of 7-10%, and median 5 year survival rate of approximately 90% (Giles et al 2010). Among patients with CML-CP, over 50% of patients treated with imatinib eventually develop resistance or intolerance. For 2GTKIs, when used as frontline therapy, approximately 30–40% of patients need to change therapy by 5 years. By 5 years, only ≈ 30% of patients treated with imatinib and 30–55% treated with 2GTKIs achieved a 4.5log molecular response ($MR^{4.5}$, *BCR::ABL1*$^{IS} \leq$ 0.0032%) (Cortes and Lang 2021). In a study using data (n=566) from the French Observatory and using a 1L intent-to-treat (ITT) analysis strategy, at Year 4 of follow-up, the cumulative incidence rates of MMR, MR4, MR4.5, and MR5 were 77.3%, 49.3%, 30.2%, and 18.6%, respectively. Analysis by subgroup confirmed the higher efficacy of 2G-TKIs to reach MMR, MR4, MR4.5 ($p<0.001$), and MR5 ($p=0.003$), compared with the imatinib subgroup: 89.8%, 59.1%, 39.0%, and 25.4%; respectively, in the nilotinib subgroup and 86.7%, 84.8%, 75.0%, and 60.0% in the dasatinib subgroup vs. 73.6%, 44.0%, 24.7%, and 14.3% in the imatinib subgroup at Year 4 (Saugues et al 2022).

According to SEER data in the US, the median age at death for CML is 77 years, with a 5-year relative survival of 70.6%. The age-adjusted death rate was 0.3 per 100,000 men and women per year; when assessed by race/ethnicity and sex, the range was 0.1 to 0.4 per 100,000 per year (SEER 2024).

A systematic literature review to evaluate the specific causes of deaths in CML-CP patients receiving second or third-line TKI therapy reported that 5% of second-line and 10% of third-line patients died during the study follow-up period. For second-line, (7 studies, n=1926), mortality was attributed to disease progression for 41% of deaths, 2% to treatment-related causes, 3% were treatment-unrelated, and 50% were unspecified adverse events (AEs), not likely related to study drug. In third line (2 studies, n=144), 71% deaths were attributed to disease progression, 7% treatment-related AEs, 14% treatment-unrelated and 7% unspecified AEs (Pearson et al 2016). Despite improvements in survival with available TKI therapy, there remains an unmet need in this population for additional treatment options.

In a multicenter retrospective chart review study from France that evaluated 157 adult patients with CML-CP who failed on two or more TKIs, therapy received in 3L included dasatinib (31.8%), nilotinib (19.1%), imatinib (17.8%), ponatinib (16.6%), bosutinib (14.0%), and allo-SCT (0.6%). Of the 145 patients with documented responses, 42% experienced MMR at 12 months and median event-free survival was 53.6 months (95% CI: 44.0, 67.5). Sustained MR4.5 (defined as achieving MR4.5 or better, i.e., BCR::ABL1 ≤0.0032%) in all consecutive assessments performed for at least 2 years (i.e., 730.5 days) was achieved by 11.7% of patients for a median duration of 134.2 months (Nicolini et al 2023). In a study of patients with CML (CP, 97%) who received bosutinib as 3L (38%) or fourth-line (51%) therapy, cumulative complete cytogenetic and MMR rates in CP patients were 67% and 55%, respectively. After a

median follow-up of 21.5 months, 9 patients (11%) in CP died. Estimated OS rates at 1 year and 2 years post-bosutinib initiation were 95% and 91%, respectively. Overall, 33 out of 87 patients (38%) discontinued bosutinib initiation due to: lack of efficacy / disease progression, 17%; AEs, 14%; other reasons, 5%; or death, 2%. There were 82 patients (94%) who experienced ≥ 1 AE, possibly related to bosutinib, with the most commonly being diarrhea (52%) (Claudiani et al 2022). With median follow-up at 73 months and median duration of 9 months with 3L therapy treatment, the 5-year survival rates were 57%, 68%, and 80% in patients who received imatinib, 2G-TKIs, and ponatinib, respectively (Sasaki et al 2020).

Despite improvements in survival with available TKI therapy, there remains an unmet need in the target population for efficacious treatments that also preserve quality of life, safety, and tolerability.

Important co-morbidities:

Comorbidities reported in adult CML patients are summarized in Table 2-3.

Table 2-3 Comorbidities in adult chronic myeloid leukemia patients

Comorbidity (%)	3L or more	1L (imatinib or 2GTKIs)		1L		
	Bosutinib (n=87)	18 to 64-year-old (n=316)	≥65-year-old (n=136)	Imatinib (n=733)	Dasatinib (n=212)	Nilotinib (n=262)
Vascular disease	25	NR	NR	NR	NR	NR
Hypertension	14	NR	NR	17	14	19
Chronic pulmonary disease	11	1	3	5	2	4
Diabetes mellitus	10	7	8	11	10	11
Renal disease	10	NR	NR	2	1	2
Gastrointestinal disease	6	NR	NR	NR	NR	NR
Connective tissue disease	5	1	2	NR	NR	NR
Chronic heart failure	3	0	2	NR	NR	NR
Malignant Lymphoma	3	NR	NR	NR	NR	NR
Malignant solid tumor	3	NR	NR	NR	NR	NR
Liver disease	0	5	2	3	3	3
Peripheral vascular disease	NR	2	7	NR	NR	NR
Myocardial infarction	NR	0	7	NR	NR	NR

Comorbidity (%)	3L or more	1L (imatinib or 2GTKIs)		1L		
Moderate/severe renal disease	NR	2	4	NR	NR	NR
Peptic ulcer disease	NR	2	4	7	9	8
Any tumor except for CML	NR	1	4	NR	NR	NR
Demetia	NR	1	1	NR	NR	NR
Cerebrovascular accident/ disease	NR	0	1	2	NR	NR
Dyslipidemia	NR	NR	NR	10	8	13
NR= Not reported Source: Claudiani et al 2022, Yang et al 2022, Ono et al 2023						

Gugliotta et al (2013) reported a subanalysis of the DASISION study to assess the impact of baseline comorbidities on the safety and efficacy of first-line dasatinib and imatinib in CML-CP patients. The authors reported that 48% of patients on dasatinib and 46% on imatinib had 2 or more comorbidities. In order of frequency, these were gastrointestinal (33-35%), muscle-skeletal (27-31%), endocrine-metabolic (excluding diabetes 17-21%), cardiovascular (CV; 13-17%), respiratory (13-14%), dermatologic (12%), hepatobiliary (9-12%), hyperlipidemia (7-9%), diabetes mellitus (5-7%), and renal (5-7%).

In a retrospective evaluation of a cohort of 85 Italian CML patients treated with ponatinib (due to inefficacy of previous TKI in 81.1% and intolerance in 18.9%) outside clinical trials, Caocci et al (2019) reported the CV comorbidities and risk factors of those patients before they started treatment with ponatinib (Table 2-4). Reported frequencies of hypertension, cardiovascular disease, and pneumonia and pleurisy among CML-CP patients who received ≥ 3L TKIs were 79%, 35%, and 25%, respectively, at baseline in a study in Italy (Breccia et al 2022).

Table 2-4 Prevalence of cardiovascular risk factors and diseases in adult chronic myeloid leukemia patients treated with ponatinib[1]

Cardiovascular risk factors and diseases	Prevalence
CV risk factors	
Hypertension	23.5%
Dyslipidemia	28.2%
Obesity (Body Mass Index > 24.5)	57.6%
Severe renal insufficiency	1.2%
Diabetes	14.1%
SCORE* risk ≤ 5% (low to int.)	82.3%
SCORE* risk > 5% (high to very high)	17.7%
Cardiovascular disease before ponatinib treatment	
Myocardial infarction/angina	4.7%
Arrhythmia	3.5%

Cardiovascular risk factors and diseases	Prevalence
Other cardiac diseases	5.8%
Peripheral arterial disease	0.0%
Stroke	0.0%
Hypertension	23.5%
Peripheral venous disease	0.0%
Primary antithrombotic prophylaxis^	20.0%
Secondary antithrombotic prophylaxis^^	7.0%
* Systematic Coronary Risk Evaluation (SCORE) risk - a 10-year risk estimation of fatal CV disease based on sex, age, smoking habits, systolic blood pressure, and total cholesterol levels; ^aspirin; ^^ aspirin, ticlopidine, and clopidogrel. The cohort included patients treated with ponatinib (Second line: 27%, Third line: 43.5%, Fourth line: 29.5%). [1]Caocci et al (2019).	

In the general population, the prevalence of chronic diseases is high among patients older than 65 years including hypertension (66%), lipid metabolism (41%), diabetes (30%), coronary heart disease (25%), cancer (17%), heart failure (14%), chronic obstructive pulmonary disease (12%), osteoporosis (12%), chronic kidney disease (11%) and stroke (6%). More than half of the subjects had between 1 and 3 chronic diseases (men: 57.7% and women: 59.3%). Approximately 25% of subjects had 4 or more chronic diseases (men: 26.6% and women: 23.6%) (Jacob et al 2016). In concordance with the median age of diagnosis of CML being 65 years, diseases more common in the elderly population like CV disease, hypertension, hyperlipidemia and diabetes are the most common comorbidities seen in patients with CML-CP. In addition, CML patients on third-line therapy may also have long-term toxicities from previous therapy with other TKI, including CV, pulmonary, gastrointestinal, and endocrine toxicities as comorbidities (Caldemeyer et al 2016).

2.1.2 Indication: Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase with the T315I mutation

Mutations within the adenosine triphosphate (ATP) binding site of the BCR::ABL1 oncoprotein which impede drug binding, are a common cause of TKI resistance with a frequency ranging from 12% to 63% in patients failing imatinib in 1L treatment. In 2L treatment, between 14% and 33% of patients with CML treated with dasatinib or nilotinib develop new *BCR::ABL1* mutations (Soverini et al 2014, Soverini et al 2018). Substitution of the threonine-315 residue with isoleucine (T315I mutation) is the most frequently identified *BCR::ABL1* mutation representing 12% to 23% of all point mutations (Soverini et al 2006, Apperley 2007, Nicolini et al 2013, Miller et al 2014, Nicolini et al 2017, Liu et al 2020).

The main existing treatment options

The *BCR::ABL1* T315I mutation confers a high-level of cross-resistance to most of the available TKIs indicated for CML-CP including imatinib and all 2G-TKIs (dasatinib, nilotinib and bosutinib). For these patients, ponatinib is currently the only approved TKI. Updated results from Ponatinib Ph^+ ALL and CML Evaluation (PACE) showed that the MMR rate remained stable (58%) with a longer median follow up of 56.8 months (Cortes et al 2018, García-

Gutiérrez, Hernández-Boluda 2019). However, ponatinib is associated with an increased risk of cardiovascular (CV) adverse events (AEs) (hypertension, peripheral arterial occlusive disease, ischemic heart disease, cerebrovascular accidents, venous thrombo-embolism, and platelet dysfunction) and its use is not recommended in patients who present with risk factors or comorbidities such as CV and arterial occlusive disease (Hochhaus et al 2020a). In the PACE study assessing ponatinib in the CML-CP cohort (Cortes et al 2018), after a median follow-up of 56.8 months (range 0.1-73.1 months), CV, cerebrovascular, and peripheral vascular occlusive AEs (arterial occlusive events) occurred in 16%, 13%, and 14% of patients, respectively, with the majority being SAEs.

After ponatinib failure, in the absence of alternative T315I-targeted therapies, the prognosis is dismal with a reported OS rate of 54% at 1 year and a median OS of 16.6 months. Although 70% of patients may achieve MMR with allogeneic-stem cell transplantation (allo-SCT) after ponatinib, the response is not durable (median OS=13 months; Boddu et al 2018). On the other hand, allo-SCT carries a risk of morbidity and mortality and it is available only to patients with good performance status and normal organ functions, and for whom an appropriate donor is available (Jabbour, Kantarjian 2018).

Natural history of the indicated condition in the population, including mortality and morbidity

Patients with the T315I mutation have worse outcomes in terms of OS and progression free survival (PFS), and they have a higher risk of progression to accelerated and blast phases when compared to patients not harboring the T315I mutation (Soverini et al 2014, Cortes et al 2018). In a study conducted by Cortes et al 2018, the 5-year OS rate in patients with CML-CP was 73% in those resistant to or intolerant of previous TKI and 66% in those with the T315I mutation. In a multicenter epidemiologic study conducted across 9 countries, the median OS from T315I mutation detection was 22.4 months and median PFS was 11.5 months for CML-CP patients (Nicolini et al 2009). In a study in France (Nicolini et al 2023) among patients who harbored the T315I mutation (n=17), the median OS since T315I identification was 5 years (interquartile range: 3 to 10). In a study in the US among patients with CMP-CP with T315l mutation (50 evaluable adult patients), 24% did not experience any major cytogenic response: only 50% showed MR4.5 and median OS was 133 months (95% CI: 52, 213). The 5-year OS rate from the first time T315I mutation was detected, was 70% (Haddad et al 2023).

2.2 Part II: Module SII: Non-clinical part of the safety specification

Table 2-5 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity	
Reproductive toxicity In embryofetal development studies, fetal malformations (cardiac malformations) and increased visceral and skeletal variants were observed in the rats and increased incidence of resorptions indicative of embryo-fetal mortality and a low incidence of cardiac malformations indicative of dysmorphogenesis were observed in rabbits. Asciminib was embryotoxic, fetotoxic and teratogenic at 150 mg/kg/day and 50 mg/kg/day in rats and rabbits, respectively. The maternal systemic exposure (AUC) at these dose levels in these animal models were: • 15- or 4-fold higher, respectively than those achieved in patients at the dose of 40 mg b.i.d. • 10- or 3-fold higher, respectively than those achieved in patients at the dose of 80 mg q.d. • 2-fold or below, respectively, than those achieved in patients at the dose of 200 mg b.i.d. No effects on reproductive function (mean day to mating, mating and fertility indices) in the rat fertility study, but a slight reduction in male sperm motility or sperm count in individual animals, and embryo lethality was noted at 200 mg/kg/day. Although no toxicokinetic assessment were included in the fertility study in rats, based upon the exposure achieved in the 26 week rat toxicity study, the lowest AUC exposure in males at 200 mg/kg was 203000 ng*hr/mL; exposures were 19-fold or 13-fold or 2-fold higher than those achieved in patients at the dose of 40 mg b.i.d. or 80 mg q.d. or 200 mg b.i.d., respectively.	Based on findings in animal studies, asciminib can cause fetal harm when administered to a pregnant woman. Based on routine pharmacovigilance activities and the evaluation of cumulative data available including cases reporting elective termination or therapeutic abortion in the Clinical Database and Novartis Safety Database, the review did not reveal any new safety finding or a particular pattern of reproductive toxicity with asciminib. However, patient should be aware of the potential for fetal abnormalities. Reproductive toxicity is an important potential risk.
Genotoxicity Asciminib does not show mutagenic, clastogenic, or aneugenic potential in vitro or in vivo.	Based on the current available non-clinical data, there is no concern relevant to human usage.
Carcinogenicity In a 2-year rat carcinogenicity study, an increase in ovarian Sertoli cell hyperplasia was observed in female animals at doses equal to or above 30 mg/kg/day. Benign Sertoli cell tumors in the ovaries were observed in female rats at the highest dose of 66 mg/kg/day. AUC exposures to	Based on the currently available non-clinical data, the relevance of these findings to humans is unknown. Based on routine pharmacovigilance activities to date and the evaluation of cumulative data available in the Clinical Database and Novartis Safety Database, there is no evidence of a

asciminib in female rats at 66 mg/kg/day were generally 8-fold or 5-fold higher than those achieved in patients at the dose of 40 mg twice daily or 80 mg once daily, respectively, and equivalent to those achieved in patients at the dose of 200 mg twice daily. No asciminib-related neoplastic or hyperplastic findings were noted in males.	potential safety signal of any ovarian malignant or benign tumors in asciminib treated patients.
Phototoxicity The in vivo mouse oral photo-local lymph node assay demonstrated a phototoxic potential at dose ≥ 200 mg/kg/day. At the no-observed-adverse-effect level (NOAEL) of 60 mg/kg/day, the Cmax was 12000 ng/mL, exposure 15-fold, 6-fold or 2-fold than the Cmax exposure in patients at the dose of 40 mg b.i.d., 80 mg q.d., or 200 mg b.i.d., respectively.	Infrequent phototoxicity-related events were reported in the clinical development program. None of these AEs were grade 3/4 or serious adverse events (SAEs). The vast majority of events recovered without any treatment.
Effects on the pancreas Pancreatic acinar atrophy was observed in dogs at AUC exposures below those achieved in patients at the 40 mg b.i.d., 80 mg q.d. or 200 mg b.i.d. dose. There was a correlation between the presence of increased serum amylase and lipase activities and the presence of pancreatic acinar cell damage at necropsy. The changes showed a trend towards reversibility.	Pancreatic enzyme increase and pancreatitis events were reported in the clinical development program. Acute pancreatitis (including isolated pancreatic enzyme elevations) is an important identified risk.
Effects on the liver Elevations in liver enzymes and/or bilirubin values were observed in rats, dogs and monkeys. Histopathologically, hepatic changes were characterized by centrilobular hepatocyte hypertrophy, slight bile duct hyperplasia and increased individual hepatocyte necrosis in rats and reversible diffuse hepatocellular hypertrophy in monkeys. These liver changes in rat occurred at exposures which were equivalent to those achieved in patients at the 40 mg b.i.d. or 80 mg q.d. dose or lower than those achieved in patients at 200 mg b.i.d. dose. In dog and monkey, they occurred at AUC exposures which were 12- and 18-fold higher than the one achieved in patients at the 40 mg b.i.d. dose, respectively. When compared to the exposure achieved in patients at 80 mg q.d., these effects occurred at AUC exposures that were approximately 8- and 12-fold higher in the dog and monkey, respectively. When compared to the exposures achieved in patients at 200 mg b.i.d., these effects occurred at AUC that were equivalent to and up to approximately 2-fold higher in the dog and monkey, respectively. These changes were fully reversible.	Mild to moderate, reversible hepatic enzyme abnormalities were reported in the clinical development program, with no evidence of irreversible liver damage. Hepatotoxicity is an important potential risk.

Effects on hematopoietic system A minimal to mild, regenerative reduction in red blood cells mass in rat, dog and monkey has been observed and was consistent with a regenerative, extravascular, hemolytic anemia. These changes occurred in monkeys and dogs at AUC exposures approximately: • 14- to 12-fold higher than the one achieved in patients at the 40 mg b.i.d. dose. • 10- to 13-fold higher than those achieved in patients at the 80 mg q.d. dose. In rat, these changes occurred at an exposure in terms of AUC equivalent to the one achieved in patients at the 40 mg b.i.d. dose, and 80 mg q.d., respectively. When compared to the exposures achieved in patients at 200 mg b.i.d., these effects occurred at AUC equivalent to and up to approximately 2-fold higher in the dog and monkey, respectively and below the exposure observed in rats.	Anemia, all grades and grade 3/4, was reported in the clinical development program. Myelosuppression is an important identified risk.
Effects on the duodenum Minimal mucosal hypertrophy/hyperplasia (increase in thickness of the mucosa with frequent elongation of villi) was present in the duodenum of rats treated at high doses of asciminib (600 mg/kg/day); the exposures in terms of AUC were: • 30-fold higher than the one achieved in patients at the 40 mg b.i.d. dose. • 22-fold higher than those achieved in patients at the 80 mg q.d. dose. • 4-fold higher than those achieved in patients at the 200 mg b.i.d. dose. These changes were fully reversible.	Mild to moderate gastrointestinal (GI) AEs (predominantly diarrhea, nausea, and vomiting) were reported in clinical trials with asciminib, with no fatal or life-threatening events. It is considered to have no impact on the benefit-risk balance of asciminib. Of note, GI side effects are frequently reported toxicities for all TKIs.
Effects on adrenal gland In rats and monkeys, minimal or slight hypertrophy of the adrenal gland and mild or moderate decreased vacuolation in the zona fasiculata occurred. Exposures, in terms of AUC, were: • in rats, 19-fold higher than those achieved in patients at the 40 mg b.i.d. dose and, in monkeys, equivalent to those achieved in patients at the 40 mg b.i.d. . • 13-fold higher (in rats) and equivalent (in monkeys) to those achieved in patients at the 80 mg q.d. dose. • 2-fold higher in rats than those achieved in patients at the 200 mg b.i.d. and lower in monkeys than those achieved in patients at the 200 mg b.i.d.	The relevance to humans is unclear at this time.

The adrenal gland findings may be indicative of stress and increased production of corticosteroids, although an additional more direct effect on adrenals cannot be completely excluded. These changes were fully reversible.	
Safety Pharmacology	
Cardiovascular findings Asciminib showed extremely low to no effects on IKs and hCav1.2 ion channels (inhibition by 5.2% and 11% at 30 µM, respectively) or in the Nav1.5 patch clamp assay (IC50 29.7 µM). The IC50 for asciminib in the human ether-a-go-go-related gene (hERG) patch clamp was 11.4 µM (4498 ng/mL), which provides an estimated safety margin > 200 fold, > 100 fold and > 30 fold when compared to free exposure in patients at dose of 40 mg b.i.d., 80 mg q.d., and 200 mg b.i.d. respectively. Moderate CV effects (increased heart rate, decreased systolic pressure, decreased mean arterial pressure, and decreased arterial pulse pressure) were observed with asciminib in jacket telemetered male dogs at single dose of 600 mg/kg or in the invasive telemetry CV safety study at 60 mg/kg. There was no QTc prolongation. Based on the exposure achieved in the 4-week dog toxicity study, the anticipated Cmax at 600 mg/kg in dogs was estimated to be ≈ 142000 ng/mL, which corresponds to a free Cmax of 6.3 µM (free fraction in dog: 0.02) value 100-fold, 60-fold and 18-fold higher than that achieved in patients at 40 mg b.i.d., 80 mg q.d., and 200 mg b.i.d., respectively.	The concentration-effect analysis indicated a lack of clinically relevant effect on cardiac repolarization with asciminib at 40 mg b.i.d. or 80 mg q.d. or 200 mg b.i.d. Few events of electrocardiogram QT prolonged were reported in the clinical studies. However, none of these events were associated with clinical symptoms. Considering the reported AEs (without clinical implications), QT prolongation is considered as an important identified risk.
Nervous system Little to no amounts of asciminib were detected in rat brain/ CNS. Study in the rat did not reveal any effects on the CNS (functional observations battery).	Based on the current available data, there is no concern relevant to human usage.
Respiratory system Study in the rat did not reveal any effects on the respiratory system (plethysmography).	Based on the current available data, there is no concern relevant to human usage.
Suicidality assessments Asciminib was assessed for its off-target activity on 144 G protein-coupled receptors, transporters, ion channels, nuclear receptors and enzymes. Effects >50% at 10 µM was only observed against 5-lipoxygenase (IC50 3.3 µM), vesicular monoamine transporter (VMAT)-2 (IC50 3.5 µM) and 5-hydroxytryptamine (5HT) 2b serotonin receptor antagonism (IC50 5.1 µM). Effects were observed at IC50 > 10 µM, on the adenosine Ad3 receptor (IC50 21 µM), 5-HT2A antagonism	In patients treated at the recommended dose of 40 mg b.i.d., the geometric mean total Cmax at steady-state is 793 ng/mL (1.8 µM) for asciminib (Molecular weight: 449.84), which converts to a free Cmax of 0.048 µM (free-fraction in human: 0.027). In patients treated at the recommended dose of 200 mg b.i.d., the geometric mean total Cmax in plasma at steady-state is 5642 ng/mL or 12.5 µM for asciminib (MW: 449.8) and the geometric mean AUC is 75094 ng*h/mL or 167 µM

(IC50 18 µM) and norepinephrine transporter (IC50 22 µM).	(Study CABL001X2101), which converts to a free Cmax of 0.34 µM (free-fraction in human: 0.027). Considering the off-target interaction displaying the strongest affinity (IC50 3.3 µM) and comparing to the free exposure achieved in patients at 200 mg b.i.d., the calculated safety margins are all >10. Therefore, taking into consideration safety margins of >10 and the low brain penetration by asciminib following oral administration, off-target adverse reactions resulting from interactions on 5-lipoxygenase, VMAT-2 transporter and 5HT2b receptor serotonin are unlikely to develop in humans. Based on the currently available data, there is no concern relevant to human usage.

2.3 Part II: Module SIII Clinical trial exposure

The details of the clinical studies contributing to the Safety Pools are summarized in Table 2-6.

Table 2-6 Clinical studies contributing to asciminib safety pool*

Population	Study code no. // Safety Set (N)	Study description	Dose schedule	Cut-off date
Adult patients with newly diagnosed Ph+CML-CP	CABL001J12301 (also known as Study J12301) [1] // 405 patients	Registration Phase III, multicenter, open label, randomized clinical study of oral asciminib vs. IS-TKI1	80 mg q.d.	22-Oct-2024, i.e. Week 96 after LPFV// ongoing
Adult patients with Ph+ CML-CP previously treated with ≥ 2 TKIs	CABL001A2301 // 232 patients	A Phase III, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in subjects with CML-CP, previously treated with 2 or more TKIs.	40 mg b.i.d.	04-Dec-2024 (End of Study)
Adult subjects with Ph+ CML or Ph+ ALL, relapsed, refractory to or intolerant of TKIs**	CABL001X2101 // 326 patients	A Phase I, multicenter, open-label study of oral ABL001 in subjects with CML or Ph+ ALL	10, 20, 40, 80, 150, 160, 200, 280 mg b.i.d. and 40, 60, 80, 120, 160, 200 mg q.d. as single agent or in combination with imatinib, nilotinib or dasatinib**	14-Mar-2023 (Completed)

[1]In Study J12301 and prior to randomization, the Investigator, in consultation with the patient, considering patient characteristics, comorbidities and current treatment paradigms, made a selection of preference for imatinib or 2G-TKI (nilotinib, dasatinib or bosutinib) should the patient be randomized to the comparator arm. This decision was captured as pre-randomization-selected TKI (PRS-TKI). Enrollment to the 2 strata (based on the PRS-TKI) was to imatinib vs. a 2G TKI.

*The safety set includes all subjects who received at least 1 dose of study treatment.

**Subject population taking asciminib single agent for CML-CP/AP (10 mg b.i.d. to 200 mg b.i.d.) formed the part of Safety Pool.

Population	Study code no. // Safety Set (N)	Study description	Dose schedule	Cut-off date
Only single-agent asciminib-treated patients (CML-CP or -AP) are included in the All Asciminib Safety Pool and the Asciminib 3L+ Safety Pool (Table 2-6). Safety pools have been defined for studies A2301 and J2101 in Section 2.3.1, and for study J12301 in Section 2.3.2.				
Sources: Study A2301 Final Clinical Study Report (End of Study) Study X2101 final report, Study J12301 Week 96 CSR				

2.3.1 Adult patients with previously treated Ph+CML- CP

Clinical trial exposure data for "patients with previously treated Ph+ CML-CP are based on the results of 2 studies.

- Study CABL001A2301 (registration study; hereafter referred to as Study A2301)
- Study CABL001X2101 (supportive study; hereafter referred to as Study X2101).

The data from these 2 studies were pooled for the safety analysis, and 2 separate Safety Pools were defined based on various doses of single agent asciminib, as follows:

- Asciminib 40 mg b.i.d. (CP) (N=187): 156 patients from Study A2301 and 31 patients from Study X2101.
  - Study A2301: All patients randomized to receive asciminib therapy and who received at least 1 dose of study treatment. Safety data collected in patients who switched to asciminib following treatment failure with bosutinib were not included.
  - Study X2101: All patients with Ph+ CML-CP only, treated with single agent asciminib 40 mg b.i.d. (as opposed to any dose).`
- Asciminib All patients (N=356): 156 patients from Study A2301 and 200 patients from Study X2101.
  - Study A2301: All patients randomized to receive asciminib therapy and who received at least 1 dose of study treatment. Safety data collected in patients who switched to asciminib following treatment failure with bosutinib were not included.
  - Study X2101: All patients with Ph+ CMLCP or AP treated with single agent asciminib irrespective of the dose schedule.

Duration of exposure (safety set), exposure by age group and gender, and exposure by race (safety set) are provided in Table 2-7, Table 2-8 and Table 2-9, respectively.

Table 2-7 Duration of exposure: 3L+ therapy (safety set)

Duration	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%)	Asciminib 40 mg b.i.d. N=156 n (%)	Asciminib All subjects N=356 n (%)
Duration of exposure categories - n (%)			
Less than 8 weeks	10 (13.2)	12 (7.7)	24 (6.7)
At least 8 weeks	66 (86.8)	144 (92.3)	332 (93.3)
At least 16 weeks	60 (78.9)	139 (89.1)	321 (90.2)
At least 24 weeks	49 (64.5)	129 (82.7)	299 (84.0)

Duration	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%)	Asciminib 40 mg b.i.d. N=156 n (%)	Asciminib All subjects N=356 n (%)
At least 48 weeks	22 (28.9)	105 (67.3)	261 (73.3)
At least 96 weeks	19 (25.0)	88 (56.4)	227 (63.8)
At least 144 weeks	11 (14.5)	85 (54.5)	206 (57.9)
At least 192 weeks	4 (5.3)	34 (21.8)	142 (39.9)
Subject-treatment years	**83.3**	**355.2**	**1148.0**

Subject-treatment years (STY) is the sum of each subject's treatment exposure in years.
Source: Annex 7-Table 5-1.

