NOVARTIS

Patient Safety & Pharmacovigilance

Asciminib

ABL001

EU Safety Risk Management Plan

Active substance (INN or common name):	Asciminib
Product concerned (brand name):	Scemblix®
Document status:	Final
Version number:	2.1
Data lock point for this RMP	Study CABL001A2301: 22-Mar-2023 Study CABL001X2101: 14-Mar-2023 PSUR: 28-Oct-2023
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Template version 6.4, Effective from 12-Dec-2023

Rationale for submitting an updated RMP:

This Risk Management Plan (RMP) version (v) 2.1 is updated following the Committee for Medicinal Products for Human Use (CHMP)/Pharmacovigilance Risk Assessment Committee (PRAC) request for supplementary information as part of Procedure No. EMEA/H/C/005605/II/0017, dated 28-Nov-2024.

Summary of significant changes in this RMP:

- The text pertaining to the clinical trials was deleted from the relevance to human usage for reproductive toxicity in Table 3-1 and the information was moved to Module SVII Table 8-15 under the characterization of the risk subheading.
- The concluding paragraph below Table 3-1 from the non-clinical part of the safety specification was deleted because it has been inadvertently duplicated during the RMP v2.0.

Part	Major changes in RMP v 2.1 compared to RMP v 2.0
Part I	No change
Part II	
Module SI	No change
Module SII	Deleted the text from Table 3-1 pertaining to the clinical trials from the relevance to human usage for reproductive toxicity and the information is moved to Module SVII. Deleted the concluding paragraph below Table 3-1 from the non-clinical part of the safety specification because it has been inadvertently duplicated during the RMP v2.0 preparation.
Module SIII	No change
Module SIV	No change
Module SV	No change
Module SVI	No change
Module SVII	Updated the text pertaining to the clinical trials in the characterization of the risk in Table 8-15.
Module SVIII	No change
Part III	No change
Part IV	No change
Part V	No change
Part VI	No change
Part VII	
Annex Number	
Annex 1	No change
Annex 2	No change
Annex 3	No change
Annex 4	No change
Annex 5	No change
Annex 6	No change
Annex 7	No change

Part	Major changes in RMP v 2.1 compared to RMP v 2.0
Annex 8	Updated the Summary of changes with RMP version 2.1

Other RMP versions under evaluation

CCI

Details of the currently approved RMP:

Version 1.2

Approved with procedure: EMEA/H/C/005605/0000

Dated: 15-Jun-2022

QPPV name: Dr. Justin Daniels

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization applicant'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
ATP	Adenosine triphosphate
aGFR	Absolute glomerular filtration rate
ALL	Acute lymphoblastic leukemia
Allo-SCT	Allogeneic stem cell transplantation
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Accelerated phase
AST	Aspartate aminotransferase
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
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
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
Ph+	Philadelphia chromosome-positive
PK	Pharmacokinetics
PL	Package leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Product Safety Update Report
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 and 40 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.
Hyperlink to the Product Information	[Current approved SmPC]
Indications in the EEA	**Current:** Asciminib is indicated for treatment of adult patients with Philadelphia chromosome positive (Ph+) CML in chronic phase (CP), previously treated with 2 or more tyrosine kinase inhibitors (TKIs).
	Proposed: Not applicable
Dosage in the EEA	**Current:** The recommended dose of asciminib is 40 mg twice daily at approximately 12-hour intervals (b.i.d.), taken orally without food.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** 20 mg and 40 mg FCT
	Proposed: Not applicable

Is/will the product be subject to additional monitoring in the EU?	Yes

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication: Chronic Myeloid Leukemia

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). 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 2017 was 1.29 cases per 100000, being highest in Western Europe and lowest in Central Europe (GBD 2020). In the United States of America (US), the incidence is 1.9 per 100000 persons (based on Surveillance, Epidemiology, and End Results [SEER] 21 data from 2014-2018, age-adjusted to the 2000 US standard population) and it is estimated that there would be 9110 new patients with CML in 2021 (SEER 2021).

Table 2-1 Annual incidence of chronic myeloid leukemia in EU in the year 2017

	Incidence of chronic myeloid leukemia					
	Male		Female		Male and Female	
Countries	Rate*	Cases	Rate*	Cases	Rate*	Cases
France	1.86	595	1.08	364	1.46	959
Germany	1.89	777	1.56	659	1.72	1435
Italy	2.12	624	1.26	392	1.68	1016
Spain	1.77	402	0.96	227	1.36	629
United Kingdom	1.39	458	1.04	351	1.21	809
Central Europe	0.84	472	0.36	210	0.59	682
Eastern Europe	0.96	937	0.81	914	0.88	1851
Western Europe	1.72	3655	1.14	2507	1.42	6162
EU-28	1.58	3959	1.01	2636	1.29	6595

Source: GBD 2020
* per 100000, age-standardized to the Global Burden of Disease (GBD) world population

In published studies, the proportion of patients with CML who received third-line therapy has been reported to range from 5.2% (Henk et al 2015) to 14.4% (Bosi et al 2019).

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 2018, there were an estimated 61698 people living with CML in the US (SEER 2021).

Data on the complete prevalence of CML in the overall EU region are limited. According to RARECARENet (2008), the complete prevalence of CML in Europe was 32412 persons (6.3 per 100000) in 2008. In a German study, the estimated complete prevalence for 2012 was 11.2 per 100000 population (12.0 and 10.6 per 100000 population in males and females, respectively) (Lauseker et al 2016). In a study in the United Kingdom, the complete prevalence was 14.7 per 100000 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 100000 population. The complete

prevalence of CML in the Nordic countries collectively in 2016 was 13.2 per 100000 (NORDCAN 2021).

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 2014 to 2018, the median age of diagnosis of CML is 65 years (SEER 2021). 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
- 7.6% between 20 and 34 years
- 7.5% between 35 and 44 years
- 12.5% between 45 and 54 years
- 18.5% between 55 and 64 years
- 22.0% between 65 and 74 years
- 19.9% between 75 and 84 years
- 9.8% 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 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 (/100000)	Women (/100000)
All Races	2.5	1.5
White	2.5	1.5
Black	2.3	1.5
Asian/Pacific Islander	1.8	0.9
American Indian/Alaska Native	1.6	1.0
Hispanic	1.9	1.2
Non-Hispanic	2.5	1.5
Source: SEER 2021		

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 (2G-TKIs) 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 2G-TKIs is associated with an increased discontinuation rate, ranging between 60%-72% by 4-6 years after treatment initiation (Giles et al 2013, Shah et al 2014, Gambacorti-Passerini et al 2018).

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 harboring 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 Guidelines v3.2021).

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 3-5 years, untreated patients with CML-CP inevitably progress to CML-BP. Chronic myeloid leukemia-acute phase 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 is 3 to 12 months (Quintás-Cardama et al 2006, Cortes 2004). 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 3G-TKIs, the incorporation of these agents into the treatment has improved the prognosis of patients with CML 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 2G-TKIs, 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 2G-TKIs achieved a 4.5-log molecular response ($MR^{4.5}$, $BCR::ABL1^{IS} \leq 0.0032\%$) (Cortes and Lang 2021). 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 100000 men and women per year (SEER 2021). Mortality rate of CML by race/ethnicity is provided in Table 2-3, below.

Table 2-3 Mortality rate of chronic myeloid leukemia patients

Race/Ethnicity	Men (/100000 men per year)	Women (/100000 women per year)
All Races	0.4	0.2
White	0.4	0.2
Black	0.4	0.2
Asian/Pacific Islander	0.2	0.1
American Indian/Alaska Native	N/A	N/A
Hispanic	0.3	0.2
Non-Hispanic	0.4	0.2
N/A: Statistic not displayed due to low number of cases **Source:** SEER 2021		

A systematic literature review to evaluate the specific causes of deaths in CML-CP patients receiving second- or third-line 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.

Important co-morbidities

Information on comorbidities in patients with CML starting third-line therapy is not available from population-based or observational studies. The comorbidities in adult CML patients starting second-line therapy was reported in a retrospective cohort study on 878 CML patients in 2 US administrative claims databases from 1997 to 2011. The intention of the study was to analyze clinical and economic outcomes and treatment adherence of nilotinib and dasatinib as second-line treatments in imatinib-resistant or intolerant patients. Diseases were identified using reported International classification of diseases-9th revision-clinical modification codes in medical claims. This type of study has limitations since there may be some inaccuracies in coding diagnosis and procedures and they do not include patient's complete profile or relevant disease risk factors such as family history or disease severity. Table 2-4 summarizes the comorbidities of those patients before they started treatment with nilotinib or dasatinib (Guerin et al 2012).

