Amsterdam, 26 February 2025
EMADOC-1700519818-2995203
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Scemblix

International non-proprietary name: Asciminib

Procedure No. EMA/X/0000256688

Note

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

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List of abbreviations

2G	Second generation
ABL1/ABL1	*Italicized:* Abelson oncogene 1; non-italicized: Abelson protein
ABL2/ABL2	*Italicized:* Abelson related oncogene 2; non-italicized: Abelson related protein
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukemia
allo-SCT	Allogeneic stem cell transplantation
ALT	Alanine aminotransferase
AP	Accelerated phase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BCR	Breakpoint Cluster Region
BCR::ABL	Chimeric *BCR::ABL1* oncogene
BCR::ABL	BCR::ABL1 oncoprotein with dysregulated ABL1 kinase activity
b.i.d.	*bis in diem*/twice a day
BLRM	Bayesian logistic regression model
BP	Blastic phase
CCyR	Complete Cytogenetic Response
CHR	Complete hematological response
CI	Confidence Interval
CML	Chronic Myeloid Leukemia
CML-AP	Chronic myeloid leukemia in accelerated phase
CML-BP	Chronic myeloid leukemia in blast phase
CML-CP	Chronic myeloid leukemia in chronic phase
CNS	Central nervous system
COVID-19	Coronavirus Disease of 2019
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EWOC	Escalation with overdose control
FAS	Full Analysis Set
FaSSGF/IF	Fasted State Simulated Gastric Fluid/Intestinal Fluid
FCT	Film-coated tablet
FIH	First-in-human
HSCT	Hematopoietic stem cell transplant
ICH I	nternational Council for Harmonization of Technical Requirements for Pharmaceutica for Human Use
IS	International scale
KM	Kaplan-Meier
LPLV	Last patient last visit
MAP	Managed access program

MedDRA	Medical Dictionary for Regulatory Activities
MMR	Major molecular response
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIS	Non-interventional study
NMQ	Novartis MedDRA Query
OS	Overall survival
Ph+ CML	Philadelphia chromosome-positive chronic myelogenous leukemia
PFS	Progression-free survival
Ph+	Philadelphia chromosome positive
PK	Pharmacokinetics
PopPK	Population PK
q.d.	Once daily
QTcF	QT interval corrected by Fridericia's formula
RDE	Recommended dose for expansion
RDI	Relative dose intensity
SAE	Serious adverse event
SCP	Summary of clinical pharmacology

1. Administrative/regulatory information and recommendations on the procedure

1.1. Submission of the dossier

On 28 February 2025, Novartis Europharm Ltd submitted a group of variations consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type	Annexes affected
C.I.6.a	**Addition of a new indication**	**II**	**I, III and RMP**

The MAH applied for an extension application to introduce a new strength (100 mg film-coated tablets) grouped with a type II variation (C.I.6.a) to add a new indication (treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) harbouring the T315I mutation), based on final results from study CABL001X2101 and study CABL001A2004. Study CABL001X2101 is a Phase I, multicenter, open-label, dose escalation FIH study to define the MTD/RDEs, to characterize safety and tolerability, and to assess the PK profile and preliminary evidence of efficacy of asciminib given as single agent or in combination with either nilotinib or imatinib or dasatinib in patients with Ph+ CML or Ph+ ALL. Study CABL001A2004 assessed the real-world effectiveness of asciminib and treatment patterns in patients with chronic myeloid leukaemia with T315I mutation.

As a consequence, sections 1, 2, 3, 4, 5, 6 and 8 of the SmPC are updated. The package leaflet and labelling are updated in accordance. Version 3.0 of the RMP was also submitted.

As part of the application, the MAH requested a 1-year extension of the market protection.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations.

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

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

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

1.3. Scientific advice and protocol assistance

Table 1: Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
23/02/2023	**Quality**	**EMA/SA/0000117527 / Kerstin Wickström, Audrey Sultana**	**Acceptability of an additional strength biowaiver approach for the development of a 100-mg film-coated tablet.**

1.4. Information on paediatrics

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0052/2020 on the agreement of a paediatric investigation plan (PIP), on the granting of a deferral for asciminib.

At the time of submission of the application, the PIP EMEA-C2-002347-PIP01-18 was not yet completed as some measures were deferred.

1.5. Information on orphan market exclusivity

1.5.1. Similarity with authorised orphan medicinal products

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

1.6. Request for additional data exclusivity /marketing protection

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

1.6.1. CHMP recommendation on additional data exclusivity /marketing protection

On 04 November 2025, the MAH withdrew their request for additional marketing protection since the additional marketing protection was already obtained for Scemblix as part of a previously approved procedure (EMAVR0000265010).