Table 2-8 Exposure by age group and gender 3L+ therapy (safety set)

		CABL001A2301				Safety Pool	
		Bosutinib 500 mg q.d. N=76		Asciminib 40 mg b.i.d. N=156		Asciminib All subjects N=356	
Gender	Age (years)	Subjects n (%)	STY	Subjects n (%)	STY	Subjects n (%)	STY
Total	Total	76 (100)	83.3	156 (100)	355.2	356 (100)	1148.0
	18-<65	61 (80.3)	63.4	127 (81.4)	291.1	272 (76.4)	890.9
	>=65	15 (19.7)	19.9	29 (18.6)	64.2	84 (23.6)	257.1
	>=75	2 (2.6)	3.1	4 (2.6)	15.8	21 (5.9)	73.3
Female	Total	45 (59.2)	36.7	75 (48.1)	179.3	155 (43.5)	512.2
	18-<65	36 (47.4)	28.2	63 (40.4)	153.8	121 (34.0)	403.7
	>=65	9 (11.8)	8.4	12 (7.7)	25.5	34 (9.6)	108.5
	>=75	2 (2.6)	3.1	2 (1.3)	7.9	10 (2.8)	42.7
Male	Total	31 (40.8)	46.6	81 (51.9)	175.9	201 (56.5)	635.8
	18-<65	25 (32.9)	35.2	64 (41.0)	137.3	151 (42.4)	487.2
	>=65	6 (7.9)	11.4	17 (10.9)	38.6	50 (14.0)	148.6
	>=75	0		2 (1.3)	7.9	11 (3.1)	30.6

		CABL001A2301				Safety Pool	
		Bosutinib 500 mg q.d. N=76		Asciminib 40 mg b.i.d. N=156		Asciminib All subjects N=356	
Gender	**Age (years)**	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**

Subject-treatment years is the sum of each subject's treatment exposure in years; STY is based on the number of subjects in each category.

Source: Annex 7-Table 5-2

Table 2-9 Exposure by race (3L+ therapy - safety set)

	CABL001A2301				Safety Pool	
	Bosutinib 500 mg q.d. N=76		Asciminib 40 mg b.i.d. N=156		Asciminib All subjects N=356	
Race	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**
White	56 (73.7)	67.7	117 (75.0)	257.7	236 (66.3)	724.2
Asian	11 (14.5)	9.5	22 (14.1)	55.3	69 (19.4)	260.9
Black or African American	2 (2.6)	1.6	8 (5.1)	18.5	13 (3.7)	39.0
Other	7 (9.2)	4.5	5 (3.2)	17.5	25 (7.0)	87.6
Unknown	0		3 (1.9)	3.1	12 (3.4)	33.3
American Indian or Alaska Native	0		1 (0.6)	3.0	1 (0.3)	3.0

Subject-treatment years is the sum of each subject's treatment exposure in years; STY is based on the number of subjects in each category.

Source: Annex 7-Table 5-3.

2.3.2 Adult patients with newly diagnosed Ph+CML

In the Study CABL001J12301, 405 adult patients with newly diagnosed Ph+CML-CP were randomized either to asciminib or IS-TKI, refer to Table 2-6 for further details.

These comprehensive exposure analyses were based on safety data collected from the 1L registration study for asciminib, Study J12301; and two studies for 3L+, the pivotal Study A2301 and supportive Study X2101. "All Asciminib Safety Pool" (N=556), which included 200 asciminib-treated patients from Study J12301 and the patients from the Asciminib 3L+ Safety Pool (i.e., 156 patients from Study A2301 and 200 patients from Study X2101), presented in Table 2-10, Table 2-11 and Table 2-12.

Of note, prior to randomization in 1L Study J12301, the Investigator, in consultation with the patient, considered patient characteristics, comorbidities and current treatment paradigms; and made a selection of preference for imatinib or 2G-TKI (nilotinib, dasatinib or bosutinib) should the patient be randomized to the comparator arm during Study J12301. This decision was

captured as the pre-randomization-selected TKI (PRS-TKI). Enrollment to the 2 strata (based on the PRS-TKI) was to imatinib vs. a 2G TKI.

Table 2-10 Duration of exposure (Safety Set)

	Study J12301						
	Asciminib			IS-TKI			Safety Pool
Duration (w)	Imatinib stratum N=100 n (%)	2G-TKI stratum N=100 n (%)	All asciminib N=200 n (%)	Imatinib stratum N=99 n (%)	2G-TKI stratum N=102 n (%)	All comparators N=201 n (%)	All Asciminib N=556 n (%)
By category							
< 8	4 (4.0)	1 (1.0)	5 (2.5)	5 (5.1)	3 (2.9)	8 (4.0)	29 (5.2)
8 to < 16	2 (2.0)	1 (1.0)	3 (1.5)	1 (1.0)	3 (2.9)	4 (2.0)	14 (2.5)
16 to < 24	2 (2.0)	3 (3.0)	5 (2.5)	8 (8.1)	2 (2.0)	10 (5.0)	27 (4.9)
24 to < 48	4 (4.0)	3 (3.0)	7 (3.5)	13 (13.1)	4 (3.9)	17 (8.5)	45 (8.1)
48 to < 96	5 (5.0)	8 (8.0)	13 (6.5)	17 (17.2)	16 (15.7)	33 (16.4)	47 (8.5)
96 to < 144	82 (82.0)	80 (80.0)	162 (81.0)	54 (54.5)	69 (67.6)	123 (61.2)	183 (32.9)
144 to <192	1 (1.0)	4 (4.0)	5 (2.5)	1 (1.0)	5 (4.9)	6 (3.0)	69 (12.4)
≥ 192	0	0	0	0	0	0	142 (25.5)
PTY	**192.9**	**217.8**	**410.6**	**151.1**	**202.5**	**353.6**	**1558.6**
By descriptive statistics							
Mean (SD)	100.64 (34.667)	113.62 (32.819)	107.13 (34.294)	79.66 (41.357)	103.58 (37.747)	91.80 (41.247)	146.27 (108.158)
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
Minimum	0.7	5.9	0.7	2.7	1.3	1.3	0.1
Maximum	154.7	152.1	154.7	146.0	150.1	150.1	439.0

PTY is the sum of each patient's treatment exposure in years.
Source: Annex 7-Table 5-1

Table 2-11 Exposure by age group and sex

	Study J12301						
	Asciminib			IS-TKI			Safety Pool
Age group and/or sex	Imatinib stratum N=100 n (%)	2G-TKI stratum N=100 n (%)	All asciminib N=200 n (%)	Imatinib stratum N=99 n (%)	2G-TKI stratum N=102 n (%)	All comparators N=201 n (%)	All Asciminib N=556 n (%)
Overall	100 (100)	100 (100)	200 (100)	99 (100)	102 (100)	201 (100)	556 (100)
PTY	**192.9**	**217.8**	**410.6**	**151.1**	**202.5**	**353.6**	**1558.6**
By age group (y)							
18 to < 65	68 (68.0)	86 (86.0)	154 (77.0)	68 (68.7)	85 (83.3)	153 (76.1)	426 (76.6)
PTY	127.9	188.2	316.1	108.7	171.7	280.4	1207.0
65 to < 75	24 (24.0)	12 (12.0)	36 (18.0)	22 (22.2)	12 (11.8)	34 (16.9)	99 (17.8)

	Study J12301						
	Asciminib			IS-TKI			Safety Pool
Age group and/or sex	Imatinib stratum N=100 n (%)	2G-TKI stratum N=100 n (%)	All asciminib N=200 n (%)	Imatinib stratum N=99 n (%)	2G-TKI stratum N=102 n (%)	All comparators N=201 n (%)	All Asciminib N=556 n (%)
PTY	48.5	24.7	73.2	30.8	24.9	55.7	257.0
≥ 75	8 (8.0)	2 (2.0)	10 (5.0)	9 (9.1)	5 (4.9)	14 (7.0)	31 (5.6)
PTY	16.5	4.8	21.4	11.6	5.9	17.6	94.7
By sex							
Female	38 (38.0)	31 (31.0)	69 (34.5)	37 (37.4)	41 (40.2)	78 (38.8)	224 (40.3)
PTY	**70.4**	**71.1**	**141.4**	**57.7**	**81.9**	**139.6**	**653.7**
18 to < 65	24 (24.0)	28 (28.0)	52 (26.0)	20 (20.2)	32 (31.4)	52 (25.9)	173 (31.1)
PTY	42.4	64.6	107.0	33.3	64.8	98.1	510.7
65 to < 75	12 (12.0)	3 (3.0)	15 (7.5)	11 (11.1)	6 (5.9)	17 (8.5)	39 (7.0)
PTY	23.2	6.5	29.7	17.6	14.6	32.2	95.5
≥ 75	2 (2.0)	0	2 (1.0)	6 (6.1)	3 (2.9)	9 (4.5)	12 (2.2)
PTY	4.7	-	4.7	6.8	2.5	9.3	47.5
Male	62 (62.0)	69 (69.0)	131 (65.5)	62 (62.6)	61 (59.8)	123 (61.2)	332 (59.7)
PTY	**122.5**	**146.7**	**269.2**	**93.4**	**120.6**	**214.0**	**905.0**
18 to < 65	44 (44.0)	58 (58.0)	102 (51.0)	48 (48.5)	53 (52.0)	101 (50.2)	253 (45.5)
PTY	85.5	123.6	209.1	75.3	106.9	182.3	696.3
65 to < 75	12 (12.0)	9 (9.0)	21 (10.5)	11 (11.1)	6 (5.9)	17 (8.5)	60 (10.8)
PTY	25.2	18.2	43.5	13.2	10.2	23.5	161.5
≥ 75	6 (6.0)	2 (2.0)	8 (4.0)	3 (3.0)	2 (2.0)	5 (2.5)	19 (3.4)
PTY	11.8	4.8	16.6	4.8	3.4	8.3	47.2

PTY is the sum of each patient's treatment exposure in years.
Source: Annex 7-Table 5-2

Table 2-12 Exposure by race (safety set)

	Study J12301						
	Asciminib			IS-TKI			Safety Pool
Race	Imatinib stratum N=100 n (%)	2G-TKI stratum N=100 n (%)	All asciminib N=200 n (%)	Imatinib stratum N=99 n (%)	2G-TKI stratum N=102 n (%)	All comparators N=201 n (%)	All Asciminib N=556 n (%)
White or Caucasian	62 (62.0)	45 (45.0)	107 (53.5)	63 (63.6)	45 (44.1)	108 (53.7)	343 (61.7)
PTY	123.6	101.6	225.2	99.1	90.1	189.3	949.4
Asian	37 (37.0)	53 (53.0)	90 (45.0)	34 (34.3)	55 (53.9)	89 (44.3)	159 (28.6)
PTY	67.2	111.1	178.4	48.6	108.4	157.0	439.3
Other	0	0	0	0	0	0	25 (4.5)
PTY	-	-	-	-	-	-	87.6

	Study J12301						Safety Pool
	Asciminib			IS-TKI			
Race	Imatinib stratum N=100 n (%)	2G-TKI stratum N=100 n (%)	All asciminib N=200 n (%)	Imatinib stratum N=99 n (%)	2G-TKI stratum N=102 n (%)	All comparators N=201 n (%)	All Asciminib N=556 n (%)
Black or African American	1 (1.0)	1 (1.0)	2 (1.0)	1 (1.0)	1 (1.0)	2 (1.0)	15 (2.7)
PTY	2.0	2.3	4.3	1.2	1.7	2.9	43.3
Unknown	0	1 (1.0)	1 (0.5)	1 (1.0)	1 (1.0)	2 (1.0)	13 (2.3)
PTY	-	2.8	2.8	2.2	2.2	4.5	36.1
American Indian or Alaska Native	0	0	0	0	0	0	1 (0.2)
PTY	-	-	-	-	-	-	3.0

PTY is the sum of each patient's treatment exposure in years.
Source: Annex 7-Table 5-3

2.3.3 Adult patients with Ph+ CML-CP with the T315I mutation

In Study X2101, all patients (N=326) were treated with asciminib which also included adult patients with Ph+ CML or Ph+ ALL, relapsed, refractory to or intolerant of TKIs; and with a subset of CML-CP patients (N=48 patients) who were harboring the T315I mutation and treated with asciminib 200 mg b.i.d. (Table 2-13)

Table 2-13 Clinical study contributing exposure information in patients with Ph+CML-CP with the T315I mutation

Study population	Study code no. // No. patients harboring T315I mutation (Safety set)	Study description	Asciminib dosage	Data cut off (DCO) // study status
Adult patients with Ph+ CML-CP with T315I mutation	Study X2101 // 48 patients	Phase I, multicenter, open-label clinical study of oral asciminib in patients with CML or Ph+ ALL	200 mg b.i.d. as single agent[1]	14-Mar-2023 // completed

Safety set includes all patients who received at least 1 dose of study treatment.
[1] In the expansion cohort for Study X2101, patients with the T315I mutation were permitted dose modification (reduction) at 160 mg b.i.d., in case of related toxicity; re-escalation to 200 mg b.i.d. with resolution; and no increase over 200 mg b.i.d.
Sources: Section 2.1, Study X2101 Final CSR-Section 9.4.4

Clinical study exposure was assessed by analyzing duration of exposure, exposure by age group and sex, and by race (Table 2-14 through Table 2-16.

Table 2-14 - SIII.1: Duration of exposure: Patients with Ph+ CML-CP with the T315I mutation

Duration	Study X2101 Asciminib 200 mg b.i.d. – T315I mutation N=48 n (%)
Less than 8 weeks	3 (6.3)
At least 8 weeks	45 (93.8)
At least 16 weeks	44 (91.7)
At least 24 weeks	40 (83.3)
At least 48 weeks	36 (75.0)
At least 96 weeks	33 (68.8)
At least 144 weeks	27 (56.3)
At least 192 weeks	23 (47.9)
PTY	**141.7**

PTY is the sum of each patient's treatment exposure in years.
Source : Attachment to Annex 7-Table 5-1b

Table 2-15- SIII.2: Exposure by age group and by sex: Patients with Ph+ CML-CP with the T315I mutation (Safety set)

Sex	Age (y)	Study X2101 Asciminib 200 mg b.i.d. – T315I mutation N=48 Patients n (%)	PTY
Overall	**Total**	**48 (100)**	**141.7**
	18 to < 65	32 (66.7)	88.8
	≥ 65	16 (33.3)	53.0
	≥ 75	4 (8.3)	18.6
Female	**Total**	**11 (22.9)**	**22.4**
	18 to < 65	8 (16.7)	17.6
	≥ 65	3 (6.3)	4.8
	≥ 75	0	–
Male	**Total**	**37 (77.1)**	**119.4**
	18 to < 65	24 (50.0)	71.2
	≥ 65	13 (27.1)	48.2
	≥ 75	4 (8.3)	18.6

PTY is the sum of each patient's treatment exposure in years. PTY is based on the number of patients in each category.
Source : Attachment to Annex 7-Table 5-2b

Table 2-16- SIII.3: Exposure by race: Patients with Ph+ CML-CP with the T315I mutation (Safety set)

	Study X2101 Asciminib 200 mg b.i.d. – T315I mutation N=48	
Race	**Patients n (%)**	**PTY**
White	23 (47.9)	59.9
Asian	12 (25.0)	43.4
Other	6 (12.5)	22.6
Unknown	6 (12.5)	15.4
Black or African American	1 (2.1)	0.4

PTY is the sum of each patient's treatment exposure in years. PTY is based on the number of patients in each category.
Source : Attachment to Annex 7-Table 5-3b

2.4 Part II: Module SIV: Populations not studied in clinical trials

2.4.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 2-13 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
Children and adolescents (patients less than 18 years)	The safety and efficacy of asciminib in children and adolescents aged 0 to 18 years has not been established.	No	The current absence of data in the pediatric population does not represent missing information in any subgroup of the target population.
Pregnant women and women of child-bearing potential, unless they are using highly effective methods of contraception during dosing and for 3 days after last dose of asciminib	Animal reproduction studies in pregnant rats and rabbits have demonstrated that oral administration of asciminib during organogenesis induced embryotoxicity, fetotoxicity and teratogenicity. No human data are available. Thus, pregnant women and women of child-bearing potential,	No	Based on non-clinical data, reproductive toxicity has been considered as an important potential risk. Please refer to Section 2.7.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
	unless they are using highly effective contraception, were excluded from studies in the development program.		
Breast-feeding women	It is not known whether asciminib is transferred into human milk after administration. There are no data on the effects of asciminib on the breast-fed child or on milk production.	No	Breastfeeding is not recommended during treatment and for at least 3 days after stopping treatment with asciminib.
Presence of cardiac abnormality including: • History within 6 months of myocardial infarction, angina pectoris, coronary artery bypass graft Presence of cardiac conduction or repolarization abnormality, including: • Clinically significant cardiac arrhythmias (e.g. ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g. bifascicular block, Mobitz type II and third degree AV block) • QTcF ≥ 450 msec (male patients), ≥ 460 msec (female patients) • Long QT syndrome, family history of idiopathic sudden death or	Patients with history of cardiac disease with specific criteria as listed were excluded from the clinical development program as a precaution. The available concentration-dependent analysis data show a	No	QTc prolongation is an important identified risk for asciminib. Please refer to Section 2.7. Events pertaining to cardiac ischemic conditions observed in the clinical studies did not confirm a causal role of asciminib for these events.. .

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
congenital long QT syndrome: risk factors for Torsades de Pointes; concomitant medication(s) with a "Known risk of Torsades de Pointes"	slightly dose dependent, non-clinically meaningful increase in QTc.		
History of acute pancreatitis (within 1 year of study entry or past medical history of chronic pancreatitis)	Acute pancreatitis (including isolated pancreatic enzyme elevations) has been identified as a risk based on the results of non-clinical and clinical data performed in the development program. Very common frequency of laboratory abnormalities (lipase and amylase increase) and common clinical events (pancreatitis and pancreatitis acute) are assessed as related to asciminib.	No	Acute pancreatitis (including isolated pancreatic enzyme elevations) is an important identified risk for asciminib. Please refer to Section 2.7.
Patients with severe renal disease	These patients were excluded from the clinical development program as a standard precaution. Patients with mild impairment and part of the moderate renal impairment (with Creatinine clearance (CrCl) ≥ 50 mL/min) were included.	Yes	Use in patients with renal impairment is missing information. Please refer to Section 2.7.
Patients with acute or chronic liver disease	As a standard precaution, patients with chronic liver disease, active liver disease, or moderate to severe hepatic impairment (total bilirubin > 1.5x Upper limit of normal [ULN] and/or aspartate aminotransferase [AST]/	Yes	Use in patients with hepatic impairment is missing information. Please refer to Section 2.7.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
	alanine aminotransferase [ALT] > 3xULN) were excluded from the development program.		
Patients with a known history of chronic Hepatitis B virus (HBV) infection	Reactivation of HBV in patients who are chronic HBV carriers has occurred during treatment with other BCR::ABL TKIs.	No	Based on class effect of TKIs, HBV infection reactivation is considered to be an important potential risk for asciminib. Please refer to Section 2.7.
Impaired GI function or GI disease	These are precautionary measures to preclude enrolling patients with conditions which alter the absorption of oral medication in the clinical trial.	No	Mild to moderate GI AEs were reported in clinical trials, with no life-threatening events. Gastrointestinal toxicity is considered as having no impact on the benefit-risk balance of asciminib. Please refer to Section 2.7.
Patients receiving concomitant treatment with strong inducers/ inhibitors of CYP3A	Asciminib is a substrate of CYP3A. Therefore, medicinal products that are strong inhibitors or inducers of CYP3A enzymes may affect the PK of asciminib.	No	A study (CABL001A2107) demonstrated that asciminib PK were only weakly affected by co-administration of rifampicin (a strong CYP3A4 inducer), clarithromycin and itraconazole (strong CYP3A inhibitors) in healthy volunteers. Following multiple doses of the strong CYP3A inducer rifampicin, the geometric mean AUCinf, AUClast of single dose asciminib decreased by 14.9% and 12.6%, respectively, with co-administration of rifampicin. Cmax indicated asciminib administered with rifampicin was comparable to asciminib administered alone. Compared to asciminib alone, multiple doses of clarithromycin treatment (500 mg b.i.d.) increased the geometric mean

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
			AUCinf, AUClast and Cmax values following a single dose of asciminib by 36%, 37% and 19%, respectively.

2.4.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

2.4.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 2-14 SIV.2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pediatric patients	Study CABL001I12201 (in pediatric patients with Ph+CML-CP, previously treated with one or more TKI) is ongoing.
Pregnant women Breastfeeding women	Has not been included in the clinical development program.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Patients with moderate to severe hepatic impairment (total bilirubin > 1.5xULN and/or AST/ALT> 3xULN) were excluded from the clinical development program. However, a study (CABL001A2103) in patients with hepatic impairment (but no underlying malignancy) was performed to assess the PK of asciminib in these patients. In this study, there were a total of 32 subjects of which, 8 were healthy subjects and 24 were patients with hepatic impairment.
• Patients with renal impairment	Patients with severe renal impairment (CrCl < 30 mL/min) and patients with moderate renal impairment (CrCl 30-< 50 mL/min) were excluded from the clinical development program. Patients with CrCl ≥ 50 mL/min were included. A study (CABL001A2105) in patients with severe renal impairment (but no underlying malignancy) was performed to assess the PK of asciminib in these patients. In this study, there were a total of 14 subjects of which 6 were healthy subjects and

Type of special population	Exposure
	8 were patients with renal impairment (measured by absolute glomerular filtration rate [aGFR]). In Study X2101, the numbers/fractions of patients with moderate and mild renal impairment and with the T315I mutation were 4/48 (8.3%) and 21/48 (43.8%) patients, respectively. Exposures in special populations either included or not included in clinical trial development programs are provided in Table 2-19andTable 2-20 .
• Patients with cardiovascular impairment	Patients with ischemic cardiac diseases (during past 6 months before starting asciminib), or clinically significant cardiac conduction abnormalities were excluded from the development program.
Immunocompromised patients	Not included in the clinical development program.
Population with relevant different ethnic origin	Refer to Table 2-9 for exposure data by race.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other	Excluded patients with significant congenital or acquired bleeding disorder unrelated to cancer.

Table 2-15 Exposure of special populations either included or not included in clinical trial development programs (1L therapy - safety set)

	Study J12301						
	Asciminib			IS-TKI			Safety Pool
Special population	Imatinib stratum N=100 n (%)	2G-TKI stratum N=100 n (%)	All asciminib N=200 n (%)	Imatinib stratum N=99 n (%)	2G-TKI stratum N=102 n (%)	All comparators N=201 n (%)	All Asciminib N=556 n (%)
Patients with renal disease							
Mild renal impairment							
	42 (42.0)	26 (26.0)	68 (34.0)	38 (38.4)	29 (28.4)	67 (33.3)	210 (37.8)
PTY	**76.2**	**55.8**	**132.0**	**59.7**	**54.9**	**114.6**	**591.8**
Moderate renal impairment							
	7 (7.0)	6 (6.0)	13 (6.5)	6 (6.1)	5 (4.9)	11 (5.5)	43 (7.7)
PTY	**15.5**	**12.2**	**27.7**	**6.6**	**9.3**	**15.9**	**125.3**

Categories of renal impairment (by estimated aGFR at baseline: mild=60 mL/min to 89.9 mL/min, moderate=30 mL/min to 59.9 mL/min) are according to the Modification of diet in Renal Disease (MDRD) equation.
There were 4 patients excluded from the All Asciminib Safety Pool due to missing aGFR at baseline (SCS Section 5.1.1.5).
Patients with severe renal disease are excluded from the clinical development program as a standard precaution (Table 2-18).
Strata are described within Section 2.3.
Source : EU RMP Version 4.0 Attachment to Annex 7-Table 5-4

Table 2-16 Exposure of special populations either included or not included in clinical trial development programs (3L+ therapy - safety set)

	CABL001A2301				Safety Pool	
	Bosutinib 500 mg q.d. N=76		Asciminib 40 mg b.i.d. N=156		Asciminib All subjects N=356	
Special population	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**
Subjects with mild renal impairment	31 (40.8)	29.2	60 (38.5)	137.1	142 (39.9)	459.9
Subjects with moderate renal impairment	4 (5.3)	6.0	10 (6.4)	17.0	30 (8.4)	97.6

Subject-treatment years is the sum of each subject's treatment exposure in years; STY is based on the number of subjects in each category.

Note: Moderate: 30-59.9 ml/min, Mild: 60-89.9 ml/min, Normal: ≥90 ml/min or higher aGFR.

All subjects with moderate renal impairment had baseline aGFR ≥50 ml/min (subjects with aGFR < 50 ml/min were excluded from the clinical development program).

Five subjects in the Asciminib Safety Pool were excluded due to missing aGFR at baseline. There are 5 patients excluded in the Asciminib 3L+ Safety Pool due to missing aGFR at baseline (Section 2.3).

Source: Annex 7-Table 5-4.

Table 2-17 Exposure of special populations included or not in clinical trial development program: treatment of adult patients with Ph+ CML-CP with the T315I mutation (Safety set)

	Study X2101 Asciminib 200 mg b.i.d. – T315I mutation N=48	
Special population	**Patients n (%)**	**PTY**
Patients with renal disease		
Mild renal impairment	21 (43.8)	67.1
Moderate renal impairment	4 (8.3)	10.5

PTY is the sum of each patient's treatment exposure in years. PTY is based on the number of patients in each category.

Moderate: 30-59.9 mL/min, Mild: 60-89.9 mL/min.

Source: Attachment to Annex 7-Table 5-4b

2.5 Part II: Module SV: Post-authorization experience

2.5.1 Part II Module SV.1. Post-authorization exposure

2.5.1.1 Part II Module SV.1.1 Method used to calculate exposure

An estimate of subject exposure is calculated based on worldwide sales volume in milligrams (mg) of active substance sold during the PSUR reporting interval and based on the recommended total daily dose of 80 mg as per the CDS. The number of subjects with the T315I mutation and treated with 200 mg b.i.d. is very limited, as this mutation is rare.

Subject treatment years = Quantity of asciminib sold (mg)/ (recommended total daily dose* 365)

2.5.1.2 Part II Module SV.1.2. Exposure

The estimated exposure and cumulative exposure is provided in Table 2-22 and Table 2-23, respectively.

The patient exposure based on indications and demographics (i.e., age, sex) could not be estimated, as the specific data are not available.

Table 2-18 Estimated post marketing (non-clinical trial) exposure

Formulation	Cumulative till 28-Apr-2024	
	Amount sold (in mg)	Estimated exposure (PTY)
Asciminib FCT 20 mg	[redacted]	578
Asciminib FCT 40 mg	[redacted]	7,023
Total	[redacted]	7,601

FCT: Film-coated tablets; mg: milligrams; MS: Microsoft; PTY: Patient treatment years

Source of data: Worldwide sales volume from company database. This table includes sales data cumulatively till 28-Apr-2024. There are no sales data for 100 mg FCT anywhere in the world.

The values in this table are calculated by using formulas in MS Excel. The sum up values may not match the total, as the figures are rounded off to whole number.

The data provided in the table is the cumulative data of all the patients.

Source: PSUR (29-Oct-2023 to 28-Apr-2024)

Table 2-19 Cumulative exposure from marketing experience

	EEA (in PTY)	USA and Canada (in PTY)	Japan (in PTY)	ROW[&] (in PTY)
FCT 20 mg	92	[redacted]	[redacted]	31
FCT 40 mg	1927	[redacted]	[redacted]	1127
Total	2018	[redacted]	[redacted]	1158

EEA: European Economic Area; FCT: Film-coated tablets; ROW: Rest of the World; USA: United States of America. This table includes data obtained cumulatively till 30-Apr-2024.

Note: [&]Sales from the United Kingdom and Switzerland are considered under ROW.

The values in this table are calculated by using formulas in MS Excel. The sum up values may not match the total, as the figures are rounded off to whole number.

Source of data: worldwide sales volume

Source: PSUR (29-Oct-2023 to 28-Apr-2024)

2.6 Part II: Module SVI: Additional EU requirements for safety specifications

2.6.1 Potential for misuse for illegal purposes

No recreational or abuse potential has been identified for this product.