Table 2-4 Comorbidities (%) in adult chronic myeloid leukemia patients starting second-line therapy

Comorbidity	Nilotinib patients (n=328)	Dasatinib patients (n=550)
Anemia	72.0	65.5
Chronic pulmonary disease	21.0	17.1
Cardiovascular disease	22.6	17.8
Cerebrovascular disease	8.5	9.5
Congestive heart failure	5.2	4.9
Coagulopathy	12.8	14.4

Comorbidity	Nilotinib patients (n=328)	Dasatinib patients (n=550)
Depression	17.4	10.9
Diabetes	23.2	22.2
Fibromyalgia	7.3	11.6
Fluid electrolyte disorders	19.5	15.6
Hyperlipidemia	43.0	34.0
Hypertension	47.3	38.5
Hypothyroidism	12.8	11.5
Liver disease	5.5	5.8
Lymphoma	11.0	10.2
Macular degeneration	5.2	4.7
Neurologic disorders	7.0	4.9
Obesity	6.1	7.8
Osteoporosis	8.5	5.3
Peripheral vascular disease	13.4	6.4
Psychoses	9.5	6.4
Renal failure	17.3	4.9
Solid tumor	17.7	15.3
Valvular disease	19.5	12.4
The data reports comorbidities observed during 180 days before the start date of nilotinib/dasatinib. **Source:** Guerin et al 2012.		

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 2-5).

Table 2-5 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	

Cardiovascular risk factors and diseases	Prevalence
Myocardial infarction/angina	4.7%
Arrhythmia	3.5%
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%) in 1 study. 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).

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

Table 3-1Key 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. 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/kd/day. Benign Sertoli cell tumors in the ovaries were observed in female rats at the	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

Key Safety findings (from non-clinical studies)	Relevance to human usage
highest dose of 66 mg/kg/day. AUC exposures to 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. No asciminib-related neoplastic or hyperplastic findings were noted in males.	Safety Database, there is no evidence of a 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- or 6-fold than the Cmax exposure in patients at the dose of 40 mg b.i.d. and 80 mg q.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. or 80 mg q.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. 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. 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	Anemia, all grades and grade 3/4, was reported in the clinical development program. Myelosuppression is an important identified risk.

Key Safety findings (from non-clinical studies)	Relevance to human usage
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.	
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, exposure 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. 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: • 19-fold higher (in rats) and equivalent (in monkeys) to those achieved in patients at the 40 mg b.i.d. dose. • 13-fold higher (in rats) and equivalent (in monkeys) to those achieved in patients at the 80 mg q.d. dose. 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.	The relevance to humans is unclear at this time.
Safety Pharmacology	
Cardiovascular findings Asciminib showed extremely low to no effects on IKs and hCav1.2 ion channels (inhibition by 5.2%	The concentration-effect analysis indicated a lack of clinically relevant effect on cardiac

Key Safety findings (from non-clinical studies)	Relevance to human usage
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 or > 100 fold when compared to free exposure in patients at dose of 40 mg b.i.d. or 80 mg q.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 would correspond to a free Cmax of 6.3 µM (free fraction in dog: 0.02); value 100-fold and 60-fold higher than the one achieved in patients at 40 mg b.i.d. and 80 mg q.d., respectively.	repolarization with asciminib at 40 mg b.i.d. or 80 mg q.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 (IC50 18 µM) and norepinephrine transporter (IC50 22 µM).	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). Considering the off-target interaction displaying the strongest affinity (IC50 3.3 µM) and comparing to the free exposure achieved in patients, the calculated safety margins actually are all > 60. Therefore, taking into consideration safety margins of > 60 and the low brain penetration by asciminib following oral administration, off-target related adverse reactions resulting from interactions on 5-lipoxygenase, VMAT-2 transporter and 5HT2b receptor serotonin are unlikely to develop in humans.

Key Safety findings (from non-clinical studies)	Relevance to human usage
	Based on the current available data, there is no concern relevant to human usage.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Asciminib is indicated for the treatment of adult patients with:

- Philadelphia chromosome-positive CML in CP previously treated with 2 or more TKIs

Clinical trial exposure data for "patients with Ph+ CML previously treated with 2 or more TKIs' are based on the results of 2 studies.

- Study CABL001A2301 (registration study; hereafter referred to as Study A2301) and
- 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+ CML-CP or AP treated with single agent asciminib irrespective of the dose schedule.

The details of the clinical studies contributing to the Safety Pools are summarized in Table 4-1. Duration of exposure (safety set), exposure by age group and gender, and exposure by race (safety set) are provided in Table 4-2, Table 4-3 and Table 4-4 respectively.

Table 4-1 Clinical studies contributing to the asciminib Safety Pool*

Population	Studies	Study description	Dose schedule	Cut-off date
Adult subjects with Ph+ CML-CP previously treated with ≥ 2 TKIs	CABL001A2301	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.	22-Mar-2023 (End of Treatment period)

Population	Studies	Study description	Dose schedule	Cut-off date
Adult subjects with Ph+ CML or Ph+ ALL, relapsed, refractory to or intolerant of TKIs**	CABL001X2101	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 (End of Study)

*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.

Sources: Study A2301 EOT report, Study X2101 final report

Table 4-2 Duration of exposure (safety set)

Duration	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%)	Asciminib 40 mg b.i.d. N=156 n (%)	Asciminib 80 mg q.d. (CP) N=18 n (%)	Asciminib 40 mg b.i.d. (CP) N=187 n (%)	Asciminib All subjects N=356 n (%)
Duration of exposure categories -n (%)					
Less than 8 weeks	10 (13.2)	12 (7.7)	0	14 (7.5)	24 (6.7)
At least 8 weeks	66 (86.8)	144 (92.3)	18 (100)	173 (92.5)	332 (93.3)
At least 16 weeks	60 (78.9)	139 (89.1)	17 (94.4)	168 (89.8)	321 (90.2)
At least 24 weeks	49 (64.5)	129 (82.7)	17 (94.4)	156 (83.4)	299 (84.0)
At least 48 weeks	22 (28.9)	105 (67.3)	16 (88.9)	130 (69.5)	261 (73.3)
At least 96 weeks	19 (25.0)	88 (56.4)	16 (88.9)	110 (58.8)	227 (63.8)
At least 144 weeks	11 (14.5)	85 (54.5)	13 (72.2)	105 (56.1)	206 (57.9)
At least 192 weeks	4 (5.3)	34 (21.8)	11 (61.1)	53 (28.3)	142 (39.9)
Subject-treatment years	**83.3**	**355.2**	**79.3**	**498.6**	**1148.0**

Subject-treatment years (STY) is the sum of each subject's treatment exposure in years.

Source: Annex 7-Table 5-1.

Table 4-3 Exposure by age group and gender

		CABL001A2301				CABL001X2101		Safety Pool			
		Bosutinib 500 mg q.d. N=76		Asciminib 40 mg b.i.d. N=156		Asciminib 80 mg q.d. (CP) N=18		Asciminib 40 mg b.i.d. (CP) N=187		Asciminib All subjects N=356	
Gender	**Age (years)**	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**
Total	Total	76 (100)	83.3	156 (100)	355.2	18 (100)	79.3	187 (100)	498.6	356 (100)	1148.0
	18-<65	61 (80.3)	63.4	127 (81.4)	291,1	12 (66.7)	57.7	152 (81.3)	414.9	272 (76.4)	890.9
	>=65	15 (19.7)	19.9	29 (18.6)	64.2	6 (33.3)	21.7	35 (18.7)	83.7	84 (23.6)	257.1
	>=75	2 (2.6)	3.1	4 (2.6)	15.8	2 (11.1)	8.2	5 (2.7)	20.4	21 (5.9)	73.3

		CABL001A2301				CABL001X2101		Safety Pool			
		Bosutinib 500 mg q.d. N=76		Asciminib 40 mg b.i.d. N=156		Asciminib 80 mg q.d. (CP) N=18		Asciminib 40 mg b.i.d. (CP) N=187		Asciminib All subjects N=356	
Gender	Age (years)	Subjects n (%)	STY	Subjects n (%)	STY	Subjects n (%)	STY	Subjects n (%)	STY	Subjects n (%)	STY
Female	Total	45 (59.2)	36.7	75 (48.1)	179.3	10 (55.6)	47.9	88 (47.1)	237.5	155 (43.5)	512.2
	18-<65	36 (47.4)	28.2	63 (40.4)	153.8	7 (38.9)	31.7	74 (39.6)	206.7	121 (34.0)	403.7
	>=65	9 (11.8)	8.4	12 (7.7)	25.5	3 (16.7)	16.2	14 (7.5)	30.8	34 (9.6)	108.5
	>=75	2 (2.6)	3.1	2 (1.3)	7.9	1 (5.6)	6.3	3 (1.6)	12.6	10 (2.8)	42.7
Male	Total	31 (40.8)	46.6	81 (51.9)	175.9	8 (44.4)	31.4	99 (52.9)	261.1	201 (56.5)	635.8
	18-<65	25 (32.9)	35.2	64 (41.0)	137.3	5 (27.8)	26.0	78 (41.7)	208.2	151 (42.4)	487.2
	>=65	6 (7.9)	11.4	17 (10.9)	38.6	3 (16.7)	5.4	21 (11.2)	52.9	50 (14.0)	148.6
	>=75	0		2 (1.3)	7.9	1 (5.6)	1.8	2 (1.1)	7.9	11 (3.1)	30.6

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.