1.7. Steps taken for the assessment of the product

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

Rapporteur:	Janet Koenig
Co-Rapporteur:	Peter Mol

The application was received by the EMA on	28 February 2025
The procedure started on	27 March 2025
The CHMP Rapporteur's first Assessment Report was received on	20 June 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	18 June 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	27 June 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 July 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	24 July 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	09 October 2025
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	17 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	11 December 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	23 January 2026
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 February 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion to extend the marketing authorisation of Scemblix on	26 February 2026

1.8. CHMP outcome

1.8.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.4 of this report.

1.8.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 0of this report.

1.8.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Scemblix 100 mg film-coated tablets is favourable in the following indication:

Scemblix is indicated for the treatment of adult patients with Ph+ CML-CP with the T315I mutation who are resistant to, intolerant to or ineligible for ponatinib (see section 5.1).

The CHMP therefore recommends the extension of the marketing authorisation for Scemblix, subject to the conditions described in the following sections.

1.8.4. Other conditions and requirements of the marketing authorisation

Periodic safety update reports

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

1.8.5. Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

1.8.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

2. Introduction

Therapeutic Context

Philadephia chromosome positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP) is a rare

disease with a prevalence 1:17000 in EU and an incidence 1.2-1.5:100000. With introduction of TKIs the prognosis improved so much, that for responding patients near normal life expectancy can be expected.

T315I mutation occurs in 1-5% of CML patients, mostly while on treatment. CML T315I is resistant to all approved TKI, with the exception of ponatinib.

Since 2013 ponatinib is approved for CML with T315I mutation in chronic phase, accelerated phase and blast phase. Approval of ponatinib for CML with T315I mutation in chronic phase was based on a cohort of the PACE Trial, a single-arm, open-label, international, multicenter trial which enrolled 64 patients with CML with T315I mutation in chronic phase. In this cohort an MMR of 58% was reported. In 2018, from PACE trial 5-year OS rate of 66% was reported for patients with CML harbouring the T315I mutation (Cortes, Kim et al. 2018). Later, the OPTIC trial reported a 4-year OS rate for CML-T315I of 86% (ponatinib 45mg group) (Deininger, Apperley et al. 2024).

In case of suboptimal response allogeneic stem transplantation should be considered.

2.1. Aspects of development

See earlier assessment reports for general development.

2.2. Description of the product

Scemblix (asciminib, known also as ABL001), administered orally, is a potent inhibitor of ABL/BCR::ABL1 tyrosine kinase. It inhibits the ABL1 kinase activity of the BCR::ABL1 fusion protein, by specifically targeting the ABL myristoyl pocket.

2.3. Inspection issues

2.3.1. GMP inspection(s)

No inspection required.

2.3.2. GLP inspection(s)

No inspection required.

2.3.3. GCP inspection(s)

No inspection required.

3. Quality aspects

3.1. Introduction

The application is a line extension to register the new strength of 100 mg film-coated tablets to the currently approved Scemblix 20 mg and 40 mg film-coated tablets.

The finished product is presented as film-coated tablets containing 100 mg of asciminib as active substance (108.1 mg of asciminib hydrochloride).

Other ingredients are lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, polyvinyl alcohol, titanium dioxide (E171), magnesium stearate, talc, colloidal silicon dioxide, iron oxide (black and red, E172), lecithin and xanthan gum.

The product is supplied in PA-AL-PVC/Alu blisters containing 10 film-coated tablets. Packs contain 60 or 120 film-coated tablets.

3.2. Active substance

The 100 mg strength uses the same source of active substance already approved for the 20 mg and 40 mg film-coated tabled. There are no changes to the content of CTD module 3.2.S.

3.3. Finished medicinal product

Description of the product and pharmaceutical development

The development of the formulation has been sufficiently described. The active substance is already approved for 20 mg and 40 mg strengths and there are no changes to the active substance.

The excipients were selected based on the already approved strengths. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in introduction paragraph above.

The biowaiver of different strengths of asciminib film-coated tablet has been justified. According to the "Guideline on the Investigation of Bioequivalence", (CPMP/QWP/EWP/1401/98 Rev. 1/Corr) the following conditions have been fulfilled:

- The pharmaceutical products are manufactured by the same manufacturing process,
- The qualitative composition of the different strengths is the same,
- The ratio between the amounts of excipients is similar,
- Similarity of in vitro dissolution have been demonstrated at different pH values within the applied product series. (The use of 60 instead 50 RPM is justified).

The discriminative power of the selected dissolution method (pH 3) has been shown during the marketing authorisation application procedure of the other strengths. The specification is therefore justified; and the dissolution profiles of all strengths are comparable. Furthermore, a method development report for the 100 mg strength has been presented, which verifies the validity of the method. Therefore, the proposed dissolution method and specification is accepted.

The development of the manufacturing process has been described in detail and is based on the currently approved manufacturing process for the 20 mg and 40 mg film-coated tablets. A process based on dry granulation followed by compression is used for all tablet strengths.