2.7 Part II: Module SVII: Identified and potential risks

2.7.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

2.7.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

The safety data for asciminib were reviewed in light of the updated Good Pharmacovigilance Practice Module V (Revision 2; Mar-2017). Based on the revised definition of "important" safety concern, the list of risks and the related adverse reactions in the Summary of Product Characteristics (SmPC) that were not considered important for inclusion in the list of safety concerns in the RMP and the reasons for non-inclusion are provided below:

Table 2-20 Risks not considered important for inclusion in the list of safety concerns

Risk	Reason for not being an important risk
Gastrointestinal toxicity	Known risks that require no further characterization and are followed up via routine pharmacovigilance, namely, through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member State where the product is authorized). **Data from non-clinical studies** In non-clinical studies, minimal mucosal hypertrophy/hyperplasia changes were observed with 30-fold or 22-fold higher than that achieved in patients with the 40 mg b.i.d. or 80 mg q.d. dose of asciminib, respectively. **Data from Study A2301 Primary endpoint analysis** Primary endpoint analysis data from Study A2301 demonstrated that GI toxicity events were predominantly diarrhea, nausea, and vomiting. These events occurred in a lower proportion of patients in the asciminib treatment group compared with the bosutinib treatment group; most of these reported AEs were grade 1 or 2 and were reversible. No patient required dose reduction or drug withdrawal due to GI toxicity in the asciminib treatment group. Drug interruption was less frequent in the asciminib treatment group due to GI toxicity vs bosutinib treatment group (4.5% vs 13.2%, respectively). Concomitant medication for management of these events was needed in 15.4% of patients in the asciminib treatment group, as compared to 57.9% patients in bosutinib group (Study A2301 Primary endpoint analysis-Section 12.3.7.6). **Data from Study X2101 Primary analysis** Primary analysis data from Study X2101 demonstrated that the majority of AEs are mild to moderate and were manageable with routine clinical practice guidelines. The most frequently reported AEs were nausea, diarrhea, vomiting, abdominal pain, constipation and upper abdominal pain. No life-threatening events were reported and only 1 event led to

Risk	Reason for not being an important risk
	permanent discontinuation (Study X2101 Primary analysis-Section 12.3.1.8). **Data from Study X2101 Supplement** Data from Study X2101 supplement showed that the incidence of GI toxicity events suspected to be treatment related increased by 2 patients and grade 3 events increased by 1 new patient; no increases in the incidence was noted for SAEs, grade 4 or 5 or AEs leading to study treatment discontinuation since the previous cut-off (Annex 7-Table 2.11_wk96). **Data of Safety Pools from Study A2301 Primary endpoint analysis and Study X2101 Primary analysis** In asciminib All patients Safety Pool, the incidence in the asciminib 40 mg b.i.d. Safety Pool was 37.4%, similar to the incidence observed in the asciminib treatment group in Study A2301 (31.4%). A higher incidence of GI toxicity events was noted in the asciminib All patients Safety Pool (47.8%) relative to the asciminib treatment group in Study A2301; this was primarily attributable to higher incidences of the following events: nausea, diarrhea, vomiting, abdominal pain, and constipation (Annex 7-Table 2.1-1). **Data from Week-96 analysis** **Study A2301 asciminib 40 mg b.i.d. dose:** Fifty-two patients (33.3%), an increase of 3 patients in the asciminib treatment group since the Week-24 cut-off, had AEs related to GI toxicity; 1 grade 3 non-cardiac chest pain in a patient, which occurred together with dizziness, dyspnea, and fatigue (all grade 2), considered by Investigator as related to a severe panic attack (Annex 7-Listing 14.3.2-6_wk96). No increases were noted in the incidence of grade 4 events, SAEs, and AEs leading to study treatment discontinuation due to GI toxicity events since the Week-24 cut-off (Annex 7-Table 14.3.1-14_wk96), (Annex 7-Table 2.1-1). **Asciminib Safety Pools:** In the asciminib 40 mg b.i.d. and asciminib All patients Safety Pool, 73 patients (39.0%; increase of 3 patients) and 176 patients (49.4%; increase of 6 patients) respectively had GI toxicity events. In both the asciminib safety pools, the incidences of treatment related AEs, SAEs, grade ≥ 3 AEs, and AEs leading to study treatment discontinuation remained consistent (with differences not exceeding 2%) with those reported in the primary analyses (Annex 7-Table 2.1-1, Annex 7-Table 2.1-1_wk96).
Hypersensitivity	Risks with minimal clinical impact on patients (in relation to the severity of the indication treated) **Data from non-clinical studies** Hypersensitivity was not evident in non-clinical studies. **Data from Study A2301 Primary endpoint analysis** Patients with known or suspected hypersensitivity to investigational medicinal product or any of its excipients were excluded from Study A2301. Primary endpoint analysis showed that most of the hypersensitivity events observed in Study A2301 and in the asciminib Safety Pool were grade 1/2 skin disorders (primarily rash), which recovered without change / interruption in the asciminib dosage regimen (Study A2301 Primary endpoint analysis-Section 12.3.7.3). **Data from Study X2101 Primary analysis**

Risk	Reason for not being an important risk
	One patient in Study X2101 (in the 150 mg b.i.d. cohort) had a grade 5 circulatory collapse. Ten days after study treatment discontinuation due to lack of efficacy, the patient had tumor lysis syndrome (grade 4), and upper gastrointestinal hemorrhage (grade 3), along with 3 episodes of circulatory collapse which was not caused due to hypersensitivity reaction. The patient died on the same day due to leukemia (circulatory collapse was contributory factor). Another patient (having history of heart failure and hypertension) in the 80 mg q.d. cohort experienced grade 3 circulatory collapse, not caused due to hypersensitivity reaction (Study X2101 Primary analysis-Section 12.3.1.8). Two cases of hypersensitivity were identified resulting in the permanent discontinuation of asciminib in Study X2101. One patient (200 mg b.i.d. cohort), having history of asthma and hypersensitivity, reported grade 3 bronchospasm; while another patient (40 mg b.i.d. cohort), having history of hypersensitivity and obliterative bronchiolitis, experienced grade 2 urticaria due to allergic reaction following asciminib administration (Study X2101 Primary analysis-Section 12.3.1.8). **Data from Study X2101 Supplement** The supplement data also showed that the number of patients did not increase for SAEs and grade ≥ 3 AEs and AEs leading to study treatment discontinuation (Annex 7-Table 2.1-1_wk96). **Data of Safety Pools from Study A2301 Primary endpoint analysis and Study X2101 Primary analysis** In asciminib All patients Safety Pool, the incidence of hypersensitivity events was similar in the asciminib 40 mg b.i.d. Safety Pool and the asciminib treatment group in Study A2301. However, a higher incidence, primarily due to rash was observed in the asciminib All patients Safety Pool (29.5%), relative to that reported in Study A2301 (17.9%). In the asciminib All patients Safety Pool, the incidence of individual hypersensitivity events was low with the exception of rash (14.6%). As discussed in the Study X2101 above, 1 patient had a fatal circulatory collapse. Investigator did not suspect a relationship between circulatory collapse and asciminib (Annex 7-Table 2.1-1). **Data from Week-96 analysis** **Study A2301 asciminib 40 mg b.i.d. dose:** Thirty-two patients (20.5%), an increase of 4 patients in the asciminib treatment group since the Week-24 cut-off, had AEs related to hypersensitivity. There was an increase of 1 patient with a treatment-related AE (rash maculopapular). No increases were noted in the incidence of grade 3 events, grade 4 events, SAEs, and AEs leading to study treatment discontinuation since the Week-24 cut-off (Annex 7-Table 14.3.1-14_wk96, Annex 7-Table 2.1-1). **Asciminib Safety Pools:** In the asciminib 40 mg b.i.d. and asciminib All patients Safety Pool, 44 patients (23.5%; increase of 4 patients) and 111 patients (31.2%; increase of 6 patients), respectively had hypersensitivity related events. In both the asciminib safety pools, the incidences of treatment-related AEs, SAEs, grade ≥ 3 AEs, and AEs leading to study treatment discontinuation remained consistent (with differences not exceeding 2%) with those reported in the primary analyses (Annex 7-Table 2.1-1, Annex 7-Table 2.1-1_wk96).
Phototoxicity	Known risks that do not impact the risk-benefit profile **Data from non-clinical studies**

Risk	Reason for not being an important risk
	A phototoxic potential of asciminib was identified in in vitro. In mice, asciminib showed dose dependent phototoxic effects starting at 200 mg/kg/day. At the NOAEL (60 mg/kg/day), the exposure was 15fold or 6fold higher than the exposure in patients, at the recommended dose of 40 mg b.i.d. or 80 mg q.d., respectively, based on Cmax in plasma. **Data from Study A2301 Primary endpoint analysis and from Study X2101 Primary analysis** No events related to phototoxicity were reported in Study A2301. In primary analysis of Study X2101, no grade 3/4 event or SAEs related to phototoxicity were reported with asciminib monotherapy during the treatment of patients with CML-CP/AP. The reported AEs were mild in severity (grade 1/2), and majority recovered without any change in the dose of asciminib. These events are manageable with routine clinical practice guidelines, and do not impact the benefit-risk profile of the drug (Study A2301 Primary endpoint analysis–Section 12.3.7.3, Study X2101 Primary analysis-Section 12.3.1.8, Annex 7-Table 2.11). **Data of Safety Pools from Study A2301 Primary endpoint analysis and Study X2101 Primary analysis** In the asciminib 40 mg b.i.d. Safety Pool, 2 patients (1.1%) and in the asciminib All patients Safety Pool 11 patients (3.1%) had phototoxicity events. None of these events were of grade ≥ 3 severity and none was SAE. Events in the asciminib 40 mg b.i.d. Safety Pool were photosensitivity reaction and sunburn (each in 1 patient), of which photosensitivity reaction was suspected to be treatment related (as assessed by the investigator). The events in the asciminib All patients Safety Pool were photosensitivity reaction (2.2%; 8 patients), sunburn (0.8%; 3 patients) and retinal phototoxicity (0.3%, 1 patient). Treatment related AEs were noted in 5 patients (1.4%; 4 patients with photosensitivity and 1 retinal phototoxicity) (Annex 7-Table 2.1-1). **Data from Week-96 analysis** **Study A2301 asciminib 40 mg b.i.d. dose:** There were no additional cases of phototoxicity observed in Study A2301 since the Week-24 cut-off (Annex 7-Table 14.3.1-14_wk96, Annex 7-Table 2.1-1). **Asciminib Safety Pools**: In the asciminib 40 mg b.i.d. and asciminib All patients Safety Pool, 2 patients (1.1%; no new patients) and 12 patients (3.4%; increase of 1 patient), respectively had phototoxicity events. In both the asciminib Safety Pools, the incidences of treatment-related AEs, SAEs, grade ≥ 3 AEs, and AEs leading to study treatment discontinuation remained consistent (with differences not exceeding 2%) with those reported in the primary analyses (Annex 7-Table 2.1-1, Annex 7-Table 2.1-1_wk96).

2.7.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 2-21 Important identified risks

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
Acute pancreatitis (including isolated pancreatic enzyme elevations)	Non-clinical studies in dogs demonstrated pancreatic acinar atrophy at AUC exposure equivalent to those achieved in patients at 40 mg b.i.d. or 80 mg q.d. dose. In clinical experience, very common events of laboratory abnormalities (lipase and amylase increase) and common clinical events (pancreatitis and pancreatitis acute) were assessed as related to asciminib treatment. There is potential of acute pancreatitis to become fulminant or chronically intermittent, which may lead to necrotizing pancreatitis with a fatal outcome. Considering the potential mild to moderate impact on the benefit-risk of asciminib, acute pancreatitis (including isolated pancreatic enzyme elevations) is considered as important identified risk.
Myelosuppression	A minimal to mild, regenerative reduction in red blood cells mass in rat, dog and monkey has been observed and was consistent with a regenerative, extravascular, hemolytic anemia. However, myelosuppression was not evident in non-clinical studies with asciminib. Myelosuppression, including thrombocytopenia, anaemia and neutropenia is an on-target effect of asciminib, and it could be related to the therapeutic action of the drug. In the clinical experience, a high incidence of events (including grade 3/4 events) was observed with asciminib. However, these were manageable with dose modifications and standard clinical practice guidelines. Thrombocytopenia has potential for hemorrhagic events, and neutropenia is a risk factor for infections. Considering the wide-ranging possible implications (which sometimes might be life-threatening or fatal) of myelosuppressive action of asciminib, there is a potential moderate impact on the benefit-risk profile of the drug and is therefore, considered as an important identified risk.
QTc prolongation	Review of nonclinical data showed that IC50 for asciminib in the hERG patch clamp assay was 11.4 µM, which translates into a wide clinical safety margin at therapeutic doses (40 mg b.i.d. and 80 mg q.d.), Moderate cardiovascular effects were observed in the non-clinical studies in dogs; however, no episodes of QTc prolongation were observed. Concentration-QTcF analysis of data from Study X2101 identified a positive relationship with asciminib treatment. However, estimated mean and upper bound of the 90% CI QTcF increase did not exceed 10 ms (regulatory threshold for clinical significance) at any of the therapeutic doses. Two patients (non-serious, grade 1 and grade 3) reported an AE of electrocardiogram QT prolonged in Study A2301, which were not associated other clinical signs/symptoms of arrhythmia. Also, in Study CABL001A2107, 3 healthy subjects experienced electrocardiogram QT prolonged (> 60 ms from the lowest baseline value) within 1 hour following administration of asciminib single dose (40 mg) in combination with quinidine. These events were not associated with clinical signs or symptoms and resolved following discontinuation of study treatment.

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
	Considering the events reported in the clinical studies, and the potential impact of its sequelae on the benefit-risk balance for an individual patient (including Torsades de Pointes), QTc prolongation is considered as an important identified risk.

Table 2-22 Important potential risks

Risk	Risk-benefit impact (Reasons for classification as important potential risk)
Hepatotoxicity	In animal studies, elevations in liver enzymes and/or bilirubin were observed. Alongside, histopathological findings included centrilobular hepatocyte hypertrophy, bile duct hyperplasia and increased individual hepatocyte necrosis at an exposure equivalent to human exposure of 40 mg b.i.d. or 80 mg q.d. dose. There have been reports of mild to moderate reversible hepatic enzyme abnormalities and blood bilirubin increase in clinical studies. However, these abnormalities were not associated with clinically relevant events. There was no evidence of progressive or irreversible liver damage with asciminib. Elevation of liver enzymes may be a manifestation of potential liver injury. Considering this, the risk of hepatotoxicity is considered as an important potential risk.
Hepatitis B virus infection reactivation	Reactivation of HBV has occurred in patients who are chronic carriers of this virus following administration of other BCR::ABL TKIs. However, the clinical evidence is limited due to exclusion of such patients from the clinical development program. Considering the class effect observed with other TKIs, this risk could have a potential low impact on the benefit-risk profile of asciminib and is considered an important potential risk.
Reproductive toxicity	Non-clinical data provides evidence towards the fetal malformation due to in-utero exposure to asciminib. However, limited human exposure in this patient population preclude comprehensive assessment of the risk for humans. Considering the moderate to high implications for individual health (miscarriage, fetus survival/fetal abnormalities), this risk could have moderate to severe impact on the benefit-risk profile of asciminib and is considered as an important potential risk.

Table 2-23 Missing information

Missing information	Risk-benefit impact (Reasons for classification as missing information)
Long-term safety	Asciminib is potentially a life-long treatment, with limited knowledge of long-term safety concerns. In Study A2301, the exposure data for at least 192 weeks in 3 (1.9%) out of 156 patients are available; the median duration of exposure for asciminib was 103.14 weeks (Annex 7-Table 1.2-1_wk96). In the Safety Pool comprising of all subjects who took asciminib monotherapy (N=356) in Study A2301 and Study X2101, the exposure data is available for at least 192 weeks in 81 (22.8%) out of 356 patients; overall, the median duration of exposure to asciminib single agent in Safety Pool 356 patients with CML-CP/-AP was 115.57 weeks (Annex 7-Table 1.2-1_wk96).

Missing information	Risk-benefit impact (Reasons for classification as missing information)
	Limited long-term safety information is available for asciminib.
Use in patients with renal impairment	A study (CABL001A2105) assessed the effect of severe renal impairment on the PK of asciminib. The exposure of asciminib (AUCinf) increased by 56% in patients with severe renal impairment compared with patients with normal renal function. The Cmax and the time to reach maximum plasma concentration values were similar in both cohorts, suggesting there was no difference in the absorption of the drug. Patients having mild or early stages of moderate renal impairment were allowed for inclusion in the clinical development program (Study A2301: patients having mild or moderate renal impairment [up to creatinine clearance ≥ 50 mL/min] were allowed; Study X2101: patients having creatinine < 1.5 × ULN were allowed). In the All patients Safety Pool (N=351), no difference (> 10%) is observed in the incidence of Adverse Event of Special Interest (AESIs) in patients having mild renal impairment (N=142) as compared to normal renal function (N=179). However, a higher incidence (> 10%) of certain AESIs (edema and fluid retention and myelosuppression [including erythropenia and leukopenia]) has been observed in patients with moderate renal impairment (N=30) as compared to patients with normal renal function (N=179) (Annex 7-Table 5.1-8.3_wk96). Of note, fluid retention and anemia are very common co-manifestation of chronic renal impairment and are consistent with the classic symptomatology of renal impairment. Considering the small number of patients with baseline moderate renal impairment in the All patients Safety Pool (N=30), it is currently not clear if asciminib use in patients with renal impairment is associated with a higher risk for AEs. Considering this, the safety concern of 'Use in patients with renal impairment' is considered missing information for asciminib.
Use in patients with hepatic impairment	A dedicated study in patients with hepatic impairment (Study CABL001A2103) was conducted and results showed no relevant impact of mild or moderate hepatic impairment on the pharmacokinetics (PK) of asciminib. Asciminib exposure (AUCinf) increased by 22% (higher exposure was mainly driven by 1 patient), 3% and 66% in patients with mild, moderate and severe hepatic impairment, respectively, compared to patients with normal hepatic function. However, considering the large therapeutic window of the drug, this is not considered clinically relevant. Additionally, patients with mild hepatic impairment (by National Cancer Institute [NCI] criteria) were included in the development program of asciminib. In the All patients Safety Pool (N=356), a higher incidence (> 10%) of certain AESIs (hypersensitivity, GI toxicity, myelosuppression, and pancreatic toxicity) has been observed in patients with mild hepatic impairment (N=48) as compared to patients with normal hepatic function (N=308) (Annex 7-Table 5.1-8.7_w k96). There was no difference though in the frequency and severity of the hepatic toxicity events (including severity) in asciminib treatment patients with mild hepatic impairment compared to those patients with normal hepatic function. Considering the low number of patients having mild hepatic impairment (N=48), it is currently not clear if asciminib use in patients with hepatic impairment is associated with a higher risk for

Missing information	Risk-benefit impact (Reasons for classification as missing information)
	AEs.

2.7.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

There are no new safety concerns and reclassification in this RMP version.

2.7.2.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

2.7.2.1.1 Important Identified Risk: acute pancreatitis (including isolated pancreatic enzyme elevations)

Table 2-24 Clinical trial data of acute pancreatitis (including isolated pancreatic enzyme elevations) (1L therapy - Safety set)

	Study J12301						Safety Pool
	Asimina			IS-TKI			
Acute pancreatitis (including isolated pancreatic enzyme elevations)	Imatinib stratum N=100 n (%) (95% CI)	2G-TKI stratum N=100 n (%) (95% CI)	All asciminib N=200 n (%) (95% CI)	Imatinib stratum N=99 n (%) (95% CI)	2G-TKI stratum N=102 n (%) (95% CI)	All comparators N=201 n (%) (95% CI)	All Asciminib N=556 n (%) (95% CI)
No. pts ≥ 1 event	21 (21.0) (13.4, 30.2)	8 (8.0) (3.6, 15.2)	29 (14.5) (10.0, 20.2)	16 (16.2) (9.6, 25.0)	18 (17.6) (10.8, 26.4)	34 (16.9) (12.0, 22.8)	114 (20.5) (17.2, 24.2)
Asciminib vs. IS-TKI Risk diff. (95% CI):			-2.42 (-12.23, 7.28)				_
Exposure-adjusted overall incidence:							
n (EAIR / 100 PTY)	21 (13.3)	8 (3.9)	29 (8.0)	16 (12.4)	18 (10.5)	34 (11.3)	114 (9.5)
Cumulative incidence proportion at: n (%) cum IP							
Week 8 (Day 56)	13 (13.0) 13.00	2 (2.0) 2.00	15 (7.5) 7.50	12 (12.1) 12.12	6 (5.9) 5.88	18 (9.0) 8.96	54 (9.7) 9.71
Week 24 (Day 168)	19 (19.0) 19.00	3 (3.0) 3.00	22 (11.0) 11.00	14 (14.1) 14.14	11 (10.8) 10.78	25 (12.4) 12.44	80 (14.4) 14.39
Week 48 (Day 336)	21 (21.0) 21.00	3 (3.0) 3.00	24 (12.0) 12.00	14 (14.1) 14.14	11 (10.8) 10.78	25 (12.4) 12.44	95 (17.1) 17.09
Week 96 (Day 672)	21 (21.0) 21.00	8 (8.0) 8.00	29 (14.5) 14.50	16 (16.2) 16.16	15 (14.7) 14.71	31 (15.4) 15.42	105 (18.9) 18.88
Asciminib vs. IS-TKI Risk diff. (95% CI):							

	Study J12301						Safety Pool
	Asimina			IS-TKI			
Acute pancreatitis (including isolated pancreatic enzyme elevations)	**Imatinib stratum N=100 n (%) (95% CI)**	**2G-TKI stratum N=100 n (%) (95% CI)**	**All asciminib N=200 n (%) (95% CI)**	**Imatinib stratum N=99 n (%) (95% CI)**	**2G-TKI stratum N=102 n (%) (95% CI)**	**All comparators N=201 n (%) (95% CI)**	**All Asciminib N=556 n (%) (95% CI)**
Week 8 (Day 56)			-1.46 (-11.25, 8.27)				–
Week 24 (Day 168)			-1.44 (-11.25, 8.27)				–
Week 48 (Day 336)			-0.44 (-10.26, 9.27)				–
Week 96 (Day 672)			-0.92 (-10.75,8.77)				-
No. pts ≥ 1 event by PT: n (%)							
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)
Hyperlipasaemia	0	0	0	0	0	0	4 (0.7)
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)**
Lipase increased	4 (4.0)	0	4 (2.0)	2 (2.0)	5 (4.9)	7 (3.5)	37 (6.7)
Amylase increased	0	0	0	0	0	0	7 (1.3)
Hyperlipasaemia	0	0	0	0	0	0	4 (0.7)
Pancreatitis	0	1 (1.0)	1 (0.5)	1 (1.0)	0	1 (0.5)	4 (0.7)
Pancreatitis acute	0	0	0	1 (1.0)	0	1 (0.5)	1 (0.2)
Grade 4 AEs	**2 (2.0)**	**0**	**2 (1.0)**	**0**	**1 (1.0)**	**1 (0.5)**	**11 (2.0)**
Lipase increased	2 (2.0)	0	2 (1.0)	0	0	0	10 (1.8)
Amylase increased	0	0	0	0	1 (1.0)	1 (0.5)	1 (0.2)
Grade 5 AEs	**0**	**0**	**0**	**0**	**0**	**0**	**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)**
Lipase increased	16 (16.0)	6 (6.0)	22 (11.0)	13 (13.1)	13 (12.7)	26 (12.9)	77 (13.8)
Amylase increased	8 (8.0)	1 (1.0)	9 (4.5)	3 (3.0)	5 (4.9)	8 (4.0)	43 (7.7)
Pancreatitis	0	1 (1.0)	1 (0.5)	1 (1.0)	0	1 (0.5)	9 (1.6)
Hyperlipasaemia	0	0	0	0	0	0	4 (0.7)
Pancreatitis acute	1 (1.0)	0	1 (0.5)	0	0	0	3 (0.5)
SAEs	**1 (1.0)**	**1 (1.0)**	**2 (1.0)**	**1 (1.0)**	**0**	**1 (0.5)**	**7 (1.3)**
Pancreatitis	0	1 (1.0)	1 (0.5)	1 (1.0)	0	1 (0.5)	3 (0.5)
Pancreatitis acute	1 (1.0)	0	1 (0.5)	1 (1.0)	0	1 (0.5)	3 (0.5)
Lipase increased	1 (1.0)	0	1 (0.5)	0	0	0	1 (0.2)

Acute pancreatitis (including isolated pancreatic enzyme elevations)	Study J12301 Asimina Imatinib stratum N=100 n (%) (95% CI)	Asimina 2G-TKI stratum N=100 n (%) (95% CI)	Asimina All asciminib N=200 n (%) (95% CI)	IS-TKI Imatinib stratum N=99 n (%) (95% CI)	IS-TKI 2G-TKI stratum N=102 n (%) (95% CI)	IS-TKI All comparators N=201 n (%) (95% CI)	Safety Pool All Asciminib N=556 n (%) (95% CI)
Amylase increased	0	0	0	0	0	0	1 (0.2)
Action taken							
Drug withdrawn	3 (3.0)	0	3 (1.5)	1 (1.0)	0	1 (0.5)	13 (2.3)
Drug adjusted	0	0	0	0	0	0	21 (3.8)
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)
Medication or therapy taken	1 (1.0)	1 (1.0)	2 (1.0)	0	0	0	9 (1.6)
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)
Recovered/resolved with sequelae	0	0	0	0	0	0	1 (0.2)
Missing	0	0	0	0	0	0	1 (0.2)

Number (N) represent counts of pts (patients). A patient may be counted in several rows for action taken and outcome.
EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event). Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100).
MedDRA Version 27.1, CTCAE Version 5.0, Case Retrieval Strategy version released 28-Nov-2024.
Source : Annex 7 EU RMP Version 4.0

Table 2-25 Clinical trial data of acute pancreatitis (including isolated pancreatic enzyme elevations) (3L+ therapy - Safety set)

Acute pancreatitis (including isolated pancreatic enzyme elevations)	CABL001A2301 Bosutinib 500 mg q.d. N=76 n (%) 95% CI	CABL001A2301 Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Safety Pool Asciminib All subjects N=356 n (%) 95% CI
No. pts ≥ 1 event	7 (9.2) (3.8, 18.0)	13 (8.3) (4.6, 13.8)	85 (23.9) (19.6,28.6)

Acute pancreatitis (including isolated pancreatic enzyme elevations)	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Exposure-adjusted overall incidence, n (EAIR per 100 STY)	7 (9.0)	13 (3.8)	85 (9.9)
Cumulative incidence proportion at n (%) cum IP			
Week 8 (Day 56)	1 (1.3) 1.32	7 (4.5) 4.49	39 (11.0) 10.96
Week 24 (Day 168)	4 (5.3) 5.26	10 (6.4) 6.41	58 (16.3) 16.29
Week 48 (Day 336)	6 (7.9) 7.89	12 (7.7) 7.69	71 (19.9) 19.94
Week 60 (Day 420)	7 (9.2) 9.21	12 (7.7) 7.69	71 (19.9) 19.94
Week 96 (Day 672)	7 (9.2) 9.21	13 (8.3) 8.33	76 (21.3) 21.35
No. pts ≥ 1 event by PT: n (%)			
Lipase increased	5 (6.6)	8 (5.1)	69 (19.4)
Amylase increased	4 (5.3)	9 (5.8)	42 (11.8)
Pancreatitis	0	0	8 (2.2)
Hyperlipasaemia	0	0	4 (1.1)
Pancreatitis acute	0	0	2 (0.6)
Maximum grade			
Grade 3 AEs	4 (5.3)	4 (2.6)	41 (11.5)
Lipase increased	4 (5.3)	4 (2.6)	33 (9.3)
Amylase increased	0	1 (0.6)	7 (2.0)
Hyperlipasaemia	0	0	4 (1.1)
Pancreatitis	0	0	3 (0.8)
Pancreatitis acute	0	0	1 (0.3)
Grade 4 AEs	0	2 (1.3)	9 (2.5)
Lipase increased	0	2 (1.3)	8 (2.2)
Amylase increased	0	0	1 (0.3)
Grade 5 AEs	0	0	0
Treatment-related AEs	3 (3.9)	8 (5.1)	66 (18.5)
Lipase increased	2 (2.6)	5 (3.2)	55 (15.4)
Amylase increased	1 (1.3)	7 (4.5)	34 (9.6)
Pancreatitis	0	0	8 (2.2)
Hyperlipasaemia	0	0	4 (1.1)
Pancreatitis acute	0	0	2 (0.6)
SAEs	0	0	5 (1.4)
Pancreatitis	0	0	2 (0.6)
Pancreatitis acute	0	0	2 (0.6)
Amylase increased	0	0	1 (0.3)

Acute pancreatitis (including isolated pancreatic enzyme elevations)	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Action taken			
Drug withdrawn	0	3 (1.9)	10 (2.8)
Dose adjusted	0	0	21 (5.9)
Drug interrupted	3 (3.9)	5 (3.2)	35 (9.8)
Dose not changed/NA/Unknown	6 (7.9)	12 (7.7)	76 (21.3)
Medication or therapy taken	0	0	7 (2.0)
AE outcome			
Recovered/resolved	7 (9.2)	13 (8.3)	83 (23.3)
Recovering/resolving	0	1 (0.6)	18 (5.1)
Not recovered/not resolved	1 (1.3)	2 (1.3)	21 (5.9)
Recovered/resolved with sequelae	0	0	1 (0.3)
Fatal	0	0	0
Unknown	0	0	0

Number (N) represent counts of patients. A patient may be counted in several rows for action taken and outcome.
EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event). Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100). MedDRA Version 26.0, CTCAE Version 4.03, Case Retrieval Strategy version released 22-Nov-2022.
Source: Annex 7-Table 4.2-6b.

Table 2-26 Clinical trial data of acute pancreatitis (including isolated pancreatic enzyme elevations): Patients with the T315I mutation treated with asciminib 200 mg b.i.d.