Source: Annex 7-Table 5-2

Table 4-4 Exposure by race (safety set)

	CABL001A2301				CABL001X2101		Safety Pool			
	Bosutinib 500 mg q.d. N=76		Asciminib 40 mg b.i.d. N=156		Asciminib 80 mg q.d. (CP) N=18		Asciminib 40 mg b.i.d. (CP) N=187		Asciminib All subjects N=356	
Race	Subjects n (%)	STY	Subjects n (%)	STY	Subjects n (%)	STY	Subjects n (%)	STY	Subjects n (%)	STY
White	56 (73.7)	67.7	117 (75.0)	257.7	13 (72.2)	59.7	139 (74.3)	353.7	236 (66.3)	724.2
Asian	11 (14.5)	9.5	22 (14.1)	55.3	2 (11.1)	9.7	28 (15.0)	87.8	69 (19.4)	260.9
Black or African American	2 (2.6)	1.6	8 (5.1)	18.5	1 (5.6)	6.0	10 (5.3)	32.1	13 (3.7)	39.0
Other	7 (9.2)	4.5	5 (3.2)	17.5	2 (11.1)	3.9	6 (3.2)	18.8	25 (7.0)	87.6
Unknown	0		3 (1.9)	3.1	0		3 (1.6)	3.1	12 (3.4)	33.3
American Indian or Alaska Native	0		1 (0.6)	3.0	0		1 (0.5)	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.

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

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

Table 5-1 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 data are available yet.	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, fetotoxocity and teratogenicity. No human data are available. Thus, pregnant women and women of child-bearing potential, unless they are using highly effective contraception, were excluded from studies in the development program.	No	Based on non-clinical data, reproductive toxicity has been considered as an important potential risk. Please refer Section 8.
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:	Patients with history of cardiac disease with	No	Events pertaining to cardiac ischemic

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
• 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 congenital long QT syndrome: risk factors for Torsades de Pointes; concomitant medication(s) with a “Known risk of Torsades de Pointes”	specific criteria as listed were excluded from the clinical development program as a precaution. The available concentration-dependent analysis data show a slightly dose dependent, non-clinically meaningful increase in QTc.		conditions observed in the clinical studies did not confirm a causal role of asciminib for these events. However, these events (along with CNS ischemic conditions) will be reviewed on ongoing basis as a part of Periodic Safety Update Report. QTc prolongation is an important identified risk for asciminib. Please refer to Section 8.
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	No	Acute pancreatitis (including isolated pancreatic enzyme elevations) is an important

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
	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.		identified risk for asciminib. Please refer to Section 8.
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 8.
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]/ alanine aminotransferase [ALT] > 3xULN) were excluded from the development program.	Yes	Use in patients with hepatic impairment is missing information. Please refer to Section 8.
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 8.
Impaired GI function or GI disease	These are precautionary measures to preclude enrolling patients with	No	Mild to moderate GI AEs were reported in clinical trials, with no

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
	conditions which alter the absorption of oral medication in the clinical trial.		life-threatening events. Gastrointestinal toxicity is considered as having no impact on the benefit-risk balance of asciminib. Please refer to Section 8.
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 AUCinf, AUClast and Cmax values following a single dose of asciminib by 36%, 37% and 19%, respectively.

5.2 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.

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

Table 5-2 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 8 were patients with renal impairment (measured by absolute glomerular filtration rate [aGFR]). Exposure of special populations either included or not included in clinical trial development programs is provided in Table 5-3.
• 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 4-4 for exposure data by race.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other	Excluded patients with significant congenital or

Type of special population	Exposure
	acquired bleeding disorder unrelated to cancer.

Table 5-3 Exposure of special populations either included or not included in clinical trial development programs (safety set)

	CABL001A2301				CABL001X2101		Safety Pool			
	Bosutinib 500 mg q.d. N=76		Asciminib 40 mg b.i.d. N=156		Asciminib 80 mg q.d. (CP) N=18		Asciminib 40 mg b.i.d. (CP) N=187		Asciminib All subjects N=356	
Special population	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**	**Subjects n (%)**	**STY**
Subjectswith moderate renal impairment	4 (5.3)	6.0	10 (6.4)	17.0	3 (16.7)	14.4	13 (7.0)	35.2	30 (8.4)	97.6
Subjects with mild renal impairment	31 (40.8)	29.2	60 (38.5)	137.1	7 (38.9)	26.6	73 (39.0)	189.2	142 (39.9)	459.9

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.

Source: Annex 7-Table 5-4.

6 Part II Safety specification Module SV: Post-authorization experience

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

6.1.1 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 reporting interval and the recommended total daily dose of 80 mg as per the CDS.

6.1.2 Part II Module SV.1.2. Exposure

Asciminib is approved in more than 70 countries for subjects with Ph+ CML in CP previously treated with two or more TKIs.

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

The estimated exposure and cumulative exposure is provided in the Table 6-1 and Table 6-2, respectively.

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

Table 6-1 Estimated post marketing (non-clinical trial) exposure

Formulation	Cumulative till 28 Oct 2023	
	Amount sold (in mg)	Estimated exposure (STY)
Asciminib FCT 20 mg	CCI	318
Asciminib FCT 40 mg	CCI	4,002
Total	CCI	4,320

FCT: Film-coated tablets; mg: milligrams; MS: Microsoft; STY: Subject treatment years

Source of data: Worldwide sales volume from company database.

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

Table 6-2 Cumulative exposure from marketing experience

	EEA (in STY)	USA and Canada (in STY)	Japan (in STY)	ROW[&] (in STY)
FCT 20 mg	39	CCI	CCI	17
FCT 40 mg	987	CCI	CCI	519
Total	1,026	CCI	CCI	536

	EEA (in STY)	USA and Canada (in STY)	Japan (in STY)	ROW[&] (in STY)
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 31-Oct-2023 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				

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

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

8 Part II Safety specification Module SVII: Identified and potential risks

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

8.1.1 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:

Reason for non-inclusion as a safety concern	Safety concerns	Rationale for non-inclusion as an RMP safety concern
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)	Gastrointestinal toxicity	**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

Reason for non-inclusion as a safety concern	Safety concerns	Rationale for non-inclusion as an RMP safety concern
		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 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

Reason for non-inclusion as a safety concern	Safety concerns	Rationale for non-inclusion as an RMP safety concern
		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).
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	Hypersensitivity	**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** 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).

Reason for non-inclusion as a safety concern	Safety concerns	Rationale for non-inclusion as an RMP safety concern
		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).

Reason for non-inclusion as a safety concern	Safety concerns	Rationale for non-inclusion as an RMP safety concern
		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).
Known risks that do not impact the risk-benefit profile	Phototoxicity	**Data from non-clinical studies** 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 CMLCP/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

Reason for non-inclusion as a safety concern	Safety concerns	Rationale for non-inclusion as an RMP safety concern
		(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).

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

Table 8-1 Important identified risks

Risks	Risk-benefit impact (Reasons for classification as important identified risks)
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

Risks	Risk-benefit impact (Reasons for classification as important identified risks)
	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.