Asciminib 100 mg film-coated tablets are packaged in polyamide-aluminium-polyvinylchloride / aluminium (PA-AL-PVC)/AL blister packs. Packs contain 60 or 120 film-coated tablets. The provided specifications and information for the proposed container closure systems are considered sufficient. The product packaging materials comply with EU Regulation 2011/10. Declarations of compliance by material suppliers were provided. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by Novartis Pharma Stein AG, Schaffhauserstrasse, 4332 Stein, Switzerland. Batch release is performed at Novartis Farmaceutica S.A., Gran Via de les Corts Catalanes, 764, 08013 Barcelona, Spain; Novartis Pharma GmbH, Roonstrasse 25, 90429 Nuernberg, Germany; or Novartis Pharma GmbH, Sophie-Germain-Strasse 10, Nuremberg, 90443, Germany. For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The manufacturing process consists of five main steps:**Error! Reference source not found.** standard unit operations of dry granulation, screening, blending, tableting and film-coating. The process is considered to be a standard manufacturing process.

The in-process controls are adequate for this type of manufacturing process/pharmaceutical form. A comprehensive holding time study of the intermediate unpacked bulk film-coated tablets was performed. The holding time of 12 months is justified if the unpacked film-coated tablets are packed in LDPE bag, closed and placed in a triple foil (PETP/AL/PE) bag with silica gel desiccant and stored not above 25°C.

Major steps of the manufacturing process have been validated for three commercial batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product Specifications

The finished product specifications include relevant parameters for this dosage form: appearance (visual), mean mass, identity (UV, HPLC), water content (loss on drying), dissolution (HPLC), uniformity of dosage units (Ph. Eur.), assay (HPLC), degradation products (HPLC), microbial enumeration tests (Ph. Eur.).

With exception of the strength relevant parameters like appearance or mean mass, there are no changes to the specification for the line-extension.

The analytical methods are identical to those approved for the existing strengths. The use of NIRS real time release testing (RTRT) performed in lieu of end product testing is only used for the 20 mg and 40 mg film-coated tablets and is not proposed for 100 mg film-coated tablets. The methods have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The batch analyses data, which includes data for three commercial scale batches, together with the results obtained from the validation of the manufacturing process, stability testing confirm the

consistency of the manufacturing process and its ability to manufacture to the intended product specification.

An elemental impurities risk assessment performed by the proposed finished product manufacturer, in line with the guideline ICH Q3D - Guideline for Elemental Impurities was provided. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

The nitrosamine risk assessment performed contains relevant information and addresses all risk factors related to the manufacture of the active substance and the finished product in line with current Q&A EMA/409815/2020 requirements. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

Stability of the product

Stability data from three registration batches of 100 mg finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH), 18 months under intermediate conditions (30°C / 75 % RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

No significant change was observed at each storage condition. Based on the outcome of photo-stability studies in compliance with the ICH Guideline on Photostability Testing of New Drug Substances and Products, the finished product is considered photo-stable. Furthermore, the finished product has an acceptable physical and chemical stability up to 6 months at 5ºC/ambient RH and -20ºC in PA-AL-PVC/Alu blisters, so does not require any restriction concerning refrigeration or freezing.

The recommended storage conditions "Do not store above 25°C. Store in the original package." have been adequately proposed for the 100 mg strength, based on disproportionation of the active substance observed at elevated temperature and humidity conditions in the 20 mg and 40 mg strengths. Disproportionation primarily occurs under accelerated conditions with high temperature and moisture, where the crystalline salt form of asciminib hydrochloride may convert into the crystalline free base modification A. This transformation directly affects the product's dissolution characteristics. Although this has not been directly observed for the 100 mg strength, the storage condition is proposed as a precautionary measure.

Based on the provided stability data, the proposed shelf-life of 24 months with the storage condition "Do not store above 25°C. Store in the original package." is accepted.

Post-approval change management protocol(s)

Not applicable

Adventitious agents

Lactose monohydrate is the only excipient of animal origin. Declaration of TSE compliance is provided for lactose monohydrate. Information presented regarding TSE compliance is sufficient.

GMO

Not applicable

3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.5. Conclusions on chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

3.6. Recommendation(s) for future quality development

Not applicable.

4. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

4.1. Pharmacology

Asciminib inhibited proliferation of cells expressing T315I-mutant BCR::ABL1 in low nanomolar concentration range. The compound demonstrated tumour regression in mice bearing nilotinib- resistant KCL-22 tumours harbouring the T315I mutation. These data from the initial MAA dossier support the use of asciminib in the newly proposed indication (treatment of adult patients with Ph+ CML-CP harbouring the T315I mutation).

Patients with Ph+ CML-CP harbouring the T315I mutation receive a different dose than those within the approved