Acute pancreatitis (including isolated pancreatic enzyme elevations)	Study X2101 Asciminib 200 mg b.i.d. - T315I mutation N=48 n (%) (95% CI)
No. pts ≥ 1 event	15 (31.3) (18.6, 46.2)
Exposure-adjusted overall incidence:	
n (EAIR / 100 PTY)	15 (15.3)
Cumulative incidence proportion at: n (%) cum IP	
Week 8 (Day 56)	7 (14.6) 14.58
Week 24 (Day 168)	9 (18.8) 18.75
Week 48 (Day 336)	11 (22.9) 22.92

Acute pancreatitis (including isolated pancreatic enzyme elevations)	Study X2101 Asciminib 200 mg b.i.d. - T315I mutation N=48 n (%) (95% CI)
Week 60 (Day 420)	11 (22.9) 22.92
No. pts ≥ 1 event by PT: n (%)	
Lipase increased	14 (29.2)
Amylase increased	6 (12.5)
Hyperlipasaemia	1 (2.1)
Pancreatitis	1 (2.1)
Maximum grade	
Grade 3 AEs	**8 (16.7)**
Lipase increased	7 (14.6)
Amylase increased	2 (4.2)
Hyperlipasaemia	1 (2.1)
Grade 4 AEs	**3 (6.3)**
Lipase increased	3 (6.3)
Grade 5 AEs	**0**
Treatment-related AEs	**12 (25.0)**
Lipase increased	11 (22.9)
Amylase increased	5 (10.4)
Hyperlipasaemia	1 (2.1)
Pancreatitis	1 (2.1)
SAEs	**0**
Action taken	
Drug withdrawn	1 (2.1)
Dose adjusted	5 (10.4)
Drug interrupted	8 (16.7)
Dose not changed/NA/unknown	12 (25.0)
Medication or therapy taken	1 (2.1)
AE outcome	
Recovered/resolved	14 (29.2)
Recovering/resolving	3 (6.3)
Not recovered/not resolved	4 (8.3)
Recovered/resolved with sequelae	0
Fatal	0
Unknown	0

	Study X2101 Asciminib 200 mg b.i.d. - T315I mutation N=48 n (%) (95% CI)
Acute pancreatitis (including isolated pancreatic enzyme elevations)	

No. (n) represent counts of patients. A patient may be counted in several rows for action taken and outcome.
EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event). Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100). MedDRA Version 26.0, CTCAE Version 4.03, Case Retrieval Strategy version released 22-Nov-2022.
Source: Attachment to Annex 7-Table 5-6c

Table 2-27 Characterization of acute pancreatitis (including isolated pancreatic enzyme elevations)

Acute pancreatitis (including isolated pancreatic enzyme elevations)	**Details**
Potential mechanisms	The mechanism by which asciminib may cause increased levels of amylase and lipase, or pancreatitis is not understood.
Evidence source(s) and strength of evidence	There are very common events of laboratory abnormalities (increased lipase and amylase) and common clinical events (pancreatitis and pancreatitis acute) reported in clinical development program. Evidence sources characterizing the risk included Study J12301, Study A2301 and Study X2101; Study X2101 included patients with the T315I mutation (for more details, refer to Section 2.3).
Characterization of the risk	Non-clinical data Toxicity studies performed in rats, dogs and cynomolgus monkeys identified the pancreas as potential target tissue. Further details are provided in Table 2-5. Clinical data **Data from J12301 study**: Acute pancreatitis (including isolated pancreatic enzyme elevations) occurred at a similar frequency with asciminib vs. IS-TKIs (all grades: 14.5% vs. 16.9%; grade ≥ 3: 3.5% vs. 4.5%) and with imatinib (all grades: 16.2% and grade ≥ 3: 3.0%) and 2G-TKI (all grades: 17.6% and grade ≥ 3: 5.9%). ■ **Asciminib 80 mg q.d. (N=200):** When assessing PTs, occurrences of all individual acute pancreatitis events were comparable in patients treated with asciminib vs. IS-TKIs, and with imatinib and 2G-TKI. SAEs and events leading to drug interruption or drug withdrawal were low and comparable in all treatment groups. There was no patient with dose adjustment. Of note, there were 2 patients (1.0%) treated with asciminib with grade 4 increased lipase. There was 1 patient each (0.5%) treated with asciminib with clinical events of pancreatitis and acute pancreatitis.

Acute pancreatitis (including isolated pancreatic enzyme elevations)	Details
	■ **IS-TKI (N=201):** Only grade 4 increased amylase was reported in 1 patient. There were no other grade 4 events reported. When treated with IS-TKIs, clinical pancreatic toxicity was reported: 1 patient with acute pancreatitis and 1 patient with both pancreatitis and acute pancreatitis (SCS Section 2.6.5). **All Asciminib Safety Pool (N=556)** The overall incidence of patients treated with asciminib observed with Acute pancreatitis (including isolated pancreatic enzyme elevations) was: all grades, 20.5%; grade 3, 8.3%; grade 4, 2.0%. The 2 most frequent PTs were increased lipase at an incidence of 17.3% of patients and increased amylase at 9.5% of patients. SAEs were reported at 1.3% of patients; and the most frequent being pancreatitis (3 patients, 0.5%) and acute pancreatitis (3 patients, 0.5%). The reported events were managed with either dose adjustment (3.8%) or drug interruption (7.6%); alternatively, the dose was not changed/NA/unknown in 18.5% of patients. In general, this phenomenon was consistently observed, e.g., maximum grade 3 AEs, treatment-related AEs, dose adjusted, dose interruption, dose not changed, when reviewing the data in the All Asciminib Safety Pool (N=556) and in the Asciminib 3L+ Safety Pool (N=356). As shown, in the **Asciminib 3L+ Safety Pool (N=356)**, the incidence of Acute pancreatitis (including isolated pancreatic enzyme elevations) was: all grades, 23.9%; grade 3, 11.5%; grade 4, 2.5%. The most frequently observed events were increased lipase (19.4%) and increased amylase (11.8%). The number of patients with pancreatitis, hyperlipasemia, and pancreatitis acute were 8 patients, 4 patients, and 2 patients, respectively, in the Asciminib 3L+ Safety Pool. Events suspected to be treatment related by the Investigator were reported in 18.5% of patients in the Asciminib 3L+ Safety Pool. SAEs were reported in 1.4% of patients in the Asciminib 3L+ Safety Pool. The reported events were managed with either dose adjustment (5.9%) or drug interruption (9.8%). Treatment discontinuation was reported in 2.8% of patients in the Asciminib 3L+ Safety Pool. Acute pancreatitis (including isolated pancreatic enzyme elevations) was ongoing in 5.9% of patients in the Asciminib 3L+ Safety Pool, as of DCO. **Data from Study A2301 (end of treatment) and Study X2101 (final analysis)** **Study A2301 asciminib 40 mg b.i.d. dose:** Acute pancreatitis grouped adverse events (AEs) (including isolated pancreatic enzyme elevations) occurred in similar proportions of patients in

Acute pancreatitis (including isolated pancreatic enzyme elevations)	Details
	the asciminib arm (8.3% all grades; grade 3, 2.6%; grade 4, 1.3%) and in the bosutinib arm (9.2% all grades; grade 3, 5.3%); grade 4, patients0%). The events were suspected to be treatment related in 8 patients (5.1%) in the asciminib arm and 3 patients (3.9%) in the bosutinib arm. None of these events were serious. Patients with acute pancreatitis grouped AEs (including isolated pancreatic enzyme elevations) were managed with drug interruption in 5 (3.2%) patients in asciminib arm and 3 (3.9%) patients in bosutinib arm. Treatment discontinuation was reported in 3 (1.9%) patients in the asciminib arm. Acute pancreatitis (including isolated pancreatic enzyme elevations) events were ongoing in 2 (1.3%) patients in the asciminib arm and in 1 (1.3%) patient in the bosutinib arm. No clinical events for Pancreatic toxicity were reported (Study A2301 EOT report-Section 12.2.7 and Study A2301 EOT report-Table 12-10). The Exposure-adjusted overall incidence for acute pancreatitis (including isolated pancreatic enzyme elevations) events were 3.8 per 100 STY in the asciminib arm and 9.0 per 100 STY in the bosutinib arm. Study X2101 asciminib 80 mg q.d. dose group: Acute pancreatitis grouped AEs (including isolated pancreatic enzyme elevations) occurred in 6 (33.3%) patients of which 3 patients (16.7%) had a Grade 3 event. All of the reported events were suspected to be treatment related. None of the reported events were serious. Patients with acute pancreatitis grouped AEs (including isolated pancreatic enzyme elevations) were managed with either dose adjustment (2 (11.1%) patients) or drug interruption (2 (11.1%) patients). No treatment discontinuation was reported. Acute pancreatitis (including isolated pancreatic enzyme elevations) events were ongoing in 2 (11.1%) patients. The exposure-adjusted overall incidence was 10.3 per 100 STY. Asciminib Safety Pools: The incidence of acute pancreatitis (including isolated pancreatic enzyme elevations) events was higher in the asciminib 40 mg b.i.d. safety pool (16% all grades; grade 3, 7%; grade 4, 2.1%) and asciminib all patient's safety pool (23.9% all grades; grade 3, 11.5%; grade 4, 2.5%) compared to the asciminib arm in Study A2301 (8.3% all grades; grade 3, 2.6%; grade 4, 1.3%). The cumulative incidence of acute pancreatitis (including isolated pancreatic enzyme elevations) events at all the time-points was higher (by at least 4.5%) compared to the asciminib treatment group in Study A2301. Most frequently observed events were lipase increase and amylase increase. The number of patients with pancreatitis, hyperlipasemia and pancreatitis acute were 2 patients, 2 patients and 1 patient in asciminib 40 mg b.i.d. Safety Pool and 8 patients, 4 patients and 2 patients in asciminib All patients Safety Pool, respectively.

Acute pancreatitis (including isolated pancreatic enzyme elevations)	**Details**
	The events suspected to be treatment related by Investigator were reported in 23 (12.3%) patients in the asciminib 40 mg b.i.d safety pool and 66 (18.5%) patients in asciminib all patient's safety pool. SAEs were reported in similar proportion of patients, 1.1% in asciminib 40 mg b.i.d safety pool and 1.4% in asciminib all patient's safety pool. The reported events were managed with either dose adjustment (3 (1.6%) patients in asciminib 40 mg b.i.d safety pool and 21 (5.9%) patients in asciminib all patient's safety pool) or drug interruption (12 (6.4%) patients in asciminib 40 mg b.i.d safety pool and 35 (9.8%) patients in asciminib all patient's safety pool). Treatment discontinuation was reported in 6 (3.2%) patients in asciminib 40 mg b.i.d safety pool and 10 (2.8%) patients in asciminib all patient's safety pool. Acute pancreatitis (including isolated pancreatic enzyme elevations) events were ongoing in 6 (3.2%) patients in asciminib 40 mg b.i.d safety pool and 21 (5.9%) patients in asciminib all patient's safety pool at the time of data cut-off. The exposure-adjusted overall incidence was 7.0 per 100 STY in asciminib 40 mg b.i.d safety pool and 9.9 per 100 STY in asciminib all patient's safety pool. **Study X2101: patients with the T315I mutation** **Asciminib 200 mg b.i.d. (N=48):** Acute pancreatitis (including isolated pancreatic enzyme elevations) occurred in 31.3% of patients with Ph+ CML-CP with the T315I mutation and who received asciminib 200 mg b.i.d. dose. Grade 3 events were reported in 16.7% and Grade 4 events in 6.3% of patients. The events suspected to be treatment related by the Investigator were reported in 25.0% of patients. No SAE occurred. The events were successfully managed by dose adjustment (16.7%) or dose interruptions (25.0%). Treatment discontinuation was low and was reported in 1 patient (2.1%). Acute pancreatitis (including isolated pancreatic enzyme elevations) was ongoing in 8.3% patients, as of DCO. The exposure-adjusted overall incidence was 15.3 / 100 PTY in patients with the T315I mutation.
Risk factors and risk groups	History of amylase and lipase elevation and pancreatitis.
Preventability	Serum lipase and amylase levels should be assessed monthly during treatment with asciminib, or as clinically indicated. Patients should be monitored for signs and symptoms of acute pancreatitis (including isolated pancreatic enzyme elevations). More frequent monitoring should be performed in patients with a history of pancreatitis. If lipase and amylase elevation are accompanied by abdominal symptoms, treatment should be temporarily withheld, and appropriate diagnostic tests should be considered to exclude pancreatitis.

Acute pancreatitis (including isolated pancreatic enzyme elevations)	Details
	Based on the severity of lipase and amylase elevation, the dose should be reduced, temporarily withheld or permanently discontinued.
Impact on the benefit-risk balance of the product	Amylase elevation and lipase elevation may be indicative of pancreatitis. Acute pancreatitis may become fulminant or chronically intermittent and can lead to necrotizing pancreatitis with a fatal outcome. Considering the potential serious impact of the reported events, there is mild to moderate impact on the benefit risk profile of asciminib.
Public health impact	Given the relatively low prevalence of CML in the overall population and the frequency of this risk, the potential public health impact is low.

2.7.2.1.2 Important identified risk: myelosuppression

Table 2-28 Clinical trial data of myelosuppression (1L therapy - Safety set)

	Study J12301						Safety Pool
	Asciminib			IS-TKI			
Myelosuppression	Imatinib stratum N=100 n (%) (95% CI)	2G-TKI stratum N=100 n (%) (95% CI)	All asciminib N=200 n (%) (95% CI)	Imatinib stratum N=99 n (%) (95% CI)	2G-TKI stratum N=102 n (%) (95% CI)	All comparators N=201 n (%) (95% CI)	All Asciminib N=556 n (%) (95% CI)
No. pts ≥ 1 event	41 (41.0) (31.2, 51.2)	46 (46.0) (36.0, 56.2)	87 (43.5) (36.6, 50.6)	51 (51.5) (41.2, 61.6)	65 (63.7) (53.6, 73.0)	116 (57.7) (50.6, 64.6)	220 (39.6) (35.4, 43.8)
Asciminib vs. IS-TKI							
Risk diff. (95% CI):			-14.21 (-23.94, -4.26)				–
Exposure-adjusted overall incidence							
n (EAIR / 100 PTY)	41 (34.0)	46 (36.5)	87 (35.3)	51 (65.9)	65 (74.7)	116 (70.6)	220 (19.5)
Cumulative incidence proportion at: n (%) cum IP							
Week 8 (Day 56)	39 (39.0) 39.00	42 (42.0) 42.00	81 (40.5) 40.50	46 (46.5) 46.46	51 (50.0) 50.00	97 (48.3) 48.26	175 (31.5) 31.47
Week 24 (Day 168)	40 (40.0) 40.00	44 (44.0) 44.00	84 (42.0) 42.00	49 (49.5) 49.49	58 (56.9) 56.86	107 (53.2) 53.23	199 (35.8) 35.79
Week 48 (Day 336)	40 (40.0) 40.00	45 (45.0) 45.00	85 (42.5) 42.50	50 (50.5) 50.51	61 (59.8) 59.80	111 (55.2) 55.22	208 (37.4) 37.41
Week 96 (Day 672)	41 (41.0) 41.00	45 (45.0) 45.00	86 (43.0) 43.00	51 (51.5) 51.52	64 (62.7) 62.75	115 (57.2) 57.21	211 (37.9) 37.95
Asciminib vs. IS-TKI							

	Study J12301						Safety Pool
	Asciminib			IS-TKI			
Myelosuppression	Imatinib stratum N=100 n (%) (95% CI)	2G-TKI stratum N=100 n (%) (95% CI)	All asciminib N=200 n (%) (95% CI)	Imatinib stratum N=99 n (%) (95% CI)	2G-TKI stratum N=102 n (%) (95% CI)	All comparators N=201 n (%) (95% CI)	All Asciminib N=556 n (%) (95% CI)
Risk diff. (95% CI):							
Week 8 (Day 56)			-7.76 (-17.65, 2.07)				–
Week 24 (Day 168)			-11.23 (-21.05, -1.32)				–
Week 48 (Day 336)			-12.72 (-22.50, -2.79)				–
Week 96 (Day 672)			-14.21 (-23.95,-4.27)				–
No. pts ≥ 1 event by PT: n (%)							
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)
Haemoglobin decreased	0	0	0	0	0	0	2 (0.4)
Anaemia macrocytic	0	0	0	0	0	0	1 (0.2)
Myelosuppression	0	0	0	0	0	0	1 (0.2)
Pancytopenia	0	0	0	0	0	0	1 (0.2)
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							

	Study J12301						Safety Pool
	Asciminib			IS-TKI			
Myelosuppression	Imatinib stratum N=100 n (%) (95% CI)	2G-TKI stratum N=100 n (%) (95% CI)	All asciminib N=200 n (%) (95% CI)	Imatinib stratum N=99 n (%) (95% CI)	2G-TKI stratum N=102 n (%) (95% CI)	All comparators N=201 n (%) (95% CI)	All Asciminib N=556 n (%) (95% CI)
Grade 3 AEs	**16 (16.0)**	**12 (12.0)**	**28 (14.0)**	**17 (17.2)**	**26 (25.5)**	**43 (21.4)**	**60 (10.8)**
Thrombocytopenia	7 (7.0)	2 (2.0)	9 (4.5)	3 (3.0)	6 (5.9)	9 (4.5)	23 (4.1)
Neutropenia	3 (3.0)	0	3 (1.5)	7 (7.1)	9 (8.8)	16 (8.0)	16 (2.9)
Neutrophil count decreased	3 (3.0)	5 (5.0)	8 (4.0)	5 (5.1)	4 (3.9)	9 (4.5)	12 (2.2)
Anaemia	1 (1.0)	1 (1.0)	2 (1.0)	4 (4.0)	5 (4.9)	9 (4.5)	11 (2.0)
Platelet count decreased	2 (2.0)	3 (3.0)	5 (2.5)	1 (1.0)	4 (3.9)	5 (2.5)	8 (1.4)
Lymphocyte count decreased	2 (2.0)	2 (2.0)	4 (2.0)	3 (3.0)	0	3 (1.5)	4 (0.7)
Lymphopenia	1 (1.0)	0	1 (0.5)	1 (1.0)	1 (1.0)	2 (1.0)	2 (0.4)
White blood cell count decreased	1 (1.0)	1 (1.0)	2 (1.0)	5 (5.1)	2 (2.0)	7 (3.5)	2 (0.4)
Febrile neutropenia	0	0	0	0	0	0	1 (0.2)
Leukopenia	0	0	0	3 (3.0)	3 (2.9)	6 (3.0)	1 (0.2)
Grade 4 AEs	**3 (3.0)**	**9 (9.0)**	**12 (6.0)**	**7 (7.1)**	**8 (7.8)**	**15 (7.5)**	**67 (12.1)**
Thrombocytopenia	2 (2.0)	4 (4.0)	6 (3.0)	0	1 (1.0)	1 (0.5)	40 (7.2)
Neutropenia	2 (2.0)	1 (1.0)	3 (1.5)	4 (4.0)	1 (1.0)	5 (2.5)	25 (4.5)
Platelet count decreased	1 (1.0)	4 (4.0)	5 (2.5)	1 (1.0)	3 (2.9)	4 (2.0)	14 (2.5)
Neutrophil count decreased	0	2 (2.0)	2 (1.0)	2 (2.0)	2 (2.0)	4 (2.0)	11 (2.0)
Leukopenia	0	0	0	1 (1.0)	0	1 (0.5)	1 (0.2)
Pancytopenia	0	0	0	0	0	0	1 (0.2)
Anaemia	0	0	0	0	1 (1.0)	1 (0.5)	0
Lymphopenia	0	0	0	1 (1.0)	0	1 (0.5)	0
Grade 5 AEs	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Treatment-related AEs	**37 (37.0)**	**42 (42.0)**	**79 (39.5)**	**47 (47.5)**	**59 (57.8)**	**106 (52.7)**	**178 (32.0)**
Thrombocytopenia	15 (15.0)	12 (12.0)	27 (13.5)	13 (13.1)	17 (16.7)	30 (14.9)	93 (16.7)
Neutropenia	11 (11.0)	9 (9.0)	20 (10.0)	16 (16.2)	14 (13.7)	30 (14.9)	68 (12.2)
Platelet count decreased	10 (10.0)	18 (18.0)	28 (14.0)	14 (14.1)	19 (18.6)	33 (16.4)	43 (7.7)
Neutrophil count decreased	11 (11.0)	17 (17.0)	28 (14.0)	16 (16.2)	20 (19.6)	36 (17.9)	43 (7.7)

	Study J12301						Safety Pool
	Asciminib			IS-TKI			
Myelosuppression	**Imatinib stratum N=100 n (%) (95% CI)**	**2G-TKI stratum N=100 n (%) (95% CI)**	**All asciminib N=200 n (%) (95% CI)**	**Imatinib stratum N=99 n (%) (95% CI)**	**2G-TKI stratum N=102 n (%) (95% CI)**	**All comparators N=201 n (%) (95% CI)**	**All Asciminib N=556 n (%) (95% CI)**
Anaemia	6 (6.0)	11 (11.0)	17 (8.5)	23 (23.2)	19 (18.6)	42 (20.9)	42 (7.6)
White blood cell count decreased	9 (9.0)	11 (11.0)	20 (10.0)	17 (17.2)	12 (11.8)	29 (14.4)	32 (5.8)
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)	3 (3.0)	9 (4.5)	12 (12.1)	2 (2.0)	14 (7.0)	9 (1.6)
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)	2 (2.0)	4 (2.0)	3 (3.0)	2 (2.0)	5 (2.5)	4 (0.7)
Febrile neutropenia	0	1 (1.0)	1 (0.5)	0	0	0	3 (0.5)
Anaemia macrocytic	0	0	0	0	0	0	1 (0.2)
Myelosuppression	0	0	0	0	0	0	1 (0.2)
Pancytopenia	0	0	0	0	0	0	1 (0.2)
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
SAEs	**0**	**1 (1.0)**	**1 (0.5)**	**1 (1.0)**	**2 (2.0)**	**3 (1.5)**	**7 (1.3)**
Thrombocytopenia	0	1 (1.0)	1 (0.5)	0	1 (1.0)	1 (0.5)	5 (0.9)
Febrile neutropenia	0	1 (1.0)	1 (0.5)	0	0	0	3 (0.5)
Platelet count decreased	0	0	0	1 (1.0)	0	1 (0.5)	2 (0.4)
Anaemia	0	0	0	0	1 (1.0)	1 (0.5)	1 (0.2)
Neutropenia	0	0	0	0	0	0	1 (0.2)
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)
Drug 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)
Medication or therapy taken	8 (8.0)	13 (13.0)	21 (10.5)	11 (11.1)	20 (19.6)	31 (15.4)	75 (13.5)
AE outcome							

	Study J12301						Safety Pool
	Asciminib			IS-TKI			
Myelosuppression	Imatinib stratum N=100 n (%) (95% CI)	2G-TKI stratum N=100 n (%) (95% CI)	All asciminib N=200 n (%) (95% CI)	Imatinib stratum N=99 n (%) (95% CI)	2G-TKI stratum N=102 n (%) (95% CI)	All comparators N=201 n (%) (95% CI)	All Asciminib N=556 n (%) (95% CI)
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)
Recovered/resolved with sequelae	0	0	0	0	0	0	1 (0.2)
Unknown	0	0	0	0	0	0	1 (0.2)
Missing	0	0	0	0	0	0	1 (0.2)

Number (N) represent counts of patients. A patient may be counted in several rows for action taken and outcome.
EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event). Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100). Myelosuppression includes Erythropenia, Leukopenia, Neutropenia, Thrombocytopenia, cytopenias affecting more than one lineage.

MedDRA Version 27.1, CTCAE Version 5.0, Case Retrieval Strategy version released 28-Nov-2024.

Source : Annex 7 EU RMP Version 4.0

Table 2-29 Clinical trial data of myelosuppression (3L+ therapy - Safety set)

Myelosuppression*	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
No. pts ≥ 1 event	28 (36.8) (26.0,48.6)	60 (38.5) (30.8, 46.6)	133 (37.4) (32.4, 42.6)
Exposure-adjusted overall incidence, n (EAIR per 100 STY)	28 (42.7)	60 (22.1)	133 (14.8)
Cumulative incidence proportion at n (%) cum IP			
Week 8 (Day 56)	20 (26.3) 26.32	50 (32.1) 32.05	94 (26.4) 26.40
Week 24 (Day 168)	26 (34.2) 34.21	58 (37.2) 37.18	115 (32.3) 32.30
Week 48 (Day 336)	26 (34.2) 34.21	58 (37.2) 37.18	123 (34.6) 34.55

Myelosuppression*	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Week 60 (Day 420)	27 (35.5) 35.53	58 (37.2)37.18	123 (34.6) 34.55
Week 96 (Day 672)	28 (36.8) 36.84	59 (37.8) 37.82	125 (35.1) 35.11
No. pts ≥ 1 event by PT: n (%)			
Thrombocytopenia	11 (14.5)	36 (23.1)	82 (23.0)
Neutropenia	13 (17.1)	30 (19.2)	56 (15.7)
Anaemia	6 (7.9)	16 (10.3)	45 (12.6)
Platelet count decreased	5 (6.6)	11 (7.1)	23 (6.5)
Neutrophil count decreased	4 (5.3)	8 (5.1)	19 (5.3)
White blood cell count decreased	3 (3.9)	3 (1.9)	12 (3.4)
Leukopenia	2 (2.6)	2 (1.3)	7 (2.0)
Lymphopenia	0	0	4 (1.1)
Febrile neutropenia	0	1 (0.6)	3 (0.8)
Haemoglobin decreased	0	0	2 (0.6)
Anaemia macrocytic	0	0	1 (0.3)
Lymphocyte count decreased	1 (1.3)	0	0
Monocyte count decreased	0	1 (0.6)	1 (0.3)
Myelosuppression	0	0	1 (0.3)
Pancytopenia	1 (1.3)	0	1 (0.3)
Normocytic anaemia	1 (1.3)	0	0
Maximum grade			
Grade 3 AEs	14 (18.4)	17 (10.9)	32 (9.0)
Neutropenia	5 (6.6)	8 (5.1)	13 (3.7)
Thrombocytopenia	3 (3.9)	10 (6.4)	14 (3.9)
Anaemia	2 (2.6)	0	9 (2.5)
Neutrophil count decreased	3 (3.9)	3 (1.9)	4 (1.1)
Platelet count decreased	2 (2.6)	3 (1.9)	3 (0.8)
Leukopenia	0	0	1 (0.3)
Febrile neutropenia	0	0	1 (0.3)
Lymphopenia	0	0	1 (0.3)
Myelosuppression	0	0	1 (0.3)
Lymphocyte count decreased	1 (1.3)	0	0
White blood cell count decreased	2 (2.6)	0	0
Grade 4 AEs	4 (5.3)	25 (16.0)	55 (15.4)
Thrombocytopenia	2 (2.6)	16 (10.3)	34 (9.6)
Neutropenia	1 (1.3)	12 (7.7)	22 (6.2)
Platelet count decreased	0	2 (1.3)	9 (2.5)

Myelosuppression*	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Neutrophil count decreased	0	3 (1.9)	9 (2.5)
Leukopenia	0	0	1 (0.3)
Pancytopenia	1 (1.3)	0	1 (0.3)
Grade 5 AEs	0	0	0
Treatment-related AEs	21 (27.6)	47 (30.1)	99 (27.8)
Thrombocytopenia	11 (14.5)	31 (19.9)	66 (18.5)
Neutropenia	11 (14.5)	24 (15.4)	48 (13.5)
Anaemia	3 (3.9)	8 (5.1)	25 (7.0)
Neutrophil count decreased	2 (2.6)	5 (3.2)	15 (4.2)
Platelet count decreased	3 (3.9)	8 (5.1)	15 (4.2)
White blood cell count decreased	1 (1.3)	3 (1.9)	12 (3.4)
Leukopenia	2 (2.6)	2 (1.3)	7 (2.0)
Lymphopenia	0	0	4 (1.1)
Febrile neutropenia	0	1 (0.6)	2 (0.6)
Anaemia macrocytic	0	0	1 (0.3)
Myelosuppression	0	0	1 (0.3)
Pancytopenia	1 (1.3)	0	1 (0.3)
Normocytic anaemia	1 (1.3)	0	0
SAEs	1 (1.3)	2 (1.3)	6 (1.7)
Thrombocytopenia	0	1 (0.6)	4 (1.1)
Febrile neutropenia	0	1 (0.6)	2 (0.6)
Platelet count decreased	0	1 (0.6)	2 (0.6)
Anaemia	0	0	1 (0.3)
Neutropenia	0	0	1 (0.3)
Pancytopenia	1 (1.3)	0	0
Action taken			
Drug withdrawn	4 (5.3)	6 (3.8)	10 (2.8)
Dose adjusted	3 (3.9)	9 (5.8)	24 (6.7)
Drug interrupted	13 (17.1)	36 (23.1)	52 (14.6)
Dose not changed/NA/Unknown	25 (32.9)	51 (32.7)	123 (34.6)
Medication or therapy taken	10 (13.2)	22 (14.1)	54 (15.2)
AE outcome			
Recovered/resolved	23 (30.3)	54 (34.6)	114 (32.0)
Recovering/resolving	16 (21.1)	32 (20.5)	65 (18.3)
Not recovered/not resolved	15 (19.7)	37 (23.7)	83 (23.3)
Recovered/resolved with sequelae	0	0	1 (0.3)
Fatal	0	0	0
Unknown	0	0	1 (0.3)

Myelosuppression*	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI

Number (N) represent counts of patients. A patient may be counted in several rows for action taken and outcome.

EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event).

Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100).

*Myelosuppression includes Erythropenia, Leukopenia, Thrombocytopenia, cytopenias affecting more than one lineage (Table 7-3).

MedDRA Version 26.0, CTCAE Version 4.03, Case Retrieval Strategy version released 22 Nov 2022.

Source: Annex 7-Table 5-6b.