Risks	Risk-benefit impact (Reasons for classification as important identified risks)
	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 8-2 Important potential risks

Risks	Risk-benefit impact (Reasons for classification as important potential risks)
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 8-3 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

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

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

8.2 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.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

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

8.3.1.1 Important identified risk: acute pancreatitis (including isolated pancreatic enzyme elevations)

Table 8-4 Clinical trial data of acute pancreatitis (including isolated pancreatic enzyme elevations) (Safety set)

Acute pancreatitis (including isolated pancreatic enzyme elevations)	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI	Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Number of subjects with at least one event	7 (9.2) (3.8, 18.0)	13 (8.3) (4.6, 13.8)	6 (33.3) (13.4, 59.0)	30 (16.0) (11.0, 22.2)	85 (23.9) (19.6,28.6)
Exposure-adjusted overall incidence, n (EAIR per 100 STY)	7 (9.0)	13 (3.8)	6 (10.3)	30 (7.0)	85 (9.9)
Cumulative incidence proportion at n (%) cum IP					
Week 8 (Day 56)	1 (1.3) 1.32	7 (4.5) 4.49	1 (5.6) 5.56	17 (9.1) 9.09	39 (11.0) 10.96
Week 24 (Day 168)	4 (5.3) 5.26	10 (6.4) 6.41	3 (16.7) 16.67	24 (12.8) 12.83	58 (16.3) 16.29
Week 48 (Day 336)	6 (7.9) 7.89	12 (7.7) 7.69	5 (27.8) 27.78	27 (14.4) 14.44	71 (19.9) 19.94
Week 60 (Day 420)	7 (9.2) 9.21	12 (7.7) 7.69	5 (27.8) 27.78	27 (14.4) 14.44	71 (19.9) 19.94
Week 96 (Day 672)	7 (9.2) 9.21	13 (8.3) 8.33	5 (27.8) 27.78	29 (15.5) 15.51	76 (21.3) 21.35
Number of subjects with at least one event by Preferred Term					
Lipase increased	5 (6.6)	8 (5.1)	4 (22.2)	24 (12.8)	69 (19.4)
Amylase increased	4 (5.3)	9 (5.8)	3 (16.7)	16 (8.6)	42 (11.8)
Pancreatitis	0	0	1 (5.6)	2 (1.1)	8 (2.2)
Hyperlipasaemia	0	0	0	2 (1.1)	4 (1.1)
Pancreatitis acute	0	0	0	1 (0.5)	2 (0.6)
Maximum grade					
Grade 3 AEs	4 (5.3)	4 (2.6)	3 (16.7)	13 (7.0)	41 (11.5)

Acute pancreatitis (including isolated pancreatic enzyme elevations)	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI	Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Lipase increased	4 (5.3)	4 (2.6)	3 (16.7)	11 (5.9)	33 (9.3)
Amylase increased	0	1 (0.6)	0	3 (1.6)	7 (2.0)
Hyperlipasaemia	0	0	0	2 (1.1)	4 (1.1)
Pancreatitis	0	0	0	1 (0.5)	3 (0.8)
Pancreatitis acute	0	0	0	0	1 (0.3)
Grade 4 AEs	0	2 (1.3)	0	4 (2.1)	9 (2.5)
Lipase increased	0	2 (1.3)	0	3 (1.6)	8 (2.2)
Amylase increased	0	0	0	1 (0.5)	1 (0.3)
Grade 5 AEs	0	0	0	0	0
Treatment-related AEs	3 (3.9)	8 (5.1)	6 (33.3)	23 (12.3)	66 (18.5)
Lipase increased	2 (2.6)	5 (3.2)	4 (22.2)	19 (10.2)	55 (15.4)
Amylase increased	1 (1.3)	7 (4.5)	3 (16.7)	13 (7.0)	34 (9.6)
Pancreatitis	0	0	1 (5.6)	2 (1.1)	8 (2.2)
Hyperlipasaemia	0	0	0	2 (1.1)	4 (1.1)
Pancreatitis acute	0	0	0	1 (0.5)	2 (0.6)
SAEs	0	0	0	2 (1.1)	5 (1.4)
Pancreatitis	0	0	0	0	2 (0.6)
Pancreatitis acute	0	0	0	1 (0.5)	2 (0.6)
Amylase increased	0	0	0	1 (0.5)	1 (0.3)
Action taken					
Drug withdrawn	0	3 (1.9)	0	6 (3.2)	10 (2.8)
Dose adjusted	0	0	2 (11.1)	3 (1.6)	21 (5.9)
Drug interrupted	3 (3.9)	5 (3.2)	2 (11.1)	12 (6.4)	35 (9.8)
Dose not changed/NA/Unknown	6 (7.9)	12 (7.7)	6(33.3)	27 (14.4)	76 (21.3)
Medication or therapy taken	0	0	0	2 (1.1)	7 (2.0)
AE outcome					
Recovered/resolved	7 (9.2)	13 (8.3)	6 (33.3)	30 (16.0)	83 (23.3)
Recovering/resolving	0	1 (0.6)	2 (11.1)	4 (2.1)	18 (5.1)
Not recovered/not resolved	1 (1.3)	2 (1.3)	2 (11.1)	6 (3.2)	21 (5.9)
Recovered/resolved with sequelae	0	0	0	1 (0.5)	1 (0.3)
Fatal	0	0	0	0	0
Unknown	0	0	0	0	0

Numbers (n) represent counts of subject. A subject may be counted in several rows for action taken and outcome.

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

Cum IP = cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason).

NA = Not applicable.

MedDRA version 26.0, CTCAE version 4.03, Case Retrieval Strategy version released 2022-11-22.

Cum IP presented as percentage (cum IP * 100).

Source: Annex 7-Table 4.2-6b.

Table 8-5 Important identified risk acute pancreatitis (including isolated pancreatic enzyme elevations): Other details

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.
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 3-1. **Clinical data** **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 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

Acute pancreatitis (including isolated pancreatic enzyme elevations)	Details
	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. 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.
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

Acute pancreatitis (including isolated pancreatic enzyme elevations)	**Details**
	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.
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.

8.3.1.2 Important identified risk: myelosuppression

Table 8-6 Clinical trial data of myelosuppression (Safety set)

Myelosuppression*	**CABL001A2301**		**CABL001X2101**	**Safety Pool**	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	**Asciminib 40 mg b.i.d. N=156 n (%) 95% CI**	**Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI**	**Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI**	**Asciminib All subjects N=356 n (%) 95% CI**
Number of subjects with at least one event	28 (36.8) (26.0,48.6)	60 (38.5) (30.8, 46.6)	9 (50.0) (26.0,74.0)	73 (39.0) (32.0, 46.4)	133 (37.4) (32.4, 42.6)
Exposure-adjusted overall incidence, n (EAIR per 100 STY)	28 (42.7)	60 (22.1)	9(14.6)	73 (19.1)	133 (14.8)
Cumulative incidence proportion at n (%) cum IP					
Week 8 (Day 56)	20 (26.3) 26.32	50 (32.1) 32.05	5 (27.8) 27.78	59 (31.6) 31.55	94 (26.4) 26.40
Week 24 (Day 168)	26 (34.2) 34.21	58 (37.2) 37.18	7 (38.9) 38.89	69 (36.9) 36.90	115 (32.3) 32.30
Week 48 (Day 336)	26 (34.2) 34.21	58 (37.2) 37.18	8 (44.4) 44.44	69 (36.9) 36.90	123 (34.6) 34.55
Week 60 (Day 420)	27 (35.5) 35.53	58 (37.2)37.18	8 (44.4) 44.44	69 (36.9) 36.90	123 (34.6) 34.55
Week 96 (Day 672)	28 (36.8) 36.84	59 (37.8) 37.82	8 (44.4) 44.44	70 (37.4) 37.43	125 (35.1) 35.11
Number of subjects with at least one event by Preferred Term					
Thrombocytopenia	11 (14.5)	36 (23.1)	5 (27.8)	43(23.0)	82 (23.0)
Neutropenia	13 (17.1)	30 (19.2)	4 (22.2)	34 (18.2)	56 (15.7)
Anaemia	6 (7.9)	16 (10.3)	4 (22.2)	22 (11.8)	45 (12.6)
Platelet count decreased	5 (6.6)	11 (7.1)	2(11.1)	15 (8.0)	23 (6.5)
Neutrophil count decreased	4 (5.3)	8 (5.1)	1 (5.6)	10 (5.3)	19 (5.3)
White blood cell count decreased	3 (3.9)	3 (1.9)	2 (11.1)	5 (2.7)	12 (3.4)

Myelosuppression*	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI	Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Leukopenia	2 (2.6)	2 (1.3)	1 (5.6)	3 (1.6)	7 (2.0)
Lymphopenia	0	0	0	1 (0.5)	4 (1.1)
Febrile neutropenia	0	1 (0.6)	0	1 (0.5)	3 (0.8)
Haemoglobin decreased	0	0	1 (5.6)	0	2 (0.6)
Anaemia macrocytic	0	0	0	0	1 (0.3)
Lymphocyte count decreased	1 (1.3)	0	0	0	0
Monocyte count decreased	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Myelosuppression	0	0	0	0	1 (0.3)
Pancytopenia	1 (1.3)	0	0	0	1 (0.3)
Normocytic anaemia	1 (1.3)	0	0	0	0
Maximum grade					
Grade 3 AEs	14 (18.4)	17 (10.9)	1 (5.6)	19 (10.2)	32 (9.0)
Neutropenia	5 (6.6)	8 (5.1)	1 (5.6)	9 (4.8)	13 (3.7)
Thrombocytopenia	3 (3.9)	10 (6.4)	0	10 (5.3)	14 (3.9)
Anaemia	2 (2.6)	0	0	2 (1.1)	9 (2.5)
Neutrophil count decreased	3 (3.9)	3 (1.9)	0	3 (1.6)	4 (1.1)
Platelet count decreased	2 (2.6)	3 (1.9)	0	3 (1.6)	3 (0.8)
Leukopenia	0	0	0	1 (0.5)	1 (0.3)
Febrile neutropenia	0	0	0	0	1 (0.3)
Lymphopenia	0	0	0	0	1 (0.3)
Myelosuppression	0	0	0	0	1 (0.3)
Lymphocyte count decreased	1 (1.3)	0	0	0	0
White blood cell count decreased	2 (2.6)	0	0	0	0
Grade 4 AEs	4 (5.3)	25 (16.0)	2 (11.1)	30(16.0)	55 (15.4)
Thrombocytopenia	2 (2.6)	16 (10.3)	2 (11.1)	17 (9.1)	34 (9.6)
Neutropenia	1 (1.3)	12 (7.7)	1 (5.6)	14 (7.5)	22 (6.2)
Platelet count decreased	0	2 (1.3)	1 (5.6)	5 (2.7)	9 (2.5)
Neutrophil count decreased	0	3 (1.9)	1 (5.6)	4 (2.1)	9 (2.5)
Leukopenia	0	0	1 (5.6)	0	1 (0.3)
Pancytopenia	1 (1.3)	0	0	0	1 (0.3)
Grade 5 AEs	0	0	0	0	0
Treatment-related AEs	21 (27.6)	47 (30.1)	6 (33.3)	56 (29.9)	99 (27.8)
Thrombocytopenia	11 (14.5)	31 (19.9)	5 (27.8)	36 (19.3)	66 (18.5)
Neutropenia	11 (14.5)	24 (15.4)	4 (22.2)	28 (15.0)	48 (13.5)
Anaemia	3 (3.9)	8 (5.1)	2 (11.1)	11 (5.9)	25 (7.0)
Neutrophil count decreased	2 (2.6)	5 (3.2)	1 (5.6)	7 (3.7)	15 (4.2)
Platelet count decreased	3 (3.9)	8 (5.1)	1 (5.6)	11 (5.9)	15 (4.2)
White blood cell count decreased	1 (1.3)	3 (1.9)	2 (11.1)	5 (2.7)	12 (3.4)
Leukopenia	2 (2.6)	2 (1.3)	1 (5.6)	3 (1.6)	7 (2.0)
Lymphopenia	0	0	0	1 (0.5)	4 (1.1)
Febrile neutropenia	0	1 (0.6)	0	1 (0.5)	2 (0.6)
Anaemia macrocytic	0	0	0	0	1 (0.3)
Myelosuppression	0	0	0	0	1 (0.3)
Pancytopenia	1 (1.3)	0	0	0	1 (0.3)
Normocytic anaemia	1 (1.3)	0	0	0	0

Myelosuppression*	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI	Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
SAEs	1 (1.3)	2 (1.3)	0	2 (1.1)	6 (1.7)
Thrombocytopenia	0	1 (0.6)	0	1 (0.5)	4 (1.1)
Febrile neutropenia	0	1 (0.6)	0	1 (0.5)	2 (0.6)
Platelet count decreased	0	1 (0.6)	0	1 (0.5)	2 (0.6)
Anaemia	0	0	0	0	1 (0.3)
Neutropenia	0	0	0	0	1 (0.3)
Pancytopenia	1 (1.3)	0	0	0	0
Action taken					
Drug withdrawn	4 (5.3)	6 (3.8)	0	6 (3.2)	10 (2.8)
Dose adjusted	3 (3.9)	9 (5.8)	2 (11.1)	11 (5.9)	24 (6.7)
Drug interrupted	13 (17.1)	36 (23.1)	2(11.1)	37 (19.8)	52 (14.6)
Dose not changed/NA/Unknown	25 (32.9)	51 (32.7)	9 (50.0)	64 (34.2)	123 (34.6)
Medication or therapy taken	10 (13.2)	22 (14.1)	4(22.2)	29 (15.5)	54 (15.2)
AE outcome					
Recovered/resolved	23 (30.3)	54 (34.6)	8 (44.4)	64 (34.2)	114 (32.0)
Recovering/resolving	16 (21.1)	32 (20.5)	4 (22.2)	38 (20.3)	65 (18.3)
Not recovered/not resolved	15 (19.7)	37 (23.7)	6 (33.3)	45 (24.1)	83 (23.3)
Recovered/resolved with sequelae	0	0	1 (5.6)	0	1 (0.3)
Fatal	0	0	0	0	0
Unknown	0	0	0	1 (0.5)	1 (0.3)

Numbers (n) represent counts of subjects. A subject may be counted in several rows for action taken and outcome.

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

Cum IP = cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason).

NA = Not applicable.

MedDRA version 26.0, CTCAE version 4.03, Case Retrieval Strategy version released 2022-11-22.

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

Cum IP presented as percentage (cum IP * 100).

Source: Annex 7-Table 5-6b.

Table 8-7 Important identified risk myelosuppression: Other details

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.
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	Details
	myelosuppression was not evident in non-clinical studies with asciminib (Table 3-1). **Clinical data** **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 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

Myelosuppression	Details
	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 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.
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.

8.3.1.3 Important identified risk: QTc prolongation

Table 8-8 Clinical trial data of QTc prolongation (Safety set)

QTc prolongation	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI	Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Number of subjects with at least one event	1 (1.3) (0.0, 7.2)	8 (5.1) (2.2, 9.8)	5 (27.8) (9.6, 53.4)	9 (4.8) (2.2, 9.0)	18 (5.1) (3.0, 7.8)
Exposure-adjusted overall incidence, n (EAIR per 100 STY)	1 (1.1)	8 (2.3)	5 (6.6)	9 (1.8)	18 (1.6)
Cumulative incidence proportion at n (%) cum IP					
Week 8 (Day 56)	1 (1.3) 1.32	2 (1.3) 1.28	0	2 (1.1) 1.07	2 (0.6) 0.56
Week 24 (Day 168)	1 (1.3) 1.32	2 (1.3) 1.28	0	2 (1.1) 1.07	2 (0.6) 0.56
Week 48 (Day 336)	1 (1.3) 1.32	4 (2.6) 2.56	2 (11.1) 11.11	4 (2.1) 2.14	7(2.0) 1.97
Week 60 (Day 420)	1 (1.3) 1.32	5 (3.2) 3.21	2 (11.1) 11.11	5 (2.7) 2.67	8 (2.2) 2.25
Week 96 (Day 672)	1 (1.3) 1.32	6 (3.8) 3.85	2 (11.1) 11.11	7 (3.7) 3.74	11 (3.1) 3.09
Number of subjects with at least one event by Preferred Term					
Syncope	1 (1.3)	3 (1.9)	2 (11.1)	4 (2.1)	8 (2.2)
Electrocardiogram QT prolonged	0	2 (1.3)	2 (11.1)	2 (1.1)	4 (1.1)
Ventricular tachycardia	0	1 (0.6)	0	1 (0.5)	2 (0.6)
Cardiac arrest	0	1 (0.6)	1 (5.6)	1 (0.5)	2 (0.6)
Loss of consciousness	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Ventricular arrhythmia	0	0	0	0	1 (0.3)
Maximum grade					
Grade 3 AEs	0	4 (2.6)	1 (5.6)	4 (2.1)	7 (2.0)
Syncope	0	1 (0.6)	1 (5.6)	1 (0.5)	3 (0.8)
Electrocardiogram QT prolonged	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Ventricular tachycardia	0	1 (0.6)	0	1 (0.5)	2 (0.6)
Loss of consciousness	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Grade 4 AEs	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Cardiac arrest	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Grade 5 AEs	0	0	1 (5.6)	0	1 (0.3)
Cardiac arrest	0	0	1 (5.6)	0	1 (0.3)
Treatment-related AEs	0	2 (1.3)	0	2 (1.1)	2 (0.6)
Electrocardiogram QT prolonged	0	2 (1.3)	0	2 (1.1)	2 (0.6)
SAEs	0	2 (1.3)	1 (5.6)	2 (1.1)	4 (1.1)
Cardiac arrest	0	1 (0.6)	1 (5.6)	1 (0.5)	2 (0.6)
Ventricular tachycardia	0	1 (0.6)	0	1 (0.5)	2 (0.6)
Action taken					
Drug withdrawn	0	0	1 (5.6)	0	1 (0.3)
Dose adjusted	0	0	0	0	0
Drug interrupted	0	2 (1.3)	0	2(1.1)	2 (0.6)
Dose not changed/NA/Unknown	1 (1.3)	8 (5.1)	4 (22.2)	9 (4.8)	17 (4.8)
Medication or therapy taken	0	2 (1.3)	1 (5.6)	2(1.1)	5 (1.4)
AE outcome					
Recovered/resolved	1 (1.3)	8 (5.1)	3 (16.7)	9 (4.8)	16 (4.5)

QTc prolongation	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI	Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Recovering/resolving	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Not recovered/not resolved	0	1 (0.6)	1 (5.6)	1 (0.5)	2 (0.6)
Recovered/resolved with sequelae	0	0	0	0	0
Fatal	0	0	1 (5.6)	0	1 (0.3)
Unknown	0	0	0	0	0

Numbers (n) represent counts of subject. A subject may be counted in several rows for action taken and outcome.