Table 2-30 Clinical trial data of Myelosuppression: Patients with the T315I mutation (Safety Set)

Myelosuppression	CABL001X2101 Asciminib 200 mg b.i.d. - T315I mutation N=48 n (%) (95% CI)
No. pts ≥ 1 event	14 (29.2) (17.0, 44.0)
Exposure-adjusted overall incidence: n (EAIR / 100 PTY)	14 (11.3)
Cumulative incidence proportion at: n (%) cum IP	
Week 8 (Day 56)	9 (18.8) 18.75
Week 24 (Day 168)	9 (18.8) 18.75
Week 48 (Day 336)	13 (27.1) 27.08
Week 60 (Day 420)	13 (27.1) 27.08
No. pts ≥ 1 event by PT: n (%)	
Thrombocytopenia	8 (16.7)
Anaemia	5 (10.4)
Neutropenia	5 (10.4)
Neutrophil count decreased	3 (6.3)
Platelet count decreased	2 (4.2)
Pancytopenia	1 (2.1)
Maximum grade	
Grade 3 AEs	**3 (6.3)**
Anaemia	2 (4.2)
Neutropenia	1 (2.1)

Myelosuppression	CABL001X2101 Asciminib 200 mg b.i.d. - T315I mutation N=48 n (%) (95% CI)
Neutrophil count decreased	1 (2.1)
Thrombocytopenia	1 (2.1)
Grade 4 AEs	**7 (14.6)**
Thrombocytopenia	4 (8.3)
Neutropenia	2 (4.2)
Neutrophil count decreased	2 (4.2)
Pancytopenia	1 (2.1)
Platelet count decreased	1 (2.1)
Grade 5 AEs	**0**
Treatment-related AEs	**9 (18.8)**
Thrombocytopenia	6 (12.5)
Neutropenia	4 (8.3)
Anaemia	3 (6.3)
Neutrophil count decreased	2 (4.2)
Pancytopenia	1 (2.1)
Platelet count decreased	1 (2.1)
SAEs	**0**
Action taken	
Drug withdrawn	1 (2.1)
Dose adjusted	3 (6.3)
Drug interrupted	3 (6.3)
Dose not changed/NA/unknown	13 (27.1)
Medication or therapy taken	5 (10.4)
AE outcome	
Recovered/resolved	10 (20.8)
Recovering/resolving	7 (14.6)
Not recovered/not resolved	8 (16.7)
Recovered/resolved with sequelae	0
Fatal	0
Unknown	0

No. (n) represent counts of patients. A patient may be counted in several rows for action taken and outcome.
EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event). Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100). Myelosuppression includes Erythropenia, Leukopenia, Thrombocytopenia, cytopenias affecting more than one lineage (Table 7-3).
MedDRA Version 26.0, CTCAE Version 4.03, Case Retrieval Strategy version released 22-Nov-2022.
Source: Attachment to Annex 7-Table 5-6c

Table 2-31 Characterization of myelosuppression

Myelosuppression	Details
Potential mechanisms	Myelosuppression-related events are very common during TKI treatment; these events are considered to be due to the combined effect of suppression of the leukemic clone and inhibition of non-leukemic hematopoiesis.
Evidence source(s) and strength of evidence	The frequency of the reported events (including grade 3/4 events) was very common; however, these events were manageable with dose modifications and standard clinical practice guidelines. Thrombocytopenia has potential for hemorrhagic events, and neutropenia is a strong risk factor for infections. Evidence sources characterizing the risk included Study J12301, Study A2301 and Study X2101; Study X2101 included patients with the T315I mutation (for more details, refer to Section 2.3).
Characterization of the risk:	**Non-clinical data** A minimal to mild, regenerative reduction in red blood cells mass in rat, dog and monkey has been observed and was consistent with a regenerative, extravascular, hemolytic anemia. However, myelosuppression was not evident in non-clinical studies with asciminib (Table 2-5). **Clinical data** **Data from J12301 study:** Myelosuppression events occurred less frequently with asciminib vs. IS-TKIs (all grades: 43.5% vs. 57.7%; grade ≥ 3: 20.0% vs. 28.9%) and with imatinib (all grades: 51.5% and grade ≥ 3: 24.2%) and 2G-TKI (all grades: 63.7% and grade ≥ 3: 33.3%) (Annex 7-Table 5-6). ■ **Asciminib 80 mg q.d. (N=200) and IS-TKI (N=201):** When treated with asciminib, the most commonly reported PTs with a difference of ≥ 5% were: ○ Anemia occurred less frequently in the asciminib group (12.5%) compared to the IS-TKI group overall (25.9%), as well as imatinib (26.3%) and 2G TKI (25.5%). ○ Neutropenia occurred less frequently in the asciminib group (10.5%) compared to the IS-TKI group overall (16.4%), as well as imatinib (16.2%) and 2G TKI (16.7%). ○ Neutrophil count decreased occurred less frequently in the asciminib group (15.0%) compared to 2G TKIs (20.6%) and was comparable with imatinib group (16.2%) as well as the IS-TKI group overall (18.4%). ○ Lymphocyte count decreased (5.0% vs. 13.1%) and WBC count decreased (11.0% vs. 17.2%) occurred less frequently in the asciminib group compared to the imatinib group and was comparable with 2G TKI group (lymphocyte count decreased: 2.9%; WBC count decreased: 12.7%) as well as the IS-TKI group overall (lymphocyte count decreased: 8.0%; WBC count decreased: 14.9%). The occurrences of all remaining Myelosuppression events were comparable between the treatment groups. SAEs occurred in a few patients across the treatment groups: the proportion was lower in patients treated with asciminib vs. IS-TKIs (0.5% vs. 1.5%). There was no event of pancytopenia. Events leading to drug interruption or drug withdrawal were low and comparable in all treatment groups. Patients who required dose adjustment reported less frequently when

Myelosuppression	Details
	treated with asciminib vs. IS-TKIs (3.5% vs. 10.4%) and similarly when events were not resolved / not recovered (15.5% vs. 30.8%, respectively). **All Asciminib Safety Pool (N=556)** The overall incidence of patients treated with asciminib observed with Myelosuppression events was: all grades, 39.6%; grade 3, 10.8%; grade 4, 12.1%. The most frequent PT was thrombocytopenia at an incidence of 19.6% of patients. Following in decreased frequency (all grades: ≥ 10%) was neutropenia (13.8%) and anemia (12.6%). Events were considered treatment related, as assessed by the Investigator, in 32.0% of patients. The incidence of SAEs reported was considered low (1.3%). The reported events were managed with dose adjustment (5.6% of patients) or more often with drug interruption (15.3% of patients). Myelosuppression is an on-target effect and is expected with asciminib treatment. Of note, asciminib treatment as 1L will lead to elimination of leukemic clones; and thus, resulting in cytopenia. Further, decreased neutrophil count is an on-target toxicity effect and is expected with asciminib treatment. There was 1 patient (0.2%) treated with asciminib (200 mg b.i.d.) during Study X2101 who reported pancytopenia and is discussed below. In the **Asciminib 3L+ Safety Pool (N=356)**, Myelosuppression events occurred at: all grades, 37.4%; grade 3, 9.0%; grade 4, 15.4%. The events suspected to be treatment related by Investigator were reported in 27.8% patients in Asciminib 3L+ Safety Pool. SAEs were reported in 1.7% of patients. The reported events were managed with either dose adjustment (6.7% of patients) or drug interruption (14.6% of patients). Treatment discontinuations were reported in 2.8% of patients. Myelosuppression events were ongoing in 23.3% patients, as of DCO. **Data from Study A2301 (end of treatment) and Study X2101 (final analysis)** **Study A2301 asciminib 40 mg b.i.d. dose:** Myelosuppression grouped AEs occurred in similar proportion in the asciminib arm (38.5% all grades; Grade 3 events, 10.9%) and bosutinib arms (36.8% all grades; Grade 3 events, 18.4%); Grade 4 events were more frequent in the asciminib arm (16.0% in the asciminib arm vs. 5.3% in the bosutinib arm). At Week 8, the cumulative incidence of myelosuppression events was higher in the asciminib treatment group (32.1%) compared to the bosutinib (26.3%) treatment group; however, the cumulative incidences at Week 24 were comparable in both the treatment groups. The myelosuppression events were primarily thrombocytopenia (23.1% vs. 14.5%) and neutropenia (19.2% vs. 17.1%) in asciminib and bosutinib treatment groups, respectively. At EOT cut off, 22-Mar-2023, in most of the patients, these events were suspected to be treatment-related by the Investigator (47 (30.1%) patients in the asciminib arm vs. 21 (27.6%) in the bosutinib arm). The proportion of patients with SAEs was low in both the treatment arms with 2 (1.3%) patients in the asciminib arm and 1 (1.3%) patient in the bosutinib arm, respectively. None of the SAEs were fatal. In both the treatment arms, these events were successfully managed by dose adjustment (9 (5.8%) in the asciminib arm vs

Myelosuppression	Details
	3 (3.9%) in the bosutinib arm) or dose interruptions (36 (23.1%) in the asciminib vs 13 (17.1%) in the bosutinib arms). Treatment discontinuations were low and similar between the 2 treatment arms (6 (3.8%) in the asciminib arm vs. 4 (5.3%) in the bosutinib arm). Myelosuppression events were ongoing in 37 (23.7%) patients in the asciminib arm and 15 (19.7%) patients in the bosutinib arm at the time of data cut-off. Despite the higher frequency of thrombocytopenia in the asciminib arm, the proportion of patients with AEs of hemorrhage was similar in asciminib and bosutinib arms: 12.8% vs. 10.5%, respectively (Table 14.3.1-14 A2301 EOT CSR). The overall incidence of "infections" (reported as an AE) associated with underlying neutropenia was 2.6% (4 patients, all associated with neutropenia grade 1-2) and 1.3% (1 patient), in the asciminib and bosutinib treatment groups, respectively. These events were low in frequencies, and the incidence rates were comparable between asciminib and bosutinib treatment groups (Annex 7-Table 5-5). The exposure-adjusted overall incidence was 22.1 per 100 STY in asciminib arm and 42.7 in bosutinib arm. **Study X2101 asciminib 80 mg q.d. dose group:** Myelosuppression grouped AEs occurred in 9 (50.0%) patients. Grade 3 events were reported in 1 (5.6%) patient and Grade 4 events in 2 (11.1%) patients. The events suspected to be treatment related by Investigator were reported in 6 (33.3%) patients. None of these events were serious. The reported events were successfully managed by dose adjustment in 2 (11.1%) patients or drug interruptions in 2 (11.1%) patients. No treatment discontinuation was reported. Myelosuppression events were ongoing in 6 (33.3%) patients at the time of data cut-off. One patient reported hemorrhagic events related to thrombocytopenia (epistaxis grade 3 associated with platelet count decreased grade 4 and 3, Study X2101 Final report-Section 12.2.1.8) infection associated with underlying neutropenia was reported in 1 patient (Annex 7-Table 5-5). The exposure-adjusted overall incidence was 14.6 per 100 STY. **Asciminib Safety Pool:** Myelosuppression grouped AEs occurred in similar proportion of patients in the asciminib 40 mg b.i.d. safety pool (39% all grades; Grade 3, 10.2%; Grade 4, 16.0%) and asciminib all patient's safety pool (37.4% all grades; Grade 3, 9.0%; Grade 4, 15.4%) compared to the asciminib arm in Study A2301 (38.5% all grades; Grade 3, 10.9%; Grade 4, 16.0%). The events suspected to be treatment related by Investigator were reported in 56 (29.9%) patients in the asciminib 40 mg b.i.d safety pool and 99 (27.8%) patients in asciminib all patient's safety pool. SAEs were reported in similar proportion of patients in 1.1% in asciminib 40 mg b.i.d safety pool and 1.7% in asciminib all patient's safety pool. The reported events were managed with either dose adjustment (11 (5.9%) patients in asciminib 40 mg b.i.d safety pool and 24 (6.7%) patients in asciminib all patient's safety pool) or drug interruption (37 (19.8%) patients in asciminib 40 mg b.i.d safety pool and 52 (14.6%) patients in asciminib all patient's safety pool). Treatment discontinuations were reported in 6 (3.2%) patients in asciminib 40 mg b.i.d safety pool and 10 (2.8%) patients in asciminib all patient's safety pool. Myelosuppression events were ongoing

Myelosuppression	Details
	in 45 (24.1%) patients in asciminib 40 mg b.i.d safety pool and 83 (23.3%) patients in asciminib all patient's safety pool at the time of data cut-off. The exposure-adjusted overall incidence was 19.1 per 100 STY in asciminib 40 mg b.i.d safety pool and 14.8 per 100 STY in asciminib all patient's safety pool. **Study X2101: patients with the T315I mutation** ■ **Asciminib 200 mg b.i.d. (N=48):** Myelosuppression events occurred in 29.2% patients with Ph+ CML-CP with the T315I mutation and receiving asciminib 200 mg b.i.d. dose. Grade 3 events were reported in 6.3% and Grade 4 events in 14.6% of patients. Events suspected to be treatment related by Investigator were reported in 18.8% of patients. As previously stated, 1 patient (2.1%) reported Grade 4 pancytopenia, which was considered treatment related, as assessed by the Investigator. The event led to study treatment discontinuation (Study X2101 Final CSR Table 12-29). Of note, no SAEs were reported. The events were successfully managed by dose interruptions (6.3%) and dose adjustment (6.3%). Treatment discontinuation was low and was reported in 1 patient (2.1%). Myelosuppression events were ongoing in 16.7% of patients, as of DCO. The exposure-adjusted overall incidence was 11.3 / 100 PTY in patients with the T315I mutation.
Risk factors and risk groups	Low blood cell counts (cytopenia) at the baseline increases the chances of further decrease in these cell counts following asciminib administration.
Preventability	Complete blood counts should be performed every 2 weeks for the first 3 months of treatment and then monthly thereafter, or as clinically indicated. Patients should be monitored for signs and symptoms of myelosuppression. Based on the severity of thrombocytopenia and/or neutropenia, the dose should be reduced, temporarily withheld or permanently discontinued.
Impact on the benefit-risk balance of the product	Considering the wide range of possible complications (which might be -life-threatening or fatal), there is a moderate impact on the benefit-risk balance of the drug.
Public health impact	Given the relatively low prevalence of CML in the overall population and the frequency of this risk, the potential public health impact is low.

2.7.2.2 Important identified risk: QTc prolongation

Table 2-32 Clinical trial data of QTc prolongation (1L therapy - Safety set)

	Study J12301						Safety Pool
	Asciminib			IS-TKI			
QTc prolongation	Imatinib stratum N=100 n (%) (95% CI)	2G-TKI stratum N=100 n (%) (95% CI)	All asciminib N=200 n (%) (95% CI)	Imatinib stratum N=99 n (%) (95% CI)	2G-TKI stratum N=102 n (%) (95% CI)	All comparators N=201 n (%) (95% CI)	All Asciminib N=556 n (%) (95% CI)
No. pts ≥ 1 event:	1 (1.0) (0.0, 5.4)	3 (3.0) (0.6, 8.6)	4 (2.0) (0.6, 5.0)	0	5 (4.9) (1.6, 11.0)	5 (2.5) (0.8, 5.8)	23 (4.1) (2.6, 6.2)
Asciminib vs. IS-TKI							
Risk diff. (95% CI)			-0.49 (-10.26, 9.27)				–
Exposure-adjusted overall incidence:							
n (EAIR / 100 PTY)	1 (0.5)	3 (1.4)	4 (1.0)	0	5 (2.5)	5 (1.4)	23 (1.5)
Cumulative incidence proportion at: n (%) cum IP							
Week 8 (Day 56)	1 (1.0) 1.00	0	1 (0.5) 0.50	0	3 (2.9) 2.94	3 (1.5) 1.49	3 (0.5) 0.54
Week 24 (Day 168)	1 (1.0) 1.00	0	1 (0.5) 0.50	0	4 (3.9) 3.92	4 (2.0) 1.99	4 (0.7) 0.72
Week 48 (Day 336)	1 (1.0) 1.00	2 (2.0) 2.00	3 (1.5) 1.50	0	4 (3.9) 3.92	4 (2.0) 1.99	11 (2.0) 1.98
Week 96 (Day 672)	1 (1.0) 1.00	2 (2.0) 2.00	3 (1.5) 1.50	0	4 (3.9) 3.92	4 (2.0) 1.99	15 (2.7) 2.70
Asciminib vs. IS-TKI							
Risk diff. (95% CI)							
Week 8 (Day 56)			-0.99 (-10.75, 8.77)				–
Week 24 (Day 168)			-1.49 (-11.25, 8.27)				–
Week 48 (Day 336)			-0.49 (-10.26, 9.27)				–
Week 96 (Day 672)			-0.49 (-10.26,9.27)				–
No. pts ≥ 1 event by PT: n (%)							
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)
Cardiac arrest	0	0	0	0	0	0	2 (0.4)
Seizure	0	0	0	0	0	0	2 (0.4)
Ventricular tachycardia	0	0	0	0	0	0	2 (0.4)
Loss of consciousness	0	0	0	0	0	0	1 (0.2)
Ventricular arrhythmia	0	0	0	0	0	0	1 (0.2)
Long QT syndrome	0	0	0	0	1 (1.0)	1 (0.5)	0

	Study J12301						Safety Pool
	Asciminib			IS-TKI			
QTc prolongation	Imatinib stratum N=100 n (%) (95% CI)	2G-TKI stratum N=100 n (%) (95% CI)	All asciminib N=200 n (%) (95% CI)	Imatinib stratum N=99 n (%) (95% CI)	2G-TKI stratum N=102 n (%) (95% CI)	All comparators N=201 n (%) (95% CI)	All Asciminib N=556 n (%) (95% CI)
Maximum grade							
Grade 3 AEs	**1 (1.0)**	**2 (2.0)**	**3 (1.5)**	**0**	**1 (1.0)**	**1 (0.5)**	**10 (1.8)**
Syncope	0	2 (2.0)	2 (1.0)	0	1 (1.0)	1 (0.5)	5 (0.9)
Electrocardiogram QT prolonged	1 (1.0)	0	1 (0.5)	0	0	0	2 (0.4)
Ventricular tachycardia	0	0	0	0	0	0	2 (0.4)
Loss of consciousness	0	0	0	0	0	0	1 (0.2)
Grade 4 AEs	**0**	**0**	**0**	**0**	**0**	**0**	**1 (0.2)**
Cardiac arrest	0	0	0	0	0	0	1 (0.2)
Grade 5 AEs	**0**	**0**	**0**	**0**	**0**	**0**	**1 (0.2)**
Cardiac arrest	0	0	0	0	0	0	1 (0.2)
Treatment-related AEs	**1 (1.0)**	**0**	**1 (0.5)**	**0**	**2 (2.0)**	**2 (1.0)**	**3 (0.5)**
Electrocardiogram QT prolonged	1 (1.0)	0	1 (0.5)	0	1 (1.0)	1 (0.5)	3 (0.5)
Long QT syndrome	0	0	0	0	1 (1.0)	1 (0.5)	0
SAEs	**0**	**0**	**0**	**0**	**1 (1.0)**	**1 (0.5)**	**4 (0.7)**
Syncope	0	0	0	0	1 (1.0)	1 (0.5)	0
Cardiac arrest	0	0	0	0	0	0	2 (0.4)
Ventricular tachycardia	0	0	0	0	0	0	2 (0.4)
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)
Medication or therapy taken	0	1 (1.0)	1 (0.5)	0	1 (1.0)	1 (0.5)	8 (1.4)
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)
Fatal	0	0	0	0	0	0	1 (0.2)

QTc prolongation	Asciminib			Study J12301 IS-TKI			Safety Pool
	Imatinib stratum N=100 n (%) (95% CI)	2G-TKI stratum N=100 n (%) (95% CI)	All asciminib N=200 n (%) (95% CI)	Imatinib stratum N=99 n (%) (95% CI)	2G-TKI stratum N=102 n (%) (95% CI)	All comparators N=201 n (%) (95% CI)	All Asciminib N=556 n (%) (95% CI)

Number (N) represent counts of patients. A patient may be counted in several rows for action taken and outcome.
EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event). Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100).
MedDRA Version 27.1, CTCAE Version 5.0, Case Retrieval Strategy version released 28-Nov-2024.
Source : Annex 7 EU RMP Version 4.0

Table 2-33 Clinical trial data of QTc prolongation (3L+ therapy - Safety set)

QTc prolongation	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
No. pts ≥ 1 event	1 (1.3) (0.0, 7.2)	8 (5.1) (2.2, 9.8)	18 (5.1) (3.0, 7.8)
Exposure-adjusted overall incidence, n (EAIR per 100 STY)	1 (1.1)	8 (2.3)	18 (1.6)
Cumulative incidence proportion at n (%) cum IP			
Week 8 (Day 56)	1 (1.3) 1.32	2 (1.3) 1.28	2 (0.6) 0.56
Week 24 (Day 168)	1 (1.3) 1.32	2 (1.3) 1.28	2 (0.6) 0.56
Week 48 (Day 336)	1 (1.3) 1.32	4 (2.6) 2.56	7(2.0) 1.97
Week 60 (Day 420)	1 (1.3) 1.32	5 (3.2) 3.21	8 (2.2) 2.25
Week 96 (Day 672)	1 (1.3) 1.32	6 (3.8) 3.85	11 (3.1) 3.09
No. pts ≥ 1 event by PT: n (%)			
Syncope	1 (1.3)	3 (1.9)	8 (2.2)
Electrocardiogram QT prolonged	0	2 (1.3)	4 (1.1)
Ventricular tachycardia	0	1 (0.6)	2 (0.6)
Cardiac arrest	0	1 (0.6)	2 (0.6)
Loss of consciousness	0	1 (0.6)	1 (0.3)
Ventricular arrhythmia	0	0	1 (0.3)
Maximum grade			
Grade 3 AEs	0	4 (2.6)	7 (2.0)
Syncope	0	1 (0.6)	3 (0.8)
Electrocardiogram QT prolonged	0	1 (0.6)	1 (0.3)

QTc prolongation	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Ventricular tachycardia	0	1 (0.6)	2 (0.6)
Loss of consciousness	0	1 (0.6)	1 (0.3)
Grade 4 AEs	0	1 (0.6)	1 (0.3)
Cardiac arrest	0	1 (0.6)	1 (0.3)
Grade 5 AEs	0	0	1 (0.3)
Cardiac arrest	0	0	1 (0.3)
Treatment-related AEs	0	2 (1.3)	2 (0.6)
Electrocardiogram QT prolonged	0	2 (1.3)	2 (0.6)
SAEs	0	2 (1.3)	4 (1.1)
Cardiac arrest	0	1 (0.6)	2 (0.6)
Ventricular tachycardia	0	1 (0.6)	2 (0.6)
Action taken			
Drug withdrawn	0	0	1 (0.3)
Dose adjusted	0	0	0
Drug interrupted	0	2 (1.3)	2 (0.6)
Dose not changed/NA/Unknown	1 (1.3)	8 (5.1)	17 (4.8)
Medication or therapy taken	0	2 (1.3)	5 (1.4)
AE outcome			
Recovered/resolved	1 (1.3)	8 (5.1)	16 (4.5)
Recovering/resolving	0	1 (0.6)	1 (0.3)
Not recovered/not resolved	0	1 (0.6)	2 (0.6)
Recovered/resolved with sequelae	0	0	0
Fatal	0	0	1 (0.3)
Unknown	0	0	0

Number (N) represent counts of patients. A patient may be counted in several rows for action taken and outcome.

EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event).

Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100).

MedDRA version 26.0, CTCAE version 4.03, Case Retrieval Strategy version released 22-Nov-2022.

Source: Annex 7-Table 5-6b.

Table 2-34 Clinical trial data of QTc prolongation: Patients with the T315I mutation (Safety Set)

QTc prolongation	CABL001X2101 Asciminib 200 mg b.i.d. - T315I mutation N=48 n (%) (95% CI)
No. pts ≥ 1 event	1 (2.1) (0.0, 11.0)
Exposure-adjusted overall incidence: n (EAIR / 100 PTY)	1 (0.7)
Cumulative incidence proportion at: n (%) cum IP	
Week 8 (Day 56)	0
Week 24 (Day 168)	0
Week 48 (Day 336)	1 (2.1) 2.08
Week 60 (Day 420)	1 (2.1) 2.08
No. pts ≥ 1 event by PT: n (%)	
Ventricular tachycardia	1 (2.1)
Maximum grade	
Grade 3 AEs	**1 (2.1)**
Ventricular tachycardia	1 (2.1)
Treatment-related AEs	**0**
SAEs	**1 (2.1)**
Ventricular tachycardia	1 (2.1)
Action taken	
Drug withdrawn	0
Dose adjusted	0
Drug interrupted	0
Dose not changed/NA/unknown	1 (2.1)
Medication or therapy taken	1 (2.1)
AE outcome	
Recovered/resolved	1 (2.1)

No. (n) represent counts of patients. A patient may be counted in several rows for action taken and outcome.

EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event). Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100). MedDRA Version 26.0, CTCAE version 4.03, Case Retrieval Strategy version released 22-Nov-2022.

Source: EU RMP Version 3.0 Attachment to Annex 7-Table 5-6c

Table 2-35 Characterization of QTc prolongation

QTc prolongation	Details
Potential mechanisms	The mechanism is unknown
Evidence source(s) and strength of evidence	QT prolongation without accompanying arrhythmia has been reported in clinical trials. Dose dependent increase in the QTc interval (though it was not clinically relevant) has also been observed in the concentration dependent analysis. Evidence sources characterizing the risk included Study J12301, Study A2301 and Study X2101; Study X2101 included patients with the T315I mutation (for more details, refer to Section 2.3).
Characterization of the risk:	**Non-clinical data** The IC50 values for the inhibitory effect of asciminib in in vitro ion channel assays (IKs and hCav1.2) was > 30 µM and in the Nav1.5 patch clamp assay, the IC50 value was 30 µM. Complete details of non-clinical data are presented in Table 2-5. **Clinical data** **Data from J12301:** QTc prolongation occurred at a similar frequency with asciminib vs. IS-TKIs (all grades: 2.0% vs. 2.5%); but, slightly less frequent with imatinib (0) and slightly more frequent with 2G-TKI (4.9%). All patients with events belonging to this risk were male. ■ **Asciminib 80 mg q.d. (N=200):** Patients treated with asciminib with events belonging to the risk were limited to syncope (3 patients, 1.5%) and electrocardiogram QT prolonged (1 patient, 0.5%). No event belonging to this risk was reported ≥ grade 4. No SAEs were reported in patients treated with asciminib. There was 1 patient each (0.5%) who required dose adjustment, dose interruption. ■ **IS-TKI (N=201):** There was no reported QTc prolongation with imatinib. With 2G-TKI, events belonging to this risk included electrocardiogram QT prolonged (2 patients, 2.0%), syncope (2 patients, 2.0%), and long QT syndrome (1 patient, 1.0 %). No event was reported ≥ grade 4. There was 1 patient (1.0%) with syncope SAE in 2G TKI stratum. **All Asciminib Safety Pool (N=556)** The incidence of QTc prolongation events in patients treated with asciminib was (all grades) 4.1% and grade ≥ 3, 2.2%. The most frequent PT was syncope (11 patients, 2.0%). In the **Asciminib 3L+ Safety Pool (N=356)**, QTc prolongation events occurred at: all grades, 5.1%; grade 3, 2.0%; grade 4, 0.3%; grade 5, 0.3%. The 1 fatal event (grade-5 cardiac arrest, 0.3%) noted in the Asciminib 3L+ Pool (80 mg q.d. cohort) was not suspected to be study treatment related (by the Investigator) and not related to electrocardiogram QT prolongation. The events suspected to be treatment related were reported at 0.6% of patients in the Asciminib 3L+ Pool. SAEs were reported at 1.1% of patients in the Asciminib 3L+ Pool.

QTc prolongation	Details
	The reported events were managed with drug interruption in 0.6% of patients in the Asciminib 3L+ Pool. Treatment discontinuation was reported in 1 patient (0.3%) in the Asciminib 3L+ Pool. QTc prolongation events were ongoing in 0.6% patients in the Asciminib 3L+ Safety Pool, as of DCO. **Data from Study A2301 (end of treatment) and Study X2101 (final analysis)** **Study A2301 asciminib 40 mg b.i.d. dose:** QTc prolongation-related events occurred in 8 patients (5.1%) in the asciminib treatment group and 1 patient (1.3%) in the bosutinib treatment group, respectively. The cumulative incidence of event identified with the search criteria of QTc prolongation was comparable in both the treatment groups at all time points. The events noted in the asciminib treatment group were syncope (3 patients, 1.9%), electrocardiogram QT prolonged (2 patients, 1.3%), cardiac arrest, loss of consciousness and ventricular tachycardia (in 1 patient each, 0.6%). The single event in the bosutinib treatment group was syncope. In the asciminib treatment group, both events of electrocardiogram QTc prolonged were suspected to be treatment related (as assessed by the investigator). Cardiac arrest (grade 4) and ventricular tachycardia (grade 3) were considered to be SAEs in the asciminib treatment group. None of the QTc prolongation events led to study drug discontinuation in either of the treatment groups. In Study A2301, one patient had grade 3 event of electrocardiogram QT prolonged which occurred on Week 1 Day 1, 2 hours after dosing: QTcF was 505 ms (> 60 ms increase from baseline). On Day 2, the event reduced to grade 2, asciminib was interrupted and after patient recovered, restarted at a reduced dose of 20 mg b.i.d. No additional episodes of QTcF > 500 ms were observed and QTcF value remained < 480 ms for most of the duration of the study. The proportion of patients with SAEs was low, 2 (1.3%) patients in the asciminib arm and none in the bosutinib arm. None of the reported SAEs were fatal. These events in the asciminib arm were successfully managed by dose interruption in 2 (1.3%) patients. No treatment discontinuations were reported. QTc prolongation events were ongoing in 1 (0.6%) patient in asciminib arm. The exposure-adjusted overall incidence was 2.3 per 100 STY in asciminib arm and 1.1 per 100 STY in bosutinib arm. **Study X2101 asciminib 80 mg q.d. dose group:** Five of the 18 patients (27.8%) had events related to QTc prolongation, grade 3 (syncope), and grade 5 (fatal) event (cardiac arrest), each in 1 patient, grade < 3, (Electrocardiogram QT prolonged) in 2 patients and syncope in 1 patient None of the events were suspected to be study treatment related. No dose adjustments or drug interruption were required for the reported events. Treatment discontinuation was reported in 1 (5.6%) patient. QTc prolongation events were ongoing in 1 (5.6%) patient, recovered in 3 (16.7%) and fatal in 1 (5.6%) patient at the time of data cut-off.