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

Cum IP = cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason).

NA = Not applicable.

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

Cum IP presented as percentage (cum IP * 100).

Source: Annex 7-Table 5-6b.

Table 8-9 Important identified risk QTc prolongation: Other details

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.
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 3-1. **Clinical data** **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

QTc prolongation	Details
	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. 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

QTc prolongation	Details
	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.
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).
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.

8.3.1.4 Important potential risk: hepatotoxicity

Table 8-10 Clinical trial data of hepatotoxicity (Safety set)

Hepatotoxicity (including laboratory terms)	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI	Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Number of subjects with at least one event	25 (32.9) (22.6, 44.6)	19 (12.2) (7.4, 18.4)	4 (22.2) (6.4, 47.6)	29 (15.5) (10.6, 21.6)	80 (22.5) (18.2, 27.2)
Exposure-adjusted overall incidence, n (EAIR per 100 STY)	25 (34.9)	19(5.8)	4(5.7)	29(6.5)	80(8.4)
Cumulative incidence proportion at n (%) cum IP					
Week 8 (Day 56)	13 (17.1) 17.11	7 (4.5) 4.49	2 (11.1) 11.11	11 (5.9) 5.88	28 (7.9) 7.87
Week 24 (Day 168)	23 (30.3) 30.26	9 (5.8) 5.77	3 (16.7) 16.67	13 (7.0) 6.95	42 (11.8) 11.80

Hepatotoxicity (including laboratory terms)	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI	Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Week 48 (Day 336)	25 (32.9) 32.89	12 (7.7) 7.69	3 (16.7) 16.67	17 (9.1) 9.09	53 (14.9) 14.89
Week 60 (Day 420)	25 (32.9) 32.89	12 (7.7) 7.69	3 (16.7) 16.67	18 (9.6) 9.63	56 (15.7) 15.73
Week 96 (Day 672)	25 (32.9) 32.89	15 (9.6) 9.62	3 (16.7) 16.67	21 (11.2) 11.23	62 (17.4) 17.42
Number of subjects with at least one event by Preferred Term					
Alanine aminotransferase increased	23 (30.3)	8 (5.1)	2 (11.1)	10 (5.3)	40 (11.2)
Aspartate aminotransferase increased	16 (21.1)	9 (5.8)	2 (11.1)	12 (6.4)	36 (10.1)
Gamma-glutamyltransferase increased	0	3 (1.9)	1 (5.6)	6 (3.2)	22 (6.2)
Blood alkaline phosphatase increased	0	2 (1.3)	1 (5.6)	3 (1.6)	12 (3.4)
Hypertransaminasaemia	0	0	1 (5.6)	1 (0.5)	6 (1.7)
Blood bilirubin increased	1 (1.3)	5 (3.2)	1 (5.6)	7 (3.7)	16 (4.5)
Hypoalbuminaemia	0	1 (0.6)	0	2 (1.1)	5 (1.4)
Bilirubin conjugated increased	0	0	0	0	3 (0.8)
Glutamate dehydrogenase increased	0	0	0	0	2 (0.6)
Hepatic steatosis	0	0	0	2 (1.1)	2 (0.6)
Ascites	0	0	0	0	1 (0.3)
Blood bilirubin unconjugated increased	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Congestive hepatopathy	0	0	0	0	1 (0.3)
Hepatic function abnormal	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Hepatic lesion	0	0	0	0	1 (0.3)
Hepatic pain	0	0	0	0	1 (0.3)
Hepatocellular injury	0	0	1 (5.6)	0	1 (0.3)
Hepatomegaly	0	0	0	0	1 (0.3)
Hyperbilirubinaemia	0	0	0	0	1 (0.3)
Liver disorder	0	0	0	0	1 (0.3)
Transaminases increased	1 (1.3)	0	0	0	0
Maximum grade					
Grade 3 AEs	13 (17.1)	3 (1.9)	1 (5.6)	4 (2.1)	15 (4.2)
Alanine aminotransferase increased	11 (14.5)	1 (0.6)	1 (5.6)	1 (0.5)	7 (2.0)
Gamma-glutamyltransferase increased	0	1 (0.6)	1 (5.6)	2 (1.1)	6 (1.7)
Aspartate aminotransferase increased	5 (6.6)	3 (1.9)	0	4 (2.1)	5 (1.4)
Hepatic pain	0	0	0	0	1 (0.3)
Hypoalbuminaemia	0	0	0	0	1 (0.3)
Liver disorder	0	0	0	0	1 (0.3)
Transaminases increased	1 (1.3)	0	0	0	0
Grade 4 AEs	0	0	0	0	3 (0.8)
Aspartate aminotransferase increased	0	0	0	0	1 (0.3)
Bilirubin conjugated increased	0	0	0	0	1 (0.3)
Gamma-glutamyltransferase increased	0	0	0	0	1 (0.3)
Grade 5 AEs	0	0	0	0	0
Treatment-related AEs	23 (30.3)	7 (4.5)	1 (5.6)	11 (5.9)	37 (10.4)
Alanine aminotransferase increased	21 (27.6)	1 (0.6)	1 (5.6)	3 (1.6)	19 (5.3)
Gamma-glutamyltransferase increased	0	0	1 (5.6)	1 (0.5)	11 (3.1)

Hepatotoxicity (including laboratory terms)	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI	Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Aspartate aminotransferase increased	14 (18.4)	2 (1.3)	0	3 (1.6)	14 (3.9)
Blood bilirubin increased	1 (1.3)	5 (3.2)	0	6 (3.2)	10 (2.8)
Hypertransaminasemia	0	0	1 (5.6)	1 (0.5)	5 (1.4)
Transaminases increased	1 (1.3)	0	0	0	0
Blood alkaline phosphatase increased	0	0	0	0	3 (0.8)
Bilirubin conjugated increased	0	0	0	0	1 (0.3)
Blood bilirubin unconjugated increased	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Glutamate dehydrogenase increased	0	0	0	0	1 (0.3)
Hypoalbuminaemia	0	0	0	0	1 (0.3)
SAEs	0	0	0	0	1 (0.3)
Liver disorder	0	0	0	0	1 (0.3)
Action taken					
Drug withdrawn	4 (5.3)	0	0	0	0
Dose adjusted	3 (3.9)	0	1 (5.6)	0	3 (0.8)
Drug interrupted	11 (14.5)	5 (3.2)	1 (5.6)	5 (2.7)	11 (3.1)
Dose not changed/NA/Unknown	21 (27.6)	16 (10.3)	4 (22.2)	26 (13.9)	76 (21.3)
Medication or therapy taken	1 (1.3)	2 (1.3)	0	3 (1.6)	10 (2.8)
AE outcome					
Recovered/resolved	22 (28.9)	17 (10.9)	4(22.2)	26(13.9)	73 (20.5)
Recovering/resolving	14 (18.4)	2 (1.3)	1 (5.6)	5 (2.7)	19 (5.3)
Not recovered/not resolved	11 (14.5)	4 (2.6)	2 (11.1)	12 (6.4)	33 (9.3)
Recovered/resolved with sequelae	0	0	0	0	1 (0.3)
Fatal	0	0	0	0	0
Unknown	0	0	0	0	0

Numbers (n) represent counts of subjects. A subject may be counted in several rows for action taken and outcome.

EAIR = exposure-adjusted incidence rate: number of subjects with an event divided by the corresponding sum of the exposure duration for all subjects, where duration of exposure in STY 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).

NA = Not applicable.

MedDRA version 26.0, CTCAE version 4.03, Case Retrieval Strategy version released 2022-11-22.

Cum IP presented as percentage (cum IP * 100).

Source: Annex 7-Table 5-7b.

Table 8-11 Important potential risk hepatotoxicity: Other details

Hepatotoxicity	Details
Potential mechanisms	The mechanism is unknown.
Evidence source(s) and strength of evidence	Current evidence is based on non-clinical 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.
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 3-1. **Clinical data** **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. 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).