QTc prolongation	Details
	In Study X2101, overall, in all subjects in single agent asciminib in CML-CP/-AP, changes in the electrocardiogram (ECG) interval during the study were considered as not clinically meaningful by the Investigator. QTcF increase > 60 ms and absolute QTcF > 500 ms was observed in 2 (1.0%) and 3 (1.5%) patients respectively; 2 of them had concurrent QTcF > 500 ms and increase > 60 ms from baseline. An increase > 30 ms to ≤ 60 ms from baseline in QTcF was reported in 27/199 (13.6%) of patients (Study X2101 final report-Section 12.2.1.9). The exposure-adjusted overall incidence was 6.6 per 100 STY. **Asciminib Safety Pools:** QTc prolongation grouped AEs occurred in similar proportion of patients in the asciminib 40 mg b.i.d. safety pool (4.8% all grades; grade 3, 2.1%; grade 4, 0.5%) and asciminib all patient's safety pool (5.1% all grades' grade 3, 2%; grade 4, 0.3%) compared to the asciminib arm in Study A2301 (5.1% all grades; grade 3, 2.6%; grade 4, 0.6%). One fatal event (cardiac arrest) was noted in the asciminib All patients Safety Pool (80 mg q.d. cohort), this event was not suspected to be study treatment related (by the investigator) and was not related to electrocardiogram QT prolongation The events suspected to be treatment related were reported in 2 (1.1%) patients in the asciminib 40 mg b.i.d. safety pool and 2 (0.6%) patients in asciminib all patient's safety pool. The reported events were managed with drug interruption in 2 (1.1%) patients in asciminib 40 mg b.i.d safety pool and 2 (0.6%) patients in all patient's safety pool. Treatment discontinuation was reported in 1 (0.3%) patient in asciminib all patient's safety pool. QTc prolongation grouped events were ongoing in 1 (0.5%) patient in asciminib 40 mg b.i.d safety pool and 2 (0.6%) patients in asciminib all patient's safety pool at the time of data cut-off. The exposure-adjusted overall incidence was 1.8 per 100 STY in asciminib 40 mg b.i.d. safety pool and 1.6 per 100 STY in asciminib all patient's safety pool. **Study X2101: patients with the T315I mutation** ■ **Asciminib 200 mg b.i.d. (N=48):** QTc prolongation events occurred in 1 patient (2.1%: grade-3 ventricular tachycardia) with Ph+ CML-CP with the T315I mutation and receiving asciminib 200 mg b.i.d. dose, which was not suspected to be treatment related by Investigator. The reported event was considered serious and was treated with concomitant medication. This patient did not require any dose adjustment or drug interruption. No treatment discontinuations were reported (Study X2101 Final CSR Section 12.2.3.8). The exposure-adjusted overall incidence was 0.7 / 100 PTY in patients with the T315I mutation.
Risk factors and risk groups	Patients with congenital long QT syndrome, or co-administration of drugs known to cause Torsades de Pointes, or electrolyte abnormalities (hypokalemia/ hypomagnesemia).

QTc prolongation	Details
Preventability	Appropriate patient screening, periodic monitoring of electrolytes and ECGs, precaution for co-administration of asciminib with drugs known to cause Torsades de Pointes.
Impact on the benefit-risk balance of the product	There is a moderate impact on the benefit-risk balance of asciminib. Regular monitoring of ECGs during treatment is required as it helps in early detection of changes in the QT interval and minimizes the risk. Severe QTc prolongation could be potentially associated with serious cardiac conditions such as Torsades de Pointes.
Public health impact	Given the relatively low prevalence of CML in the overall population and the frequency of this risk, the potential public health impact is low.

2.7.2.3 Important potential risk: hepatotoxicity

Table 2-36 Clinical trial data of hepatotoxicity (1L therapy - Safety set)

	Study J12301						Safety Pool
	Asciminib			IS-TKI			
Hepatotoxicity	Imatinib stratum N=100 n (%) (95% CI)	2G-TKI stratum N=100 n (%) (95% CI)	All asciminib N=200 n (%) (95% CI)	Imatinib stratum N=99 n (%) (95% CI)	2G-TKI stratum N=102 n (%) (95% CI)	All comparators N=201 n (%) (95% CI)	All Asciminib N=556 n (%) (95% CI)
No. pts ≥ 1 event	21 (21.0) (13.4, 30.2)	19 (19.0) (11.8, 28.0)	40 (20.0) (14.6, 26.2)	21 (21.2) (13.6, 30.6)	37 (36.3) (27.0, 46.4)	58 (28.9) (22.6, 35.6)	120 (21.6) (18.2, 25.2)
Asciminib vs. IS-TKI Risk diff. (95% CI):			-8.86 (-18.64,0.81)				–
Exposure-adjusted overall incidence:							
n (EAIR / 100 PTY)	21 (12.7)	19 (10.1)	40 (11.3)	21 (16.4)	37 (27.1)	58 (21.9)	120 (9.3)
Cumulative incidence proportion at: n (%) cum IP							
Week 8 (Day 56)	10 (10.0) 10.00	8 (8.0) 8.00	18 (9.0) 9.00	13 (13.1) 13.13	22 (21.6) 21.57	35 (17.4) 17.41	46 (8.3) 8.27
Week 24 (Day 168)	13 (13.0) 13.00	12 (12.0) 12.00	25 (12.5) 12.50	17 (17.2) 17.17	28 (27.5) 27.45	45 (22.4) 22.39	67 (12.1) 12.05
Week 48 (Day 336)	16 (16.0) 16.00	15 (15.0) 15.00	31 (15.5) 15.50	19 (19.2) 19.19	33 (32.4) 32.35	52 (25.9) 25.87	84 (15.1) 15.11
Week 96 (Day 672)	20 (20.0) 20.00	17 (17.0) 17.00	37 (18.5) 18.50	20 (20.2) 20.20	37 (36.3) 36.27	57 (28.4) 28.36	99 (17.8) 17.81
Asciminib vs. IS-TKI Risk diff. (95% CI):							

	Study J12301						Safety Pool
	Asciminib			IS-TKI			
Hepatotoxicity	Imatinib stratum N=100 n (%) (95% CI)	2G-TKI stratum N=100 n (%) (95% CI)	All asciminib N=200 n (%) (95% CI)	Imatinib stratum N=99 n (%) (95% CI)	2G-TKI stratum N=102 n (%) (95% CI)	All comparators N=201 n (%) (95% CI)	All Asciminib N=556 n (%) (95% CI)
Week 8 (Day 56)			-8.41 (-18.14, 1.31)				–
Week 24 (Day 168)			-9.89 (-19.62, -0.19)				–
Week 48 (Day 336)			-10.37 (-20.11,-0.69)				–
Week 96 (Day 672)			-9.86 (-19.62, -0.19)				–
No. pts ≥ 1 event by PT: n (%)							
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-glutamyltransferase 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)
Hypertransaminasaemia	1 (1.0)	0	1 (0.5)	0	0	0	7 (1.3)
Hypoalbuminaemia	0	0	0	0	0	0	5 (0.9)
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)
Blood bilirubin unconjugated increased	0	2 (2.0)	2 (1.0)	0	0	0	3 (0.5)
Hyperbilirubinaemia	0	2 (2.0)	2 (1.0)	0	2 (2.0)	2 (1.0)	3 (0.5)
Glutamate dehydrogenase increased	0	0	0	0	0	0	2 (0.4)
Hepatic function abnormal	1 (1.0)	0	1 (0.5)	1 (1.0)	0	1 (0.5)	2 (0.4)
Liver disorder	1 (1.0)	2 (2.0)	3 (1.5)	0	1 (1.0)	1 (0.5)	4 (0.7)
Ascites	0	0	0	0	0	0	1 (0.2)
Congestive hepatopathy	0	0	0	0	0	0	1 (0.2)
Hepatic lesion	0	0	0	0	0	0	1 (0.2)
Hepatic pain	0	0	0	0	0	0	1 (0.2)
Hepatobiliary disease	1 (1.0)	0	1 (0.5)	0	0	0	1 (0.2)
Hepatocellular injury	0	0	0	0	0	0	1 (0.2)

	Study J12301						Safety Pool
	Asciminib			IS-TKI			
Hepatotoxicity	**Imatinib stratum N=100 n (%) (95% CI)**	**2G-TKI stratum N=100 n (%) (95% CI)**	**All asciminib N=200 n (%) (95% CI)**	**Imatinib stratum N=99 n (%) (95% CI)**	**2G-TKI stratum N=102 n (%) (95% CI)**	**All comparators N=201 n (%) (95% CI)**	**All Asciminib N=556 n (%) (95% CI)**
Hepatomegaly	0	0	0	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
Maximum grade							
Grade 3 AEs	**3 (3.0)**	**0**	**3 (1.5)**	**3 (3.0)**	**8 (7.8)**	**11 (5.5)**	**18 (3.2)**
Alanine aminotransferase increased	3 (3.0)	0	3 (1.5)	1 (1.0)	8 (7.8)	9 (4.5)	10 (1.8)
Gamma-glutamyltransferase increased	1 (1.0)	0	1 (0.5)	0	0	0	7 (1.3)
Aspartate aminotransferase increased	1 (1.0)	0	1 (0.5)	0	2 (2.0)	2 (1.0)	6 (1.1)
Hepatic pain	0	0	0	0	0	0	1 (0.2)
Hypoalbuminaemia	0	0	0	0	0	0	1 (0.2)
Liver disorder	0	0	0	0	0	0	1 (0.2)
Blood bilirubin increased	0	0	0	1 (1.0)	0	1 (0.5)	0
Hepatotoxicity	0	0	0	1 (1.0)	0	1 (0.5)	0
Grade 4 AEs	**0**	**2 (2.0)**	**2 (1.0)**	**1 (1.0)**	**0**	**1 (0.5)**	**5 (0.9)**
Gamma-glutamyltransferase increased	0	1 (1.0)	1 (0.5)	0	0	0	2 (0.4)
Aspartate aminotransferase increased	0	0	0	0	0	0	1 (0.2)
Bilirubin conjugated increased	0	0	0	0	0	0	1 (0.2)
Hepatotoxicity	0	1 (1.0)	1 (0.5)	0	0	0	1 (0.2)
Alanine aminotransferase increased	0	0	0	1 (1.0)	0	1 (0.5)	0
Grade 5 AEs	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Treatment-related AEs	**14 (14.0)**	**14 (14.0)**	**28 (14.0)**	**16 (16.2)**	**31 (30.4)**	**47 (23.4)**	**65 (11.7)**

	Study J12301						Safety Pool
	Asciminib			IS-TKI			
Hepatotoxicity	Imatinib stratum N=100 n (%) (95% CI)	2G-TKI stratum N=100 n (%) (95% CI)	All asciminib N=200 n (%) (95% CI)	Imatinib stratum N=99 n (%) (95% CI)	2G-TKI stratum N=102 n (%) (95% CI)	All comparators N=201 n (%) (95% CI)	All Asciminib N=556 n (%) (95% CI)
Alanine aminotransferase increased	6 (6.0)	6 (6.0)	12 (6.0)	5 (5.1)	17 (16.7)	22 (10.9)	31 (5.6)
Gamma-glutamyltransferase increased	3 (3.0)	5 (5.0)	8 (4.0)	2 (2.0)	6 (5.9)	8 (4.0)	19 (3.4)
Blood bilirubin increased	1 (1.0)	5 (5.0)	6 (3.0)	1 (1.0)	11 (10.8)	12 (6.0)	16 (2.9)
Aspartate aminotransferase increased	0	2 (2.0)	2 (1.0)	6 (6.1)	14 (13.7)	20 (10.0)	16 (2.9)
Blood alkaline phosphatase increased	8 (8.0)	2 (2.0)	10 (5.0)	11 (11.1)	6 (5.9)	17 (8.5)	13 (2.3)
Hypertransaminasaemia	1 (1.0)	0	1 (0.5)	0	0	0	6 (1.1)
Blood bilirubin unconjugated increased	0	2 (2.0)	2 (1.0)	0	0	0	3 (0.5)
Bilirubin conjugated increased	0	2 (2.0)	2 (1.0)	0	2 (2.0)	2 (1.0)	3 (0.5)
Liver disorder	1 (1.0)	2 (2.0)	3 (1.5)	0	1 (1.0)	1 (0.5)	3 (0.5)
Glutamate dehydrogenase increased	0	0	0	0	0	0	1 (0.2)
Hepatic function abnormal	1 (1.0)	0	1 (0.5)	0	0	0	1 (0.2)
Hyperbilirubinaemia	0	1 (1.0)	1 (0.5)	0	2 (2.0)	2 (1.0)	1 (0.2)
Hypoalbuminaemia	0	0	0	0	0	0	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	1 (1.0)	1 (0.5)	0
Hepatotoxicity	0	0	0	1 (1.0)	0	1 (0.5)	0
SAEs	**0**	**1 (1.0)**	**1 (0.5)**	**0**	**0**	**0**	**2 (0.4)**
Hepatotoxicity	0	1 (1.0)	1 (0.5)	0	0	0	1 (0.2)
Liver disorder	0	0	0	0	0	0	1 (0.2)
Action taken							
Drug withdrawn	0	1 (1.0)	1 (0.5)	2 (2.0)	0	2 (1.0)	1 (0.2)
Drug 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)

	Study J12301						Safety Pool
	Asciminib			IS-TKI			
Hepatotoxicity	Imatinib stratum N=100 n (%) (95% CI)	2G-TKI stratum N=100 n (%) (95% CI)	All asciminib N=200 n (%) (95% CI)	Imatinib stratum N=99 n (%) (95% CI)	2G-TKI stratum N=102 n (%) (95% CI)	All comparators N=201 n (%) (95% CI)	All Asciminib N=556 n (%) (95% CI)
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)
Medication or therapy taken	3 (3.0)	4 (4.0)	7 (3.5)	5 (5.1)	10 (9.8)	15 (7.5)	17 (3.1)
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)
Recovered/resolved with sequelae	0	0	0	0	0	0	1 (0.2)

Number (N) represent counts of patients. A patient may be counted in several rows for action taken and outcome.
EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event). Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100).
MedDRA Version 27.1, CTCAE Version 5.0, Case Retrieval Strategy version released 28-Nov-2024
Source: EU RMP version 4.0 Annex 7

Table 2-37 Clinical trial data of hepatotoxicity (3L+ therapy - Safety set)

Hepatotoxicity (including laboratory terms)	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
No. pts ≥ 1 event	25 (32.9) (22.6, 44.6)	19 (12.2) (7.4, 18.4)	80 (22.5) (18.2, 27.2)
Exposure-adjusted overall incidence, n (EAIR per 100 STY)	25 (34.9)	19(5.8)	80(8.4)
Cumulative incidence proportion at n (%) cum IP			
Week 8 (Day 56)	13 (17.1) 17.11	7 (4.5) 4.49	28 (7.9) 7.87
Week 24 (Day 168)	23 (30.3) 30.26	9 (5.8) 5.77	42 (11.8) 11.80
Week 48 (Day 336)	25 (32.9) 32.89	12 (7.7) 7.69	53 (14.9) 14.89
Week 60 (Day 420)	25 (32.9) 32.89	12 (7.7) 7.69	56 (15.7) 15.73
Week 96 (Day 672)	25 (32.9) 32.89	15 (9.6) 9.62	62 (17.4) 17.42

Hepatotoxicity (including laboratory terms)	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
No. pts ≥ 1 event by PT: n (%)			
Alanine aminotransferase increased	23 (30.3)	8 (5.1)	40 (11.2)
Aspartate aminotransferase increased	16 (21.1)	9 (5.8)	36 (10.1)
Gamma-glutamyltransferase increased	0	3 (1.9)	22 (6.2)
Blood alkaline phosphatase increased	0	2 (1.3)	12 (3.4)
Hypertransaminasaemia	0	0	6 (1.7)
Blood bilirubin increased	1 (1.3)	5 (3.2)	16 (4.5)
Hypoalbuminaemia	0	1 (0.6)	5 (1.4)
Bilirubin conjugated increased	0	0	3 (0.8)
Glutamate dehydrogenase increased	0	0	2 (0.6)
Hepatic steatosis	0	0	2 (0.6)
Ascites	0	0	1 (0.3)
Blood bilirubin unconjugated increased	0	1 (0.6)	1 (0.3)
Congestive hepatopathy	0	0	1 (0.3)
Hepatic function abnormal	0	1 (0.6)	1 (0.3)
Hepatic lesion	0	0	1 (0.3)
Hepatic pain	0	0	1 (0.3)
Hepatocellular injury	0	0	1 (0.3)
Hepatomegaly	0	0	1 (0.3)
Hyperbilirubinaemia	0	0	1 (0.3)
Liver disorder	0	0	1 (0.3)
Transaminases increased	1 (1.3)	0	0
Maximum grade			
Grade 3 AEs	13 (17.1)	3 (1.9)	15 (4.2)
Alanine aminotransferase increased	11 (14.5)	1 (0.6)	7 (2.0)
Gamma-glutamyltransferase increased	0	1 (0.6)	6 (1.7)
Aspartate aminotransferase increased	5 (6.6)	3 (1.9)	5 (1.4)
Hepatic pain	0	0	1 (0.3)
Hypoalbuminaemia	0	0	1 (0.3)
Liver disorder	0	0	1 (0.3)
Transaminases increased	1 (1.3)	0	0
Grade 4 AEs	0	0	3 (0.8)
Aspartate aminotransferase increased	0	0	1 (0.3)
Bilirubin conjugated increased	0	0	1 (0.3)
Gamma-glutamyltransferase increased	0	0	1 (0.3)
Grade 5 AEs	0	0	0
Treatment-related AEs	23 (30.3)	7 (4.5)	37 (10.4)

Hepatotoxicity (including laboratory terms)	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Alanine aminotransferase increased	21 (27.6)	1 (0.6)	19 (5.3)
Gamma-glutamyltransferase increased	0	0	11 (3.1)
Aspartate aminotransferase increased	14 (18.4)	2 (1.3)	14 (3.9)
Blood bilirubin increased	1 (1.3)	5 (3.2)	10 (2.8)
Hypertransaminasemia	0	0	5 (1.4)
Transaminases increased	1 (1.3)	0	0
Blood alkaline phosphatase increased	0	0	3 (0.8)
Bilirubin conjugated increased	0	0	1 (0.3)
Blood bilirubin unconjugated increased	0	1 (0.6)	1 (0.3)
Glutamate dehydrogenase increased	0	0	1 (0.3)
Hypoalbuminaemia	0	0	1 (0.3)
SAEs	0	0	1 (0.3)
Liver disorder	0	0	1 (0.3)
Action taken			
Drug withdrawn	4 (5.3)	0	0
Dose adjusted	3 (3.9)	0	3 (0.8)
Drug interrupted	11 (14.5)	5 (3.2)	11 (3.1)
Dose not changed/NA/Unknown	21 (27.6)	16 (10.3)	76 (21.3)
Medication or therapy taken	1 (1.3)	2 (1.3)	10 (2.8)
AE outcome			
Recovered/resolved	22 (28.9)	17 (10.9)	73 (20.5)
Recovering/resolving	14 (18.4)	2 (1.3)	19 (5.3)
Not recovered/not resolved	11 (14.5)	4 (2.6)	33 (9.3)
Recovered/resolved with sequelae	0	0	1 (0.3)
Fatal	0	0	0
Unknown	0	0	0

Number (N) represent counts of patients. A patient may be counted in several rows for action taken and outcome.
EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event). Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100). MedDRA version 26.0, CTCAE version 4.03, Case Retrieval Strategy version released 22-Nov-2022.
Source: Annex 7-Table 5-7b.

Table 2-38 Clinical trial data of Hepatotoxicity: Patients with the T315I mutation (Safety Set)

	CABL001X2101 Asciminib 200 mg b.i.d. - T315I mutation N=48 n (%) (95% CI)
Hepatotoxicity	
No. pts ≥ 1 event	15 (31.3) (18.6, 46.2)
Exposure-adjusted overall incidence:	
n (EAIR / 100 PTY)	15 (13.2)
Cumulative incidence proportion at: n (%) cum IP	
Week 8 (Day 56)	7 (14.6) 14.58
Week 24 (Day 168)	10 (20.8) 20.83
Week 48 (Day 336)	11 (22.9) 22.92
Week 60 (Day 420)	12 (25.0) 25.00
No. pts ≥ 1 event by PT: n (%)	
Alanine aminotransferase increased	10 (20.8)
Aspartate aminotransferase increased	7 (14.6)
Gamma-glutamyltransferase increased	4 (8.3)
Bilirubin conjugated increased	2 (4.2)
Blood bilirubin increased	2 (4.2)
Blood alkaline phosphatase increased	1 (2.1)
Congestive hepatopathy	1 (2.1)
Glutamate dehydrogenase increased	1 (2.1)
Hepatic pain	1 (2.1)
Hepatomegaly	1 (2.1)
Hypertransaminasaemia	1 (2.1)
Maximum grade	
Grade 3 AEs	**6 (12.5)**
Alanine aminotransferase increased	4 (8.3)
Gamma-glutamyltransferase increased	2 (4.2)
Aspartate aminotransferase increased	1 (2.1)
Hepatic pain	1 (2.1)
Grade 4 AEs	**0**
Grade 5 AEs	**0**
Treatment-related AEs	**7 (14.6)**
Alanine aminotransferase increased	6 (12.5)
Aspartate aminotransferase increased	3 (6.3)
Gamma-glutamyltransferase increased	2 (4.2)
Bilirubin conjugated increased	1 (2.1)
Blood bilirubin increased	1 (2.1)

Hepatotoxicity	CABL001X2101 Asciminib 200 mg b.i.d. - T315I mutation N=48 n (%) (95% CI)
Glutamate dehydrogenase increased	1 (2.1)
SAEs	**0**
Action taken	
Drug withdrawn	0
Dose adjusted	2 (4.2)
Drug interrupted	2 (4.2)
Dose not changed/NA/unknown	15 (31.3)
Medication or therapy taken	2 (4.2)
AE outcome	
Recovered/resolved	14 (29.2)
Recovering/resolving	6 (12.5)
Not recovered/not resolved	5 (10.4)
Recovered/resolved with sequelae	0
Fatal	0
Unknown	0

No. (n) represents counts of patients. A subject may be counted in several rows for action taken and outcome.
EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event). Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100). MedDRA version 26.0, CTCAE version 4.03, Case Retrieval Strategy version released 22-Nov-2022.
Source: Attachment to Annex 7-Table 5-7c

Table 2-39 Characterization of hepatotoxicity

Hepatotoxicity	Details
Potential mechanisms	The mechanism is unknown.
Evidence source(s) and strength of evidence	Current evidence is based on nonclinical studies and the clinical studies. Histopathologically, hepatic changes were characterized by centrilobular hepatocyte hypertrophy, slight bile duct hyperplasia and increased individual hepatocyte necrosis in rats and reversible diffuse hepatocellular hypertrophy in monkeys. These liver changes in rat occurred at exposure equivalent to the human dose of 40 mg b.i.d. or 80 mg q.d. dose. In clinical studies, the majority of the reported events were mild to moderate, reversible hepatic enzyme or bilirubin level abnormalities, with no evidence of irreversible liver damage with the use of asciminib monotherapy for treatment of CML-CP/AP. There was no case related to Hy's law, and none of the reported events were fatal or life-threatening. Evidence sources characterizing the risk included Study J12301, Study A2301 and Study X2101; Study X2101 included patients with the T315I mutation. For more details, refer to Section 2.3.
Characterization of the risk:	**Non-clinical data** Elevations in liver enzymes and/or bilirubin values were observed in rats, dogs, and monkeys in non-clinical studies. Further details are provided in Table 2-5. **Clinical data** **Data from J12301 study:** Hepatotoxicity events occurred at a lower frequency with asciminib vs. IS-TKIs (all grades: 20.0% vs. 28.9%; grade ≥ 3: 2.5% vs. 6.0%) and with 2G-TKI (all grades: 36.3% and grade ≥ 3: 7.8%); but, marginally with imatinib (all grades:21.2% and grade ≥ 3: 4.0%). There was no case of DILI. SAEs with asciminib were limited to 1 patient (0.5%) with grade-4 hepatotoxicity PT. Based on laboratory values, ALT and/or AST increases > 3 × ULN and > 5 × ULN occurred less frequently with asciminib, compared with IS-TKIs. The majority of liver enzyme elevations as AST, ALT, and/or total bilirubin were noted as isolated increases. Concurrent elevations post-baseline, ALT or AST > 3 × ULN and bilirubin > 2 × ULN, were limited to 1 patient (0.5%) with asciminib vs. 2 patients (1.0%) with IS-TKIs (SCS Section 3.2.2). Of relevance, no patient met biochemical Hy's law criteria (ALT/AST > 3 × ULN, bilirubin > 2 × ULN, ALP < 2 × ULN) after receiving any study treatment (SCS Table 3-3). ■ **Asciminib 80 mg q.d. (N=200):** When treated with asciminib, the most commonly reported events (≥ 5% difference favoring asciminib) included: ○ Increased ALT (8.5% vs. 13.9%; 2G-TKI: 20.6%); ○ Increased AST (3.0% vs. 11.4%; 2G-TKI: 15.7%); The frequency of all remaining PTs was comparable between the treatment groups. Events leading to drug interruption or drug withdrawal were low and comparable in all treatment groups. There was 1 patient (0.5%) with dose adjustment.

Hepatotoxicity	Details
	■ **IS-TKI (N=201):** Hepatotoxicity events leading to no dose change/NA/ occurred more frequently in patients treated with IS-TKIs (25.9%), as compared to with asciminib (19.0%). Event outcome of recovered/resolved occurred more frequently in patients treated with IS-TKIs (26.9%), compared to with asciminib (17.0%); and similarly, when recovering/resolving (7.5% vs. 3.5%, respectively). However, event outcome of not recovered/not resolved was similar in patients treated with asciminib (9.5%) vs. IS-TKIs (9.0%). **All Asciminib Safety Pool (N=556)** The incidence of Hepatotoxicity events was reported in 21.6% of patients. Specifically, increased ALT was reported in 10.3% of patients and increased AST in 7.6% of patients in the All Asciminib Safety Pool. In the **Asciminib 3L+ Safety Pool (N=356)**, Hepatotoxicity events were reported at: all grades: 22.5%; grade 3, 4.2%; grade 4, 0.8%. The events suspected to be treatment related were reported in 10.4% patients in Asciminib 3L+ Safety Pool. SAEs were reported in 1 patient (0.3%) in Asciminib 3L+ Safety Pool. The reported events were managed with either dose adjustment (0.8% of patients) or drug interruption (3.1% of patients). No treatment discontinuation was reported. Hepatotoxicity events were ongoing in 9.3% of patients in Asciminib 3L+ Safety Pool, as of DCO. **Data from Study A2301 (end of treatment) and Study X2101 (final analysis)** **Study A2301 asciminib 40 mg b.i.d. dose**: Hepatotoxicity (including laboratory terms) AEs occurred in a lower proportion of patients in the asciminib arm (12.2% all grades; Grade 3, 1.9%; no Grade 4 events) compared to the bosutinib arm (32.9% all grades; Grade 3, 17.1%; no Grade 4 events). The incidence of the most frequently occurring events; alanine aminotransferase increase, and aspartate aminotransferase increase were lower in the asciminib treatment group (5.1% and 5.8%) compared to bosutinib treatment group (30.3% and 21.1%, respectively). In most of the patients, these events were suspected to be treatment-related by the Investigator (4.5% in the asciminib arm vs 30.3% in the bosutinib arm). None of these events were serious. The events were successfully managed by dose adjustment (none in the asciminib arm vs 3 (3.9%) in the bosutinib arm) or drug interruptions (5 (3.2%) in the asciminib vs 11 (14.5%) in the bosutinib arms). Treatment discontinuation due to hepatotoxicity was low (none in the asciminib arm vs 4 (5.3%) in the bosutinib arm). Hepatotoxicity events were ongoing in 4 (2.6%) patients in the asciminib arm at the time of data cut-off. In the asciminib arm, most of these AEs were grade 1 or 2, were reversible, and not considered to be clinically relevant; in contrast in the bosutinib arm, 13 (17.1%) patients had grade 3 events and 4 (5.3%) patients discontinued treatment due to hepatotoxicity. Further, in the bosutinib arm, events were not resolved in 11 (14.5%) patients.