Hepatotoxicity	Details
	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.
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.

Hepatotoxicity	Details
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.

8.3.1.5 Important potential risk: hepatitis B virus infection reactivation

Table 8-12 Clinical trial data of hepatitis B virus infection reactivation (Safety set))

Hepatitis B virus reactivation	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI	Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Number of subjects with at least one event	0	0	0	0	1 (0.3) (0.0, 1.6)
Exposure-adjusted overall incidence, n (EAIR per 100 STY)	0	0	0	0	1 (0.1)
Cumulative incidence proportion at n (%) cum IP					
Week 8 (Day 56)	0	0	0	0	0
Week 24 (Day 168)	0	0	0	0	0
Week 48 (Day 336)	0	0	0	0	0
Week 60 (Day 420)	0	0	0	0	0
Week 96 (Day 672)	0	0	0	0	1 (0.3) 0.28
Number of subjects with at least one event by Preferred Term					
Viral hepatitis carrier	0	0	0	0	1 (0.3)
Maximum grade					
Grade 3 AEs	0	0	0	0	0
Grade 4 AEs	0	0	0	0	0
Grade 5 AEs	0	0	0	0	0
Treatment-related AEs	0	0	0	0	0
SAEs	0	0	0	0	1 (0.3)
Viral hepatitis carrier	0	0	0	0	1 (0.3)
Action taken					
Drug withdrawn	0	0	0	0	0
Dose adjusted	0	0	0	0	0
Drug interrupted	0	0	0	0	0
Dose not changed/NA/Unknown	0	0	0	0	1 (0.3)
Medication or therapy taken	0	0	0	0	0
AE outcome					
Recovered/resolved	0	0	0	0	0
Recovering/resolving	0	0	0	0	0
Not recovered/not resolved	0	0	0	0	1 (0.3)
Recovered/resolved with sequelae	0	0	0	0	0
Fatal	0	0	0	0	0
Unknown	0	0	0	0	0

Hepatitis B virus reactivation	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI	Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI

Numbers (n) represent counts of subjects. A subject may be counted in several rows for action taken and outcome.

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

Cum IP = cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason).

NA = Not applicable.

MedDRA version 26.0, CTCAE version 4.03, Case Retrieval Strategy version released 2022-11-22.

Cum IP presented as percentage (cum IP * 100)

Source: Annex 7-Table 5-7b.

Table 8-13 Important potential risk hepatitis B virus infection reactivation: Other details

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.
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** **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.

Hepatitis B virus reactivation	Details
Risk factors and risk groups	None identified for HBV infection reactivation.
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.

8.3.1.6 Important potential risk: reproductive toxicity

Table 8-14 Clinical trial data of reproductive toxicity (Safety set)

Reproductive toxicity	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI	Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Number of subjects with at least one event	1 (1.3) (0.0, 7.2)	6 (3.8) (1.4, 8.2)	0	6 (3.2) (1.2, 6.8)	6 (1.7) (0.6, 3.6)
Exposure-adjusted overall incidence, n (EAIR per 100 STY)	1 (1.1)	6 (1.7)	0	6 (1.2)	6 (0.5)
Cumulative incidence proportion at n (%) cum IP					
Week 8 (Day 56)	0	0	0	0	0
Week 24 (Day 168)	1 (1.3) 1.32	2 (1.3) 1.28	0	2 (1.1) 1.07	2 (0.6) 0.56
Week 48 (Day 336)	1 (1.3) 1.32	2 (1.3) 1.28	0	2 (1.1) 1.07	2 (0.6) 0.56
Week 60 (Day 420)	1 (1.3) 1.32	3 (1.9) 1.92	0	3 (1.6) 1.60	3 (0.8) 0.84
Week 96 (Day 672)	1 (1.3) 1.32	3 (1.9) 1.92	0	3 (1.6) 1.60	3 (0.8) 0.84
Number of patients with at least one event by Preferred Term					
Pregnancy	0	3 (1.9)	0	3 (1.6)	3 (0.8)
Abortion spontaneous	0	2(1.3)	0	2 (1.1)	2 (0.6)
Congenital cardiovascular anomaly	1 (1.3)	1 (0.6)	0	1 (0.5)	1 (0.3)
Maternal exposure during pregnancy	0	2 (1.3)	0	2 (1.1)	2 (0.6)
Maximum grade					
Grade 3 AEs	0	3 (1.9)	0	3 (1.6)	3 (0.8)
Abortion spontaneous	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Maternal exposure during pregnancy	0	2 (1.3)	0	2 (1.1)	2 (0.6)
Pregnancy	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Grade 4 AEs	0	0	0	0	0
Grade 5 AEs	0	0	0	0	0
Treatment-related AEs	0	0	0	0	0
SAEs	0	0	0	0	0

Reproductive toxicity	CABL001A2301		CABL001X2101	Safety Pool	
	Bosutinib 500 mg q.d. N=76 n (%) 95% CI	Asciminib 40 mg b.i.d. N=156 n (%) 95% CI	Asciminib 80 mg q.d. (CP) N=18 n (%) 95% CI	Asciminib 40 mg b.i.d. (CP) N=187 n (%) 95% CI	Asciminib All subjects N=356 n (%) 95% CI
Action taken					
Drug withdrawn	0	1 (0.6)	0	1 (0.5)	1 (0.3)
Dose adjusted	0	0	0	0	0
Drug interrupted	0	3(1.9)	0	3 (1.6)	3 (0.8)
Dose not changed/NA/Unknown	1 (1.3)	3 (1.9)	0	3 (1.6)	3 (0.8)
Medication or therapy taken	0	2 (1.3)	0	2 (1.1)	2 (0.6)
AE outcome					
Recovered/resolved	0	4 (2.6)	0	4 (2.1)	4 (1.1)
Recovering/resolving	0	0	0	0	0
Not recovered/not resolved	1 (1.3)	2(1.3)	0	2 (1.1)	2(0.6)
Recovered/resolved with sequelae	0	0	0	0	0
Fatal	0	0	0	0	0
Unknown	0	0	0	0	0

Numbers (n) represent counts of subjects. A subject may be counted in several rows for action taken and outcome.

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

Cum IP = cumulative incidence proportion up to Day x considering competing risks (death, discontinuation due to any reason).

NA = Not applicable.

MedDRA version 26.0, CTCAE version 4.03, Case Retrieval Strategy version released 2022-11-22.

Cum IP presented as percentage (cum IP * 100).

Source: Annex 7-Table 5-7b.

Table 8-15 Important potential risk reproductive toxicity: Other details

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 non-clinical studies and the clinical studies. Cardiac malformations along with increased visceral and skeletal variants have been observed in rats. Also, increased incidence of resorptions (embryo-fetal 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.
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

Reproductive toxicity	Details
	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 3-1. **Clinical data** **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). 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. 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

<table>
<tr><th>Reproductive toxicity</th><th>Details</th></tr>
<tr><td></td><td>(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 13 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.
<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>20%</td><td>1</td><td>25%</td><td>3</td><td>23.1%</td></tr>
<tr><td>Live birth timing unknown</td><td>0</td><td>0</td><td>1</td><td>25%</td><td>1</td><td>7.7%</td></tr>
<tr><td>Elective termination</td><td>3</td><td>30%</td><td>1</td><td>25%</td><td>4</td><td>30.8%</td></tr>
<tr><td>Therapeutic abortion</td><td>2</td><td>20%</td><td>1</td><td>25%</td><td>3</td><td>23.1%</td></tr>
<tr><td>Spontaneous abortion/ miscarriage</td><td>2</td><td>20%</td><td>0</td><td>0</td><td>2</td><td>15.4%</td></tr>
<tr><td>Total</td><td>9</td><td>100%</td><td>4</td><td>100%</td><td>13</td><td>100%</td></tr>
</table></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 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.</td></tr>
<tr><td>Impact on the benefit-risk balance of the product</td><td>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.</td></tr>
</table>

Reproductive toxicity	Details
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.

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

Table 8-16 Missing information: 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 4-2 and Study A2301 EOT report). 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 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.

Table 8-17 Missing information: 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). 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 8-18 Missing information: 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

Use in patients with hepatic impairment	Details
	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.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table 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

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

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 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 topics 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)
- Hyperglycaemia

10.2 Part III.2. Additional pharmacovigilance activities

Study CABL001A2301 - A Phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with chronic myelogenous leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors

Study short name and title:

Study of efficacy of CML-CP patients treated with asciminib versus bosutinib, previously treated with 2 or more TKIs.