Hepatotoxicity	Details
	Based on the laboratory values, ALT or AST increase >3 × ULN were noted in 7.1% of patients in the asciminib arm compared with 30.3% of patients in the bosutinib arm. The majority of liver events presented as isolated AST and/or ALT increases and none were associated with combined bilirubin elevations, and there were no patients meeting the Hy's Law laboratory criteria of ALT or AST >3x ULN & BILI >2x ULN & ALP <2x ULN (Study A2301 End of treatment analysis-Section 12.2.7.4). No clinical events for Hepatotoxicity were reported (Study A2301 EOT report-Section 12.2.7 and Study A2301 EOT report-Table 12-10). The exposure-adjusted overall incidence was 5.8 per 100 STY in asciminib arm and 34.9 per 100 STY in bosutinib arm. **Study X2101 asciminib 80 mg q.d. dose group**: Hepatotoxicity (including laboratory terms) AEs occurred in 4 (22.2%) patients. Grade 3 events were reported in 1 (5.6%) patient and no patient reported with grade 4 events. The events suspected to be treatment related by Investigator was reported in 1 (5.6%) patient. None of these events were serious. The reported events were successfully managed by dose adjustment in 1 patient (5.6%) and drug interruptions in 1 (5.6%) patient. No treatment discontinuation was reported. Hepatotoxicity events were ongoing in 2 (11.1%) patients at the time of data cut-off. The exposure-adjusted overall incidence was 5.7 per 100 STY. **Asciminib Safety Pools**: Hepatotoxicity (including laboratory terms) AEs occurred slightly higher in the asciminib 40 mg b.i.d. safety pool (15.5% all grades; grade 3, 2.1%; no grade 4 events) and asciminib all patient's safety pool (22.5% all grades; grade 3, 4.2%; grade 4, 0.8%) compared to the asciminib in Study A2301 (12.2% all grades; grade 3, 1.9%; no grade 4 events). The events suspected to be treatment related were reported in 37 (10.4%) patients in the asciminib all patient's safety pool. SAEs were reported in 1 (0.3%) patient in asciminib all patient's safety pool. The reported events were managed with either dose adjustment in 3 (0.8%) patients in asciminib all patient's safety pool or drug interruption in 5 (2.7%) patients in asciminib 40 mg b.i.d. safety pool and in 11 (3.1%) patients in asciminib all patient's safety pool. No treatment discontinuation was reported in either of the safety pool. Hepatotoxicity events were ongoing in 12 (6.4%) patients in asciminib 40 mg b.i.d. safety pool and 33 (9.3%) patients in asciminib all patient's safety pool at the time of data cut-off. The exposure-adjusted overall incidence was 6.5 per 100 STY in asciminib 40 mg b.i.d. safety pool and 8.4 per 100 STY in asciminib all patient's safety pool. **Study X2101: patients with the T315I mutation** ■ **Asciminib 200 mg b.i.d. (N=48):** Hepatotoxicity events occurred in 31.3% of patients with Ph+ CML-CP with the T315I mutation and receiving asciminib 200 mg b.i.d. dose. Grade 3

Hepatotoxicity	Details
	events were reported in 12.5% of patients. No grade-4 events were reported. The events suspected to be treatment related by Investigator were reported in 14.6% of patients. None of these events were serious. The events were successfully managed by dose adjustment (4.2%) or dose interruptions (4.2%). No treatment discontinuation was reported. Hepatotoxicity events were ongoing in 10.4% of patients, as of DCO. The exposure-adjusted overall incidence was 13.2 / 100 PTY in patients with the T315I mutation.
Risk factors and risk groups	Unknown.
Preventability	Appropriate patient screening, routine laboratory testing as part of normal patient care.
Impact on the benefit-risk balance of the product	There is a mild impact on the benefit-risk balance of asciminib, due the potential risk that elevated liver enzymes may be a manifestation of potential liver injury.
Public health impact	Given the relatively low prevalence of CML in the overall population and the low-grade events associated with this risk, the potential public health impact is low.

2.7.2.4 Important potential risk: hepatitis B virus infection reactivation

Data from Study J12301 (1L therapy):

Hepatitis B reactivation was reported as an AE in one patient (1.0%) in the imatinib arm and none in the asciminib and 2G TKI groups (EU RMP version 4.0 Annex 7-Table 5-7, Table 5-7b).

A 40-year-old male patient, who received study treatment with imatinib, had a non-serious grade 1 event of hepatitis B reactivation (local laboratory test was positive for hepatitis B virus DNA) on Day 812. The event was suspected to be treatment-related by the investigator and no action was taken with imatinib due to this event. The participant was treated with entecavir, and the event was ongoing at the time of the DCO for this J12301 W96 CSR report.

Table 2-40 Clinical trial data of hepatitis B virus infection reactivation (3L+ therapy - Safety set)

Hepatitis B virus reactivation	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
No. pts ≥ 1 event	0	0	1 (0.3) (0.0, 1.6)
Exposure-adjusted overall incidence, n (EAIR per 100 STY)	0	0	1 (0.1)
Cumulative incidence proportion at n (%) cum IP			
Week 8 (Day 56)	0	0	0

Hepatitis B virus reactivation	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Week 24 (Day 168)	0	0	0
Week 48 (Day 336)	0	0	0
Week 60 (Day 420)	0	0	0
Week 96 (Day 672)	0	0	1 (0.3) 0.28
No. pts ≥ 1 event by PT: n (%)			
Viral hepatitis carrier	0	0	1 (0.3)
Maximum grade			
Grade 3 AEs	0	0	0
Grade 4 AEs	0	0	0
Grade 5 AEs	0	0	0
Treatment-related AEs	0	0	0
SAEs	0	0	1 (0.3)
Viral hepatitis carrier	0	0	1 (0.3)
Action taken			
Drug withdrawn	0	0	0
Dose adjusted	0	0	0
Drug interrupted	0	0	0
Dose not changed/NA/Unknown	0	0	1 (0.3)
Medication or therapy taken	0	0	0
AE outcome			
Recovered/resolved	0	0	0
Recovering/resolving	0	0	0
Not recovered/not resolved	0	0	1 (0.3)
Recovered/resolved with sequelae	0	0	0
Fatal	0	0	0
Unknown	0	0	0

Number (N) represent counts of patients. A patient may be counted in several rows for action taken and outcome.
EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event).
Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100).
MedDRA version 26.0, CTCAE version 4.03, Case Retrieval Strategy version released 22-Nov-2022.
Source: Annex 7-Table 5-7b.

Table 2-41 Characterization of hepatitis B virus infection reactivation

Hepatitis B virus reactivation	Details
Potential mechanisms	The mechanism of HBV infection reactivation in humans is not known. However, a publication associates HBV activation with ABL kinase inhibition: restriction of HBV replication by c-ABL–induced proteasomal degradation of the viral polymerase. Deregulation of ABL1 by BCR::ABL TKIs may be associated with HBV infection reactivation (Hou et al 2019).
Evidence source(s) and strength of evidence	Reactivation of HBV has occurred in patients who are chronic carriers of this virus following administration of other BCR::ABL TKIs. The reactivation of HBV infection was evaluated as a class risk. Nonclinical evidence is not available, and the clinical evidence is limited due to exclusion of such patients from the clinical development program. Evidence sources characterizing the risk included Study J12301, Study A2301 and Study X2101, which include patients with the T315I mutation. For more details, refer to Section 2.3.
Characterization of the risk	There is no non-clinical or clinical evidence of an association between asciminib and HBV reactivation to date; however, these events were observed with other BCR::ABL TKIs. Hepatitis B virus may lead to fulminant hepatitis with fatal outcome and therefore, patients with HBV infection have been excluded from the asciminib clinical development program. **Clinical data** **Data from J12301 study:** Hepatitis B reactivation was reported as an AE in one patient in the Imatinib arm. It was neither ≥ grade 3 nor an SAE. **All Asciminib Safety Pool (N=556)** No new event was reported in the All Asciminib Safety Pool. Of note, there was 1 patient (0.2%) who reported an event belonging to the risk who was treated with asciminib (120 mg q.d.) during Study X2101. This patient was reported with grade-1 viral hepatitis carrier status, which was considered an SAE. No action was taken with study treatment, and the event was ongoing, as of DCO (SCS Section 2.6.14). **Study A2301 asciminib 40 mg b.i.d. dose and Study X2101 asciminib 80 mg q.d. dose group:** There were no events reported in these groups. **Asciminib Safety Pool:** One (0.3%) patient was reported with an AE belonging to the risk definition. The patient had a Grade 1 event of viral hepatitis carrier, which was considered as an SAE. No action was taken with regards to the treatment and the event was ongoing at the time of cut-off. The exposure-adjusted overall incidence was 0.1 per 100 STY in asciminib all patient's safety pool. **Study X2101: patients with the T315I mutation** ■ **Asciminib 200 mg b.i.d. (N=48):** No event was reported in patients with the T315I mutation. **Safety database** There was 1 patient in Study A2202 who experienced HBV infection reactivation reported as PT viral hepatitis carrier. The case with viral hepatitis carrier, was related to hepatitis B infection and did not report reactivation of HBV infection. Both the Investigator and Novartis suspected

Hepatitis B virus reactivation	Details
	no causal relationship with the asciminib exposure (DCO: 15-Jan-2024). The detailed patient narrative is as follows: A 55-year-old female [redacted] who was enrolled in the study with normal hepatic transaminases, negative HBsAg, positive HBsAb, positive HBcAb and negative HBV DNA (less than 50 IU/mL). The patient was not aware of any prior exposure to or infection with HBV. The patient was randomized to the control arm of the study and started on dasatinib 100 mg q.d. Approximately 7 months later, she was switched to asciminib 40 mg b.i.d. due to dasatinib treatment failure. Hepatitis B viral assessments were not performed at that time. HBV DNA levels were evaluated more than 2 months after the patient switched to the asciminib treatment, as per the amended protocol requirements. HBV DNA was positive at 133 IU/ mL. Hepatic transaminase levels were within normal range. The patient was diagnosed with a reactivation of HBV infection. More than 1 month later, the asciminib treatment was interrupted due to reduced platelet counts. The patient was treated with anti-viral medication. Around 2 months after the onset of HBV infection reactivation, the HBV DNA levels dropped below 50 IU/ mL, and the patient was considered recovered from the event. The patient is continuing the anti-viral treatment and asciminib was restarted at a reduced dose of 20 mg b.i.d. due to reduced platelet counts. It was reported that the asciminib dose was not reduced due to HBV infection reactivation. Although hepatitis B reactivation is a labeled ADR for dasatinib), a causal role of asciminib cannot be ruled out considering the reasonable temporality and a possible mechanistic background, as of 15-Jan-2024.
Risk factors and risk groups	Prior HBV infection.
Preventability	Patients should be tested for HBV infection before the start of treatment with asciminib. Hepatitis B virus carriers who require treatment with asciminib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.
Impact on the benefit-risk balance of the product	Considering that causal association has not been established with asciminib, and this is being considered as risk on the basis of class effect, there might be a low impact on the benefit-risk profile of asciminib.
Public health impact	Given the relatively low prevalence of CML in the overall population and no clinical events observed with this risk, the potential public health impact is low.

2.7.2.5 Important potential risk: reproductive toxicity

Data from Study J12301 (1L therapy):

There was 1 patient each who reported maternal exposure timing unspecified PT in the asciminib and IS-TKIs treatment groups (0.5% vs. 0.5%). Failure to thrive and mastitis was reported in 1 patient each in the asciminib group (0.5%) (Annex 7 EU RMP Version 4.0).

There was 1 male adult patient (1.0%) who was diagnosed with a congenital retinal anomaly with imatinib study treatment (Table 2-46). This PT was included due to the broad nature of the risk search criteria (Table 7-3).

All events were grade 1/2 and SAEs did not occur.

Table 2-42 Clinical trial data of reproductive toxicity (3L+ therapy - Safety set)

Reproductive toxicity	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 3L+ N=356 n (%) 95% CI
No. pts ≥ 1 event	1 (1.3) (0.0, 7.2)	6 (3.8) (1.4, 8.2)	6 (1.7) (0.6, 3.6)
Exposure-adjusted overall incidence, n (EAIR per 100 STY)	1 (1.1)	6 (1.7)	6 (0.5)
Cumulative incidence proportion at n (%) cum IP			
Week 8 (Day 56)	0	0	0
Week 24 (Day 168)	1 (1.3) 1.32	2 (1.3) 1.28	2 (0.6) 0.56
Week 48 (Day 336)	1 (1.3) 1.32	2 (1.3) 1.28	2 (0.6) 0.56
Week 60 (Day 420)	1 (1.3) 1.32	3 (1.9) 1.92	3 (0.8) 0.84
Week 96 (Day 672)	1 (1.3) 1.32	3 (1.9) 1.92	3 (0.8) 0.84
No. pts ≥ 1 event by PT:			
Pregnancy	0	3 (1.9)	3 (0.8)
Abortion spontaneous	0	2(1.3)	2 (0.6)
Congenital cardiovascular anomaly	1 (1.3)	1 (0.6)	1 (0.3)
Maternal exposure during pregnancy	0	2 (1.3)	2 (0.6)
Maximum grade			
Grade 3 AEs	0	3 (1.9)	3 (0.8)
Abortion spontaneous	0	1 (0.6)	1 (0.3)
Maternal exposure during pregnancy	0	2 (1.3)	2 (0.6)
Pregnancy	0	1 (0.6)	1 (0.3)
Grade 4 AEs	0	0	0
Grade 5 AEs	0	0	0
Treatment-related AEs	0	0	0
SAEs	0	0	0
Action taken			
Drug withdrawn	0	1 (0.6)	1 (0.3)
Dose adjusted	0	0	0
Drug interrupted	0	3(1.9)	3 (0.8)
Dose not changed/NA/Unknown	1 (1.3)	3 (1.9)	3 (0.8)
Medication or therapy taken	0	2 (1.3)	2 (0.6)
AE outcome			
Recovered/resolved	0	4 (2.6)	4 (1.1)
Recovering/resolving	0	0	0
Not recovered/not resolved	1 (1.3)	2(1.3)	2(0.6)
Recovered/resolved with sequelae	0	0	0
Fatal	0	0	0
Unknown	0	0	0

Reproductive toxicity	CABL001A2301		Safety Pool
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 3L+ N=356 n (%) 95% CI

Number (N) represent counts of patients. A patient may be counted in several rows for action taken and outcome. EAIR=exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event). Cum IP=cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason). Cum IP presented as percentage (cum IP * 100). MedDRA version 26.0, CTCAE version 4.03, Case Retrieval Strategy version released 11-Nov-2022.
Source: Annex 7-Table 5-7b.

Table 2-43 Characterization of reproductive toxicity

Reproductive toxicity	Details
Potential mechanisms	The mechanism of reproductive toxicity in humans is not known, although ABL kinase activity is involved in human development.
Evidence source(s) and strength of evidence	Current evidence is based on nonclinical studies and the clinical studies. Cardiac malformations along with increased visceral and skeletal variants have been observed in rats. Also, increased incidence of resorptions (embryofetal mortality) and a low incidence of cardiac malformations (dysmorphogenesis) have been observed in rabbits. Reproductive toxicity has not been observed with asciminib with the exclusion of pregnant women and the requirement to use effective contraception methods. Males taking asciminib should not require contraception. Evidence sources characterizing the risk included Study J12301, Study A2301, and Study X2101; Study X2101 included patients with the T315I mutation. For more details, refer to Section 2.3.

Reproductive toxicity	Details
Characterization of the risk:	**Non-clinical data** In non-clinical studies, fetal malformation due to in-utero exposure to asciminib was observed. Abelson kinase is implicated in the development of mice, where knock-out animals show poor viability, are osteoporotic, and are deficient in selected B and -T-cell populations (Schwartzberg et al 1991, Li et al 2000). In addition, germline gain-of function- ABL1 mutations in humans are associated with autosomal dominant syndrome characterized by congenital heart defects and skeletal malformations (Wang et al 2017, Chen et al 2020). Information regarding the human implications are not available due to limited exposure in this population. More details on non-clinical data is provided in Table 2-5. **Clinical data** **Data from Study J12301:** The incidence of reproductive toxicity was low and comparable between the asciminib vs. IS-TKIs (0.5% vs. 1.0%). ■ **Asciminib 80 mg q.d. (N=200):** Events were reported in 3 patients: maternal exposure timing unspecified failure to thrive (2G-TKI), and mastitis (imatinib). Failure to thrive was grade 3 and an SAE. ■ **IS-TKI (N=201):** There were 2 patients with an event belonging to the risk: maternal exposure timing unspecified PT (2G-TKI) and retinal anomaly congenital PT (imatinib). **All Asciminib Safety Pool (N=556)** Reproductive toxicity events were reported in 9 patients (1.6%) (SCS W96 Appendix 1). **Data from Study A2301 (end of treatment) and Study X2101 (final analysis)** **Study A2301 asciminib 40 mg b.i.d. dose:** Reproductive toxicity grouped AEs occurred in similar proportions of patients in the asciminib arm (3.8% all grades; Grade 3, 1.9%; no Grade 4 events) and bosutinib (1.3% all grades; no Grade 3 and Grade 4 events) None of the reported events were suspected to be treatment related and considered as SAEs. These events in the asciminib arm were successfully managed by dose interruption in 3 (1.9%) patients. Treatment discontinuation was reported in 1 (0.6%) patient in the asciminib arm. Reproductive toxicity events were ongoing in 2 (1.3%) patients in the asciminib arm and 1 (1.3%) patient in the bosutinib arm. The exposure-adjusted overall incidence was 1.7 per 100 STY in asciminib arm and 1.1 in bosutinib. **Study X2101 asciminib 80 mg q.d. dose group:** No reproductive toxicity grouped AEs were reported. **Asciminib Safety Pool:** AEs belonging to the risk definition occurred in similar proportion of patients in asciminib 40 mg b.i.d. safety pool (3.2% all grades; grade 3, 1.6%; no grade 4 events) and asciminib all patient's safety pool (1.7% all grades; grade 3, 0.8%; no grade 4 events) compared to the asciminib arm in Study A2301 (3.8% all grades; grade 3, 1.9%; no grade 4 events).

Reproductive toxicity	Details
	None of the reported events were suspected to be treatment related and considered as SAEs. These reported events were managed with drug interruption in 3 (1.6%) patients in asciminib 40 mg b.i.d safety pool and 3 (0.8%) patients in asciminib all patient's safety pool. Treatment discontinuation was reported in 1 (0.5%) patient in the asciminib 40 mg b.i.d. safety pool and 1 (0.3%) patient in asciminib all patient's safety pool. Reproductive toxicity events were ongoing in 2 (1.1%) patients in asciminib 40 mg b.i.d safety pool and 2 (0.6%) patients in asciminib all patient's safety pool at the time of data cut-off. The exposure-adjusted overall incidence was 1.2 per 100 STY in asciminib 40 mg b.i.d safety pool and 0.5 in asciminib all patient's safety pool. **Study X2101: patients with the T315I mutation** ■ **Asciminib 200 mg b.i.d. (N=48):** No event was reported in patients with the T315I mutation. Based on the new information and risk evaluation presented in PSUR, the characterization of the risk has been updated with post-marketing frequency as presented in the table below. Cumulative review from all the sources including clinical trials and post-marketing reports, revealed pregnancies in 20 patients. The fetal outcomes were known for 7 pregnancies with maternal exposure reported cumulatively (normal baby, n=3; chromosomal anomaly, n=1; non-structural other abnormality, n=1; and fetal death, n=2). Further, the birth types were known for 16 pregnancies with maternal exposure reported cumulatively. The table below summarizes the cumulative experience of asciminib in the human pregnancy by birth types. Cumulative cases reporting elective termination or therapeutic abortion were analyzed and the review did not reveal any significant reason except the awareness of potential fetal abnormalities and a decision to prioritize the treatment of the underlying disease. The known risk profile remains unaltered and valid. **Cumulative experience of fetal outcomes in human pregnancy with maternal exposure and fetal outcome reported across the indications as of 28-Apr-2024:**

<table>
<tr><th>Reproductive toxicity</th><th>Details</th></tr>
<tr><td></td><td>
<table>
<tr><th rowspan="2">Fetal outcome</th><th colspan="2">Prospective reports</th><th colspan="2">Retrospective reports</th><th colspan="2">All reports with fetal outcome reported</th></tr>
<tr><th>n</th><th>%</th><th>n</th><th>%</th><th>n</th><th>%</th></tr>
<tr><td>Normal baby / normal infant</td><td>1</td><td>25.0</td><td>2</td><td>66.7</td><td>3</td><td>42.8</td></tr>
<tr><td>Chromosomal anomaly</td><td>1</td><td>25.0</td><td>0</td><td>0</td><td>1</td><td>14.3</td></tr>
<tr><td>Abnormality other, non-structural</td><td>1[1]</td><td>25.0</td><td>0</td><td>0</td><td>1[1]</td><td>14.3</td></tr>
<tr><td>Fetal death / intrauterine death</td><td>1</td><td>25.0</td><td>1</td><td>33.3</td><td>2</td><td>28.6</td></tr>
<tr><td>Total</td><td>4</td><td>100</td><td>3</td><td>100</td><td>7</td><td>100</td></tr>
<tr><td colspan="7">[1] Full-term neonate with amniotic aspiration pneumonia and recovered.
n= Number of patients.
Source: PSUR (29-Oct-2023 to 28-Apr-2024).</td></tr>
</table>

Cumulative experience of birth types in human pregnancy with maternal exposure and birth type reported across the indications as of 28-Apr-2024:
<table>
<tr><th rowspan="2">Birth type</th><th colspan="2">Prospective reports</th><th colspan="2">Retrospective reports</th><th colspan="2">All reports with delivery type reported</th></tr>
<tr><th>n</th><th>%</th><th>n</th><th>%</th><th>n</th><th>%</th></tr>
<tr><td>Full-term live birth</td><td>2</td><td>18.2%</td><td>1</td><td>20%</td><td>3</td><td>18.8%</td></tr>
<tr><td>Live birth timing unknown</td><td>0</td><td>0</td><td>1</td><td>20%</td><td>1</td><td>6.3%</td></tr>
<tr><td>Elective termination</td><td>4</td><td>36.4%</td><td>2</td><td>40%</td><td>6</td><td>37.5%</td></tr>
<tr><td>Therapeutic abortion</td><td>3</td><td>27.3%</td><td>1</td><td>20%</td><td>4</td><td>25%</td></tr>
<tr><td>Spontaneous abortion/ miscarriage</td><td>2</td><td>18.2%</td><td>0</td><td>0</td><td>2</td><td>12.5%</td></tr>
<tr><td>Total</td><td>11</td><td>100%</td><td>5</td><td>100%</td><td>16</td><td>100%</td></tr>
<tr><td colspan="7">Source: PSUR (28-Oct-2023 to 28-Apr-2024)
n= Number of patients</td></tr>
</table>

Conclusion: The current update does not alter the known risk profile. The known risk profile remains unaltered and valid.
</td></tr>
<tr><td>Risk factors and risk groups</td><td>Female patients of child-bearing potential receiving asciminib.</td></tr>
<tr><td>Preventability</td><td>Based on findings from animal studies, asciminib can cause fetal harm when administered to a pregnant woman. If it is used during pregnancy, the patient must be informed of the potential risk to the fetus. Women of childbearing potential must be advised to use effective method of contraception (methods that result in less</td></tr>
</table>

Reproductive toxicity	Details
	than 1% pregnancy rates) while receiving asciminib and for up to 3 days after ending treatment. Also, pregnancy status of female patients of childbearing potential should be verified prior to starting treatment with asciminib.
Impact on the benefit-risk balance of the product	The information regarding the human implications is not available due to limited exposure in this population. Considering the potential moderate to high implications for individual health (miscarriage, fetus survival/fetal abnormalities), it could have moderate to severe impact on the benefit-risk balance. However, as asciminib is administrated under medical supervision, due to nature of the disease, the adverse impact can be minimized.
Public health impact	Given the relatively low prevalence of CML in the overall population (especially the women among reproductive age group), the potential public health impact is low.

2.7.2.6 Part II Module SVII.3.2. Presentation of the missing information

Table 2-44 Characterization of long-term safety

Long-term safety	Details
Evidence source	Asciminib is potentially a life-long treatment, with its knowledge expanded since the IBD on long-term safety. In Study A2301, the exposure data for at least 192 weeks in 34 (21.8%) out of 156 patients are available; the median duration of exposure for asciminib was 156 weeks (Table 2-7 and Study A2301 EOT report). Evidence sources characterizing the risk included Study J12301, Study A2301, and Study X2101; Study X2101 included patients with the T315I mutation. For more details, refer to Section 2.3. **Data from Study J12301**: The median duration of exposure to study treatment was marginally longer in the asciminib group (115.79 w), compared to the IS-TKI group (108.71 w). Total exposure was also marginally different between the groups (asciminib: 410.6 PTY vs. IS-TKIs: 353.6 PTY). Within the IS-TKIs, the median duration of exposure was 100.29 w for imatinib and 115.57 w for 2G-TKI. Total exposure was 151.1 PTY for imatinib and 202.5 PTY for 2G-TKI. The difference in cumulative exposure was due to the dynamics of the clinical study recruitment (2G-TKI stratum was closed early by 3 months) (SCS Section 1.2.1). **All Asciminib** Safety Pool (N=556) The median duration of exposure to asciminib was 123.29 weeks and cumulative exposure to asciminib was 1558.6 PTY (Table 2-10). In the Asciminib 3L+ Safety Pool (N=356), exposure data were available for at least 192 weeks in 142 (39.9%) out of 356 patients, as of DCO. Novartis provides the following information in support of the current safety assessment of asciminib 80 mg q.d., which further characterize the risk with asciminib. As per the Final Analysis data from CABL001X2101 study (cut off: 14 Mar 2023), all patients with CML-CP/-AP treated with any dose of asciminib single agent had at least one AE regardless of study treatment relationship. Irrespective of the longer duration of exposure since the Primary Analysis data cut-off (02-Apr-2020) (215.4 weeks vs 124.6 weeks), there was no

Long-term safety	Details
	relevant change (<10% difference) in the severity of the AEs (grade ≥3: 71.0% at the Final Analysis data cut-off vs. 67.5% at the Primary Analysis data cut-off) and the frequency of SAEs (48.0% at Final Analysis data cut-off vs 39.5% at Primary Analysis data cut-off), AEs leading to dose modifications (53.5% at Final Analysis data cut-off vs. 47.5% at Primary Analysis data cut-off) and AEs leading to treatment discontinuation (12.5% at Final Analysis data cutoff vs. 10.0% at Primary Analysis data cutoff). In the Safety Pool comprised of all subjects who took asciminib monotherapy (n=356) in Study A2301 and Study X2101, the exposure data are available for at least 192 weeks in 142 (39.9%) out of 356 patients. **Study X2101: patients with the T315I mutation** ■ **Asciminib 200 mg b.i.d. (N=48):** Exposure data for at least 192 weeks in 23 (47.9%) out of 48 patients were available: median duration of exposure for asciminib was 181.7 weeks (Table 2-14 and Study X2101 final report). The review of the long-term safety information is available for asciminib from the final Analysis for Study X2101 (DCO: 14-Mar-2023) and cumulative PSUR (DLP: 28-Oct-2023) data did not reveal any new safety information regarding the use of asciminib over more than 2 years. No evidence was available to suggest that long-term treatment impacts the safety profile of asciminib.

Table 2-45 Characterization of use in patients with renal impairment

Use in patients with renal impairment	Details
Evidence source	A study (CABL001A2105) assessed the effect of severe renal impairment on the PK of asciminib. The exposure of asciminib (AUCinf) increased by 56% in patients with severe renal impairment compared with patients with normal renal function. The Cmax and the time to reach maximum plasma concentration values were similar in both cohorts, suggesting there was no difference in the absorption of the drug. Patients having mild or early stages of moderate renal impairment were allowed to be enrolled in the clinical development program (Study A2301: patients having mild or moderate renal impairment [up to creatinine clearance ≥ 50 mL/min] were allowed; Study X2101: patients having creatinine < 1.5 × ULN were allowed). Evidence sources characterizing the risk included Study J12301, Study A2301 and Study X2101; Study X2101 included patients with the T315I mutation. For more details, refer to Section 2.3. **Data from Study J12301**: Based on the eGFR at baseline, there were 119 patients with normal renal function, 68 with mild renal impairment, and 13 with moderate renal function treated with asciminib vs. 123 patients with normal renal function, 67 with mild renal impairment, and 11 with moderate renal function treated with IS-TKIs. As the number of patients with moderate renal impairment was considered few (13 vs. 11) (Table 2-19), data are considered limited and should be interpreted with caution (SCS Section 5.1).

Use in patients with renal impairment	Details
	In both the treatment groups, the incidence of most AEs across all the AE categories was similar for mild renal impairment and normal renal function subgroups and was comparable to the incidence of AEs observed in overall study population (SCS Section 5.1.1.5, Appendix 1-Table 6-2.4). **All Asciminib Safety Pool (N=556)** In the All Asciminib Safety Pool, 299 patients had normal renal function, 210 had mild renal impairment, and 43 had moderate renal impairment at baseline (Table 2-19). The incidence of events in all the AE categories assessed for the renal impairment subgroups in All Asciminib Safety Pool was consistent with the overall pooled dataset (SCS Appendix 1-Table 6-2.4). In the All patients Safety Pool (N=351), no difference (> 10%) is observed in the incidence of AESIs in patients having mild renal impairment (N=142) as compared to normal renal function (N=179). However, a higher incidence (> 10%) of certain AESIs (edema and fluid retention and myelosuppression [including erythropenia and leukopenia]) has been observed in patients with moderate renal impairment (N=30) as compared to patients with normal renal function (N=179) in the All Patients Safety Pool (Annex 7-Table 5.1-8.3_wk96). Of note, fluid retention and anemia are very common co-manifestation of chronic renal impairment and are consistent with the classic symptomatology of renal impairment. Considering the small number of patients with baseline moderate renal impairment in the All patients Safety Pool (N=30), it is currently not clear if asciminib use in patients with renal impairment is associated with a higher risk for AEs. Considering this, the safety concern of 'Use in patients with renal impairment' is considered missing information for asciminib.
Anticipated risk/consequence of the missing information	The anticipated risk cannot be estimated due to limited information from the clinical development program. Further characterization will occur once the data from the ongoing Study CABL001A2302 (in which patients having mild/ moderate renal impairment [CrCl ≥ 30 mL/min] are considered for enrolment) is available.