Rationale and study objectives:

There remains an unmet need for new treatment options in patients with CML who have failed at least 2 prior TKIs. Current practice suggests that a 2G-TKI will have been used for first-line therapy for about one half of the patients with CML, meaning that most patients who have failed at least 2 prior TKIs will have failed at least 1 if not 2 2G-TKIs (such as dasatinib and/or nilotinib). Potentially, such patients may also have failed bosutinib and/or ponatinib. Patients having failed at least 2 TKIs may have limited sensitivity to the remaining available agents and, thus, there exists a need for new safe and effective therapy. In addition, mutations will have

developed in 21 to 33% of patients that prevent the use of specific TKIs, increasing the need for a better and alternative compound (Soverini et al 2014).

Key study objectives include:

- To compare the major molecular response (MMR) rate at 24 weeks of asciminib versus bosutinib
- To compare the safety and tolerability profile of asciminib versus bosutinib.

Study design:

The study design incorporates a 2:1 randomization, allocating more patients to the asciminib arm in order to learn more about the safety profile of the experimental therapy, whereas the safety of bosutinib therapy is well documented. Treatment duration for each patient in the present study is for up to 96 weeks after the last randomized patient receives the first dose, or up to 48 weeks after the last patient has switched from bosutinib to asciminib whichever is longer unless patients have discontinued treatment earlier, which should be adequate to address both the primary objective of the study, i.e. determination of the MMR rate at 24 weeks, as well as secondary efficacy and safety objectives. Patients on bosutinib will be able to switch to asciminib treatment up to 96 weeks after the last patient has been randomized.

If patients in the bosutinib arm have documented treatment failure according to the 2013 European LeukemiaNet (ELN) Guidelines (Baccarani et al 2013), they will have the option to receive asciminib. Each patient who switches to asciminib after bosutinib failure can remain on asciminib treatment for up to 48 weeks after the last bosutinib failure patient has switched to asciminib during the treatment period unless patients have discontinued treatment earlier.

Study population:

Two-hundred and twenty-two patients with CML-CP who had prior treatment with 2 or more adenosine triphosphate (ATP) binding site TKIs will be randomized on a 2:1 basis to receive either asciminib or bosutinib. Patients with known history of harboring T315I and/or V299L mutations at study entry will be excluded from the trial since bosutinib, the comparator, is not approved for these patients.

Milestones:

Final report submission: 31-Jul-2025

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

10.3 Part III.3. Summary Table of additional pharmacovigilance activities

Table 10-1 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				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
CABL001A2301 A Phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors Ongoing	To compare the efficacy of asciminib with that of bosutinib in the treatment of patients with CML-CP having previously been treated with a minimum of 2 prior ATP-binding site TKIs with BCR::ABL1 ratios ≥ 1% IS at screening	Long-term safety, acute pancreatitis (including isolated pancreatic enzyme elevations), myelosuppression, QTc prolongation, hepatotoxicity	Final report submission	31-Jul-2025
CABL001A2302 A Phase 3b, multi-center, open-label, treatment optimization study of oral asciminib in patients with chronic myelogenous leukemia in chronic phase (CMLCP) previously treated with 2 or more tyrosine kinase inhibitors Ongoing	To optimize the treatment of asciminib in patients with chronic myelogenous leukemia in chronic phase (CML-CP) previously treated with 2 or more Tyrosine Kinase Inhibitors (TKIs).	Long-term safety, acute pancreatitis (including isolated pancreatic enzyme elevations), myelosuppression, QTc prolongation, hepatotoxicity. hepatitis B virus infection reactivation, use in patients with renal impairment, use in patients with hepatic impairment	Final report submission	11-Mar-2027
CABL001A2001B An open label, multi-center asciminib roll-over study to assess long-term safety in patients who have completed a Novartis sponsored asciminib study and are judged by the investigator to benefit from continued treatment Ongoing	To assess long-term safety and provide continued treatment with asciminib for patients with CML-CP who have participated in a Novartis sponsored asciminib clinical study (parent study) and, in the opinion of the investigator, would benefit from continuing treatment.	Long-term safety, acute pancreatitis (including isolated pancreatic enzyme elevations), myelosuppression, QTc prolongation, hepatotoxicity, hepatitis B virus infection reactivation	Final report submission	31-Dec-2028

11 Part IV: Plans for post-authorization efficacy studies

There are no plans for post-authorization efficacy studies.

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

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concerns	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.

Safety concerns	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information Legal status: Medical prescription only product
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 concomitantly with medicinal products known to cause Torsades de Pointes. **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.

Safety concerns	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information Legal status: Medical prescription only product
Reproductive toxicity	**Routine risk communication** SmPC Section 4.6 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.

Safety concerns	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information Legal status: Medical prescription only product

12.2 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.

12.3 Part V.3. Summary of risk minimization measures

Table 12-2 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 CABL001A2301 (Final report submission: 31-Jul-2025), CABL001A2302 (Final report submission: 11-Mar-2027), and CABL001A2001B (Final report submission: 31-Dec-2028)
Myelosuppression	**Routine risk minimization measures** SmPC Section 4.2 where posology and method of administration are described. SmPC Section 4.4 where description of the risk along	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	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	Evaluation of data from studies CABL001A2301 (Final report submission: 31-Jul-2025), CABL001A2302 (Final report submission: 11-Mar-2027), and CABL001A2001B (Final report submission: 31-Dec-2028)
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**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** Evaluation of data from studies CABL001A2301 (Final report submission: 31-Jul-2025), CABL001A2302 (Final report submission: 11-Mar-2027), and CABL001A2001B (Final report submission: 31-Dec-2028)

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

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

13 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.

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

Asciminib is indicated for the treatment of adult patients with Ph+ CML-CP previously treated with 2 or more TKIs.

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: link to the EPAR summary landing page.

13.2 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.

13.2.1 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 13-1 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

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

Important identified risks

Table 13-2 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. Adverse events of pancreatitis/ pancreatitis acute were reported in 9 patients (2.6%) in asciminib monotherapy (all doses) pool, of which 3 patients were taking asciminib 40 mg b.i.d. for treatment of CML-CP/AP (all reported from Study X2101). Additionally, the events, lipase increased and amylase increased were reported in 65 patients (18.3%) and 38 patients (10.7%); 8 patients (5.1%) and 9 patients (5.8%), in Safety Pool (comprising all the patients taking asciminib monotherapy for CML-CP/AP) and the patients taking in Study A2301, respectively.
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 CABL001A2301 Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-3 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.
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 CABL001A2301 Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-4 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.
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 CABL001A2301 Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risks

Table 13-5 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 CMLCP/AP. There was no case related to Hy's law, and none of the reported events were fatal or life-threatening.
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 CABL001A2301 Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-6 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.
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 13-7 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.
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 13-8 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 CABL001A2301 Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-9 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 13-10 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.

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

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

There are no studies which are conditions of the Marketing Authorization or specific obligation of Scemblix.

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

Table 13-11 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Study CABL001A2301: Study of efficacy of CML-CP patients treated with asciminib versus bosutinib, previously treated with 2 or more TKIs.	There remains an unmet need for new compounds in patients with CML who have failed at least 2 prior TKIs. Current practice suggests that a 2G-TKI will have been used for first line therapy for about one half of patients with CML, meaning that most patients who have failed at least two prior TKIs will have failed at least 1 if not 2 2G-TKIs (such as dasatinib and/or nilotinib). Potentially, such patients may also have failed bosutinib and/or ponatinib. Patients having failed at least 2 TKIs may have limited sensitivity to the remaining available agents and, thus, there exists a need for new safe and effective therapy. In addition, mutations will have developed in 21 to 33% of patients that prevent the use of specific TKIs, increasing the need for a better and alternative compound. Omacetaxine, a chemotherapeutic agent, is available for patients who have failed at least 2 prior TKIs under these conditions but only in the US and Canada. This agent is not available for most patients globally, where a bigger unmet medical need is present. Thus, there remains an unmet need for patients with CML who have failed at least 2 prior TKIs despite the existence of multiple agents. Key study objectives include: • To compare the major molecular response (MMR) rate at 24 weeks of asciminib versus bosutinib • To compare the safety and tolerability profile of asciminib versus bosutinib.
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:

Study short name	Rationale and study objectives
	• 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 objective includes: • To assess long term safety data and provide continued access to the study treatment received in the parent study protocol.

14 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, effective 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:

II. RELEVANT MEDICAL HISTORY

MATERNAL MEDICAL HISTORY (familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy)

Risk factor	Yes	No	Risk factor	Yes	No	Risk factor	Yes	No

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 section Additional Information (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): - -
☐	New hospitalization / prolongation of hospitalization		Cause of death: 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, ☐ NoIf yes, please specify occupation: Patient ☐ Other ☐ Health Authority Case Number:	

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

Not applicable