Table 2-46 Characterization of use in patients with hepatic impairment

Use in patients with hepatic impairment	Details
Evidence source	A dedicated study in patients with hepatic impairment (Study CABL001A2103) was conducted and results showed no relevant impact of mild or moderate hepatic impairment on the PK of asciminib. Asciminib exposure (AUCinf) increased by 22% (higher exposure was mainly driven by 1 patient), 3% and 66% in patients with mild, moderate and severe hepatic impairment, respectively, compared to patients with normal hepatic function. However, considering the large therapeutic window of the drug, this is not considered clinically relevant. Additionally, patients with mild hepatic impairment (by NCI criteria) were included in the development program of asciminib. In the All Patients Safety Pool (N=356), a higher incidence (> 10%) of certain AESIs (hypersensitivity, GI toxicity, myelosuppression, and pancreatic toxicity) has been observed in patients with mild hepatic impairment (N=48) as compared to patients with normal hepatic function (N=308) (Annex 7-Table 5.1-8.7_wk96). There was no difference though in

Use in patients with hepatic impairment	Details
	the frequency and severity of the hepatic toxicity events (including severity) in asciminib treatment patients with mild hepatic impairment compared to those patients with normal hepatic function. Considering the low number of patients having mild hepatic impairment (N=48), it is currently not clear if asciminib use in patients with hepatic impairment is associated with a higher risk for AEs. Evidence sources characterizing the risk included Study J12301, Study A2301 and Study X2101; Study X2101 included patients with the T315I mutation. For more details, refer to Section 2.3. **Data from Study J12301**: **Study J12301: Newly diagnosed patients** Based on the AST and TBL values at baseline, there were 176 patients with normal hepatic function and 24 with mild hepatic impairment treated with asciminib vs. 181 patients with normal hepatic function and 19 with mild hepatic impairment treated with IS-TKIs. As the number of patients with mild hepatic impairment was considered few (24 vs. 19) (SCS Appendix 1-Table 6-2.5), data are considered limited and should be interpreted with caution (SCS Section 5.1). In both the treatment groups, the incidence of most AEs across all the AE categories was similar for mild hepatic impairment and normal hepatic function subgroups and was comparable to the incidence of AEs observed in overall study population (SCS Section 5.1.1.6, Appendix 1-Table 6-3.5). **All Asciminib Safety Pool (N=556)** In the All Asciminib Safety Pool, most patients had normal hepatic function at baseline (484 patients) vs. the 72 patients with mild hepatic impairment: results in this subgroup analysis were comparable to the analysis of all AE categories in the overall pooled dataset (SCS Appendix 1-Table 6-2.5). In the **Asciminib 3L+ Safety Pool (N=356)**, a higher incidence (> 10%) of certain AESIs (hypersensitivity, GI toxicity, myelosuppression, and pancreatic toxicity) has been observed in patients with mild hepatic impairment (n=48) as compared to patients with normal hepatic function (n=308) (Annex 7-Table 5.1-8.7_wk96). There was no difference though in the frequency and severity of the hepatic toxicity events (including severity) in asciminib treatment patients with mild hepatic impairment compared to those patients with normal hepatic function. Considering the low number of patients having mild hepatic impairment (n=48), it is currently not clear if asciminib use in patients with hepatic impairment is associated with a higher risk for AEs.
Anticipated risk/consequence of the missing information	The anticipated risk cannot be estimated due to limited information from the clinical development program. Further characterization will occur once the data from the ongoing Study CABL001A2302 (in which patients having mild/ moderate hepatic impairment [total bilirubin ≤ 3 ULN] are considered for enrolment) is available.

2.8 Part II: Module SVIII: Summary of the safety concerns

Table 2-47 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

3 Part III: Pharmacovigilance plan (including post-authorization safety studies)

3.1 Part III.1. Routine pharmacovigilance activities

3.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

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

This checklist is provided in Annex 4 of the RMP.

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).
- Evaluation of the safety profile of the 200 mg b.i.d. dose.

3.2 Part III.2. Additional pharmacovigilance activities

Study CABL001A2302 - A Phase 3b, multi-center, open-label, treatment optimization study of oral asciminib in patients with chronic myelogenous leukemia in chronic phase (CML-CP) previously treated with 2 or more tyrosine kinase inhibitors

Study short name and title:

Asciminib treatment optimization in ≥ 3rd line CML-CP

Rationale and study objectives:

The purpose of the study is to optimize the treatment of asciminib in patients with CML-CP previously treated with 2 or more TKIs. Patients for this study will be identified based on warning criteria and resistance definition following ELN 2020 recommendations. In addition, the study will investigate the use of 2 different posologies. For this, patients will be randomized to either receive asciminib 40 mg b.i.d. or of 80 mg q.d. In patients not achieving MMR at 48 weeks or losing the response after the week 48 assessment up to Week 108, asciminib dose may be escalated to 200 mg q.d. if in the investigator's opinion the patient may benefit from the escalation. In addition, there must not be any grade 3 or 4 toxicity while on therapy, or persistent grade 2 toxicity, possibly related to asciminib and unresponsive to optimal management.

Key study objectives include:

- To estimate the MMR of all the patients at week 48 with CML-CP following 2 or more prior TKI treatments and with no evidence of MMR at baseline.
- To evaluate the safety and tolerability of asciminib in patients with CML-CP following 2 or more prior TKI treatments.

Study design:

In patients not achieving MMR at 48 weeks or losing the response after the Week 48 assessment up to Week 108, asciminib dose may be escalated to 200 mg q.d. if in the investigator's opinion the patient may benefit from the escalation. In addition, there must not be any grade 3 or 4 toxicity while on therapy, or persistent grade 2 toxicity, possibly related to asciminib and unresponsive to optimal management.

Treatment duration is 144 weeks for the individual patient. This is the maximum treatment duration for each patient.

Study population:

The trial will enroll a total of approximately 186 patients:

- 156 patients with CML-CP will be enrolled who were treated with two or more TKIs and who were either resistant (ELN 2020 warning or failure) or intolerant to the last treatment. Intolerant patients must not have achieved MMR at baseline visit. For this population, the primary endpoint for MMR at 48 weeks will be assessed.
- Up to 30 additional patients, intolerant only to their last TKI treatment and in MMR at baseline will also be enrolled. This patient population will not be part of primary endpoint analysis; however, all assessments will be done as with the 156 patients from the population of the primary endpoint analysis.

Milestones:

Final report submission: 11-Mar-2027.

Study 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

Study short name and title:

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.

Rationale and study objectives:

The purpose of this study is to assess long term safety of asciminib and to provide continued treatment to participants who have previously participated in an asciminib Novartis sponsored study and who, in the opinion of the investigator, would benefit from continuing treatment, to ensure treatment continuity for participants as in their parent study, or from switching to asciminib, but are unable to access treatment outside of a clinical study.

Key study objective include:

- To assess long term safety data and provide continued access to the study treatment received in the parent study protocol.

Study design:

Multiple treatment options will be made available in this roll-over study for participants who have completed an asciminib parent Novartis-sponsored study, but were receiving different treatment than asciminib, to ensure treatment continuity for participants who cannot access their study treatment, asciminib, asciminib in combination with imatinib, imatinib, nilotinib or bosutinib from other available sources, e.g. commercial supplies.

Eligible participants can begin treatment as soon as they are enrolled in the study with no treatment interruption while transitioning from the parent study.

Participants return to the study site at least on a quarterly basis (every 12 weeks ± 1 week) for resupply of study medication, which will be provided post-confirmation of clinical benefit and safety review of the prior 3 months at each visit. After treatment discontinuation an end of treatment visit will be performed followed by a 30-day safety follow-up.

Study population:

Male and female adult participants (≥ 18 years) with CML-CP (at the end of parent study) who are currently participating in an asciminib Novartis-sponsored study (parent study) and in the opinion of the investigator, would benefit from continued treatment but are unable to access the treatment outside of a clinical study. This roll-over study allows participants from any asciminib Novartis-sponsored study including but not limited to studies CABL001E2201, CABL001A2301 and CABL001A2202.

Milestones:

Final report submission: 31-Dec-2028.

3.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 3-1 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				
CABL001A2302 A Phase 3b, multi-center, open-label,	To optimize the treatment of asciminib in patients with chronic	Long-term safety, acute pancreatitis (including isolated pancreatic enzyme elevations),	Final report submission	11-Mar-2027

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
treatment optimization study of oral asciminib in patients with chronic myelogenous leukemia in chronic phase (CML-CP) previously treated with 2 or more tyrosine kinase inhibitors Ongoing	myelogenous leukemia in chronic phase (CML-CP) previously treated with 2 or more Tyrosine Kinase Inhibitors (TKIs).	myelosuppression, QTc prolongation, hepatotoxicity, hepatitis B virus infection reactivation, use in patients with renal impairment, use in patients with hepatic impairment		
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

4 Part IV: Plans for post-authorization efficacy studies

Table 4-1 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 respect to the proportion of participants that are in MMR at Week 48 and Week 96 To characterize the safety and tolerability profile of	Long-term efficacy, including long-term response rates, progression-free survival, and OS.	Further characterization of the safety and tolerability profile of asciminib [acute pancreatitis (including isolated pancreatic enzyme elevations), myelosuppression, QTc prolongation, hepatotoxicity, hepatitis B virus infection reactivation, Long-term Safety]	Final report submission	30-Sep-2031

Study, Status	Summary of Objectives	Efficacy uncertainties addressed	Safety concerns addressed	Milestones	Due Date
	asciminib versus 2G TKIs (nilotinib, dasatinib, or bosutinib) during the course of study treatment.				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances					
None					

5 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

5.1 Part V.1. Routine risk minimization measures

Table 5-1 Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Acute pancreatitis (including isolated pancreatic enzyme elevations).	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 Package leaflet (PL) Section 2 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4 includes following recommendations: Serum lipase and amylase levels should be assessed monthly during treatment with asciminib, or as clinically indicated. Patients should be monitored for signs and symptoms of acute pancreatitis (including isolated pancreatic enzyme elevations). More frequent monitoring should be performed in patients with a history of pancreatitis. If lipase and amylase elevation are accompanied by abdominal symptoms, treatment should be temporarily withheld and appropriate diagnostic tests should be considered to exclude pancreatitis. Based on the severity of lipase and amylase elevation, the dose should be reduced, temporarily withheld or permanently discontinued. **Other routine risk minimization measures beyond the Product Information:** Legal status: Medical prescription only product
Myelosuppression	**Routine risk communication** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC Section 4.4 includes following recommendations: Complete blood counts should be performed every 2 weeks for the first 3 months of treatment and then monthly thereafter, or as clinically indicated. Patients should be monitored for signs and symptoms of myelosuppression. Based on the severity of thrombocytopenia and/or neutropenia, the dose should be reduced, temporarily withheld or permanently discontinued. **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product

Safety concern	Routine risk minimization activities
QTc prolongation	**Routine risk communication** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.5 SmPC Section 4.8 SmPC Section 5.1 PL Section 2 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC Section 4.4 includes following recommendations: It is recommended that an ECG is performed prior to the start of treatment with asciminib and monitored during treatment as clinically indicated. Hypokalaemia and hypomagnesaemia should be corrected prior to asciminib administration and monitored during treatment as clinically indicated. Caution should be exercised when administering asciminib at 40 mg twice daily concomitantly with medicinal products known to cause Torsades de Pointes. Concomitant administration of asciminib at 200 mg twice daily with medicinal products with a known risk of Torsades de Pointes should be avoided. **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product
Important potential risks	
Hepatotoxicity	**Routine risk communication** SmPC Section 4.2 SmPC Section 4.8 SmPC Section 5.2 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product
Hepatitis B virus infection reactivation	**Routine risk communication** SmPC Section 4.4 PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC Section 4.4 includes following recommendations: Patients should be tested for HBV infection before the start of treatment with asciminib. Hepatitis B virus carriers who require treatment with asciminib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product
Reproductive toxicity	**Routine risk communication** SmPC Section 4.6

Safety concern	Routine risk minimization activities
	PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC Section 4.6 includes following recommendation: The pregnancy status of women of childbearing potential should be verified prior to starting treatment with asciminib. Sexually-active women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with asciminib and for at least 3 days after stopping treatment. The patient should be advised of a potential risk to the fetus if asciminib is used during pregnancy or if the patient becomes pregnant while taking asciminib. **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product
Missing information	
Long-term safety	**Routine risk communication** None **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product
Use in patients with renal impairment	**Routine risk communication** SmPC Section 4.2 SmPC Section 5.2 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC Section 4.2 states that no dose adjustment is required in patients with mild, moderate or severe renal impairment. **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product
Use in patients with hepatic impairment	**Routine risk communication** SmPC Section 4.2 SmPC Section 5.2 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC Section 4.2 states that no dose adjustment is required in patients with mild, moderate or severe hepatic impairment. **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product

5.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

5.3 Part V.3. Summary of risk minimization measures

Table 5-2 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 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.	**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)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
	Legal status: Medical prescription only product **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 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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** Evaluation of data from studies

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
	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	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. 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** Follow-up using a targeted checklist. **Additional pharmacovigilance activities** None
Missing information		
Long-term safety	**Routine risk minimization measures** SmPC: None PL: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
	Additional risk minimization measures None	**Additional pharmacovigilance activities** Evaluation of data from studies 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)

6 Part VI: Summary of the risk management plan for Scemblix® (asciminib)

This is a summary of the RMP for Scemblix. The RMP details important risks of Scemblix, how these risks can be minimized, and how more information will be obtained about Scemblix's risks and uncertainties (missing information).

Scemblix's SmPC and its PL give essential information to healthcare professionals and patients on how Scemblix should be used.

This summary of the RMP for Scemblix should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Scemblix's RMP.

6.1 Part VI: I. The medicine and what it is used for

Asciminib is indicated for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) and Ph+ CML-CP with the T315I mutation who are resistant to, intolerant to or ineligible for ponatinib.

Scemblix contains asciminib hydrochloride, a salt-form of asciminib which is the active substance, and it is given orally.

Further information about the evaluation of Scemblix's benefits can be found in Scemblix's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/scemblix.

6.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Scemblix, together with measures to minimize such risks and the proposed studies for learning more about Scemblix's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Scemblix is not yet available, it is listed under 'missing information' below.

6.2.1 Part VI: II.A: List of important risks and missing information

Important risks of Scemblix are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Scemblix. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 6-1 List of important risks and missing information

List of important risks and missing information	
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

6.2.2 Part VI: II.B: Summary of important risks

Table 6-2 Important identified risk: acute pancreatitis (including isolated pancreatic enzyme elevations)

Evidence for linking the risk to the medicine	There are very common events of laboratory abnormalities (increased lipase and amylase) and common clinical events (pancreatitis and pancreatitis acute) reported in clinical development program. Evidence sources characterizing the risk included Study J12301, Study A2301 and Study X2101; Study X2101 included patients with the T315I mutation (for more details, refer to Section 2.3).
Risk factors and risk groups	History of amylase and lipase elevation and pancreatitis.
Risk minimization measures	**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
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 6-3 Important identified risk: myelosuppression

Evidence for linking the risk to the medicine	The frequency of the reported events (including grade 3/4 events) was very common; however, these events were manageable with dose modifications and standard clinical practice guidelines. Thrombocytopenia has potential for hemorrhagic events, and neutropenia is a strong risk factor for infections. Evidence sources characterizing the risk included Study J12301, Study A2301 and Study X2101; Study X2101 included patients with the T315I mutation (for more details, refer to Section 2.3).
Risk factors and risk groups	Low blood cell counts (cytopenia) at the baseline increases the chances of further decrease in these cell counts following asciminib administration.
Risk minimization measures	**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 **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 6-4 Important identified risk: QTc prolongation

Evidence for linking the risk to the medicine	QT prolongation without accompanying arrhythmia has been reported in clinical trials. Dose dependent increase in the QTc interval has also been observed in the concentration dependent analysis. Evidence sources characterizing the risk included Study J12301, Study A2301 and Study X2101; Study X2101 included patients with the T315I mutation. For more details, refer to Section 2.3.
Risk factors and risk groups	Patients with congenital long QT syndrome, or co-administration of drugs known to cause Torsades de Pointes, or electrolyte abnormalities (hypokalemia/ hypomagnesemia).
Risk minimization measures	**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
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 6-5 Important potential risk: hepatotoxicity

Evidence for linking the risk to the medicine	Current evidence is based on nonclinical studies and the clinical studies. Histopathologically, hepatic changes were characterized by centrilobular hepatocyte hypertrophy, slight bile duct hyperplasia and increased individual hepatocyte necrosis in rats and reversible diffuse hepatocellular hypertrophy in monkeys. These liver changes in rat occurred at exposure equivalent to the human dose of 40 mg b.i.d. or 80 mg q.d. dose. In clinical studies, the majority of the reported events were mild to moderate, reversible hepatic enzyme or bilirubin level abnormalities, with no evidence of irreversible liver damage with the use of asciminib monotherapy for treatment of CML-CP/AP. There was no case related to Hy's law, and none of the reported events were fatal or life-threatening.

	Evidence sources characterizing the risk included Study J12301, Study A2301 and Study X2101; Study X2101 included patients with the T315I mutation. For more details, refer to Section 2.3.
Risk factors and risk groups	Unknown.
Risk minimization measures	**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
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 6-6 Important potential risk: hepatitis B virus infection reactivation

Evidence for linking the risk to the medicine	Reactivation of HBV has occurred in patients who are chronic carriers of this virus following administration of other BCR::ABL TKIs. The reactivation of HBV infection was evaluated as class risk. Nonclinical evidence is not available, and the clinical evidence is limited due to exclusion of such patients from the clinical development program. Evidence sources characterizing the risk included Study J12301, Study A2301 and Study X2101; Study X2101 included patients with the T315I mutation. For more details, refer to Section 2.3.
Risk factors and risk groups	None identified for HBV infection reactivation.
Risk minimization measures	**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

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 6-7 Important potential risk: reproductive toxicity

Evidence for linking the risk to the medicine	Current evidence is based on nonclinical studies and clinical studies. Cardiac malformations along with increased visceral and skeletal variants have been observed in rats. Also, increased incidence of resorptions (embryofetal mortality) and a low incidence of cardiac malformations (dysmorphogenesis) have been observed in rabbits. Reproductive toxicity has not been observed with asciminib with the exclusion of pregnant women and the requirement to use effective contraception methods. Males taking asciminib should not require contraception. Evidence sources characterizing the risk included Study J12301, Study A2301, and Study X2101,; Study X2101 included patients with the T315I mutation. For more details, refer to Section 2.3.
Risk factors and risk groups	Female patients of child-bearing potential receiving asciminib.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.6 where effects of asciminib in fertility, pregnancy and lactation are described. PL Section 2 where precautions, monitoring and treatment are described. Legal status: Medical prescription only product **Additional risk minimization measures** None

Table 6-8 Missing information: long-term safety

Risk minimization measures	**Routine risk minimization measures** SmPC: None PL: None **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 6-9 Missing information: use in patients with renal impairment

Risk minimization measures	**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
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CABL001A2302 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 6-10 Missing information: use in patients with hepatic impairment

Risk minimization measures	**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
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CABL001A2302 See Section II.C of this summary for an overview of the post-authorization development plan.

6.2.3 Part VI: II.C: Post-authorization development plan

6.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

Table 6-11 Studies which are conditions of the marketing authorization

Study short name	Purpose of the study:
Study 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)	**Summary of Objectives:** 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 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.

Study short name	Purpose of the study:
	Efficacy uncertainties addressed Long-term efficacy, including long-term response rates, progression-free survival, and OS. **Safety concerns addressed** Further characterization of the safety and tolerability profile of asciminib [acute pancreatitis (including isolated pancreatic enzyme elevations), myelosuppression, QTc prolongation, hepatotoxicity, hepatitis B virus infection reactivation, Long-term Safety]

6.2.3.2 II.C.2. Other studies in post-authorization development plan

Table 6-12 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Study CABL001A2302: Asciminib treatment optimization in ≥ 3rd line CML-CP	The purpose of the study is to optimize the treatment of asciminib in patients with CML-CP previously treated with 2 or more TKIs. Patients for this study will be identified based on warning criteria and resistance definition following ELN 2020 recommendations. In addition, the study will investigate the use of 2 different posology. For this, patients will be randomized to either receive asciminib 40 mg b.i.d. or of 80 mg q.d. In patients not achieving MMR at 48 weeks or losing the response after the week 48 assessment up to Week 108, asciminib dose may be escalated to 200 mg q.d. if in the investigator's opinion the patient may benefit from the escalation. In addition, there must not be any grade 3 or 4 toxicity while on therapy, or persistent grade 2 toxicity, possibly related to asciminib and unresponsive to optimal management. Key study objectives include: To estimate the MMR of all the patients at week 48 with CML-CP following 2 or more prior TKI treatments and with no evidence of MMR at baseline.
Study CABL001A2001B: 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.	The purpose of this study is to assess long term safety of asciminib and to provide continued treatment to participants who have previously participated in an asciminib Novartis sponsored study and who, in the opinion of the investigator, would benefit from continuing treatment, to ensure treatment continuity for participants as in their parent study, or from switching to asciminib, but are unable to access treatment outside of a clinical study. Key study objectives include: To assess long term safety data and provide continued access to the study treatment received in the parent study protocol.

7 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

This annex contains the targeted follow-up checklist used to collect additional data for the following asciminib RMP risk:

•

Reproductive Toxicity - Pregnancy Form (Version 5.0, 22-Aug-2022)

Spontaneous Report ☐	**Study report** ☐		**REPORT TYPE** ☐ **Initial** ☐ **Follow-Up**
	Study Drug **Study/Protocol Nº**	PATIENT ID ____ ____ Centre No. Patient No.	

☐ Pregnancy in a female patient ☐ Pregnancy in a partner of male patient

Country: Local case ID or Argus Affiliate ID:

Ia. PATERNAL INFORMATION (required only if father took the drug)

Age: years

Age Group:

Ib. MATERNAL INFORMATION

Date of Birth (DD-MMM-YYYY): - -	Age: years Age group:	. Ethnicity: ☐ Asian ☐ Black ☐ Caucasian ☐ Hispanic ☐ Other, specify:	Weight: ☐ kgs ☐ lbs Height: ☐ cm ☐ in

Date of Last Menstrual Period (LMP) (DD-MMM-YYYY): - -

Estimated Delivery Date (DD-MMM-YYYY): - - (Specify method of calculation)

☐ LMP ☐ Ultrasound, Date (DD-MMM-YYYY): - - ☐ **Other, please specify:**

Was a contraception method used? ☐ Yes ☐ No ☐ Unknown (if yes, please check type of contraception)

☐ Oral contraception (type not known)	☐ Oral contraception (Progesterone)	☐ Contraceptive Implant	☐ Intra-uterine device
☐ Oral contraception (Oestrogen + Progesterone)	☐ Transdermal contraception	☐ Contraceptive injection	☐ Condom

Do you think there was a failure in contraception? ☐ Yes ☐ No ☐ Unknown

Cause/reason for failure:

Hypertension	☐	☐	Alcohol	☐	☐	History of Infertility	☐	☐
Hypertension gestational	☐	☐	Smoking	☐	☐	Conceived with treatment (please specify the details of treatment):	☐	☐
Eclampsia	☐	☐	Thyroid disorder	☐	☐			
Diabetes	☐	☐	Infections during pregnancy	☐	☐	Other (e.g. autoimmune disease, epilepsy) :	☐	☐
Diabetes gestational	☐	☐	Environmental or occupational exposure that may pose a risk factor:	☐	☐			

PREVIOUS OBSTETRIC HISTORY

No	Gestation week at delivery or other pregnancy outcome	Outcome of the pregnancy including any previous maternal complications and previous foetal / neonatal abnormalities and type
1		
2		
3		
4		

FAMILY HISTORY

Is there any history of congenital abnormalities (major or minor) or diseases in paternal or maternal family? ☐ Yes ☐ No ☐ Unknown

If yes, please specify:

Blood relationship between parents ? ☐ Yes ☐ No ☐ Unknown

(If yes, specify degree)

DRUG INFORMATION – please list all medications, including OTC medications, and dietary supplements taken prior to or during pregnancy

Drug Names (please use Additional Information section if necessary)	Dose / Frequency	Route	Treatment Dates		Indication	Time of exposure			
			Start	Stop		Before LMP	Trimester		
							1	2	3
						☐	☐	☐	☐
						☐	☐	☐	☐
						☐	☐	☐	☐
						☐	☐	☐	☐

Were administered drugs discontinued due to pregnancy ☐ Yes ☐ No ☐ Unknown

If yes, please specify the drugs that were discontinued:

In case of exposure to a biological product, please indicate the Batch No / Expiry date:

III. PREGNANCY INFORMATION

PRENATAL TESTS

Have all routine tests and special investigations done during pregnancy (e.g. amniocentesis, ultrasound, maternal serum AFP, serology tests, etc.)? ☐ Yes, please specify below No☐ Unknown ☐

Test name	Test date	Are results available?	Abnormal results?	Please provide detailed records if any abnormality was detected
		☐ Y ☐ N	☐ Y ☐ N	
		☐ Y ☐ N	☐ Y ☐ N	
		☐ Y ☐ N	☐ Y ☐ N	

PREGNANCY STATUS / OUTCOME

a) ☐ Pregnancy ongoing Gestational age: weeks Number of embryos / foetus(es):

Last ultrasound scan date (DD-MMM-YYYY): - - - ☐ Normal ☐ Abnormal, please specify:

b) ☐ Pregnancy outcome known ☐ ⇨ please tick all that apply below

☐	Full-term live birth (between 37 and 42 weeks of gestation)	☐	Therapeutic abortion (complete also part c)	☐	Normal vaginal delivery
☐	Premature live birth (< 37 completed weeks of gestation)	☐	Elective abortion (complete also part c)	☐	C-section
☐	Post-mature live birth (>42 completed weeks of gestation)	☐	Stillbirth / late foetal death (after 22 weeks of gestation)	☐	Forceps/Ventous Delivery
☐	Spontaneous abortion / miscarriage (up to 22 weeks gestation)	☐	Other:		

For the pregnancy outcome, please also provide: Date delivery/abortion and /or Week of gestation

c) **Reason(s) for elective or therapeutic abortion?** *Complete this section only if Therapeutic abortion or Elective abortion was ticked in part b)*

☐ i) Risk to the mother Please specify	☐ ii) Concern about potential foetal anomaly	☐ Both i) and ii)	☐ Other, Please specify

In case of stillbirth or any type of abortion, was an autopsy performed?: Yes ☐ No ☐, if yes please provide the autopsy or pathology report,

MATERNAL PREGNANCY ASSOCIATED ADVERSE EVENTS: Yes ☐ No ☐
(If the mother experienced an adverse event during pregnancy, please complete an adverse event data collection form and submit as requested)

IV. NEONATE / NEWBORN INFORMATION (At the time of birth)

☐	**Live birth - Normal baby**	☐	Live with congenital / other (structural) abnormality Please specify:
☐	**Live birth with major congenital anomaly** ☐ Orofacial cleft ☐ Neural tube defects ☐ Limb deficiencies ☐ Congenital heart defects ☐ Intestinal malrotation ☐ Unilateral kidney agenesis ☐ Urethral obstruction ☐ Others **Please specify:**	☐ ☐	Fetal death / intrauterine death with fetal anomaly Fetal death / intrauterine death without fetal anomaly

☐	**Live with minor congenital anomaly minor** ☐ Hydrocele ☐ Ear lobe abnormalities ☐ Abnormalities of toes / fingers ☐ Facial asymmetry ☐ Undescended testes ☐ Simian crease ☐ Pectus excavatum ☐ Others **Please specify:**	☐	Neonatal screening for Metabolic disorders done (e.g. tandem mass spectrometry, blood spot screening): ☐ No ☐ Yes: (Please specify results) ☐ Other: Please specify

Gender: ☐ Male ☐ Female	Length:		Weight: ☐ gram ☐ lb oz
Head circumference: ☐ cm ☐ in			**Apgar Scores 1 min. 5 min. 10 min.**

	For supplementary neonate information, please use the Additional Information section (please provide copies of relevant documentation)

V. ASSESSMENT OF PREGNANCY OUTCOME

Pregnancy outcome serious? ☐ Yes ☐ No - If Yes, tick all that apply:

☐	Life-threatening	☐	Medically significant
☐	Disability/incapacity	☐	Fatal
☐	Congenital anomaly/birth defect		Date of death of the mother (DD-MMM-YYYY): - - Cause of death:
☐	New hospitalization / prolongation of hospitalization		Date of death of the neonate (DD-MMM-YYYY): - - Cause of death:

ASSESSMENT OF CAUSALITY: Please indicate the relationship between the pregnancy outcome and Novartis drug

☐Not Suspected	☐Suspected

FOR ADDITIONAL INFORMATION:

REPORTER INFORMATION *To be completed only if authorized by local data privacy regulation or if not authorized to be left blank/ redacted (before uploading into AA)*	
Reporter Name Title **Reporter Name** *First Name:* *Last Name:*	**Address:** *Street:* *City:* *State or Province:* *Postal Code:* *Country:*
Institution: Department:	Phone: Fax: E- mail:
Reporter type: Healthcare professional: ☐ Yes, ☐ Nolf yes, please specify occupation: Patient ☐ Other ☐ Health Authority Case Number:	

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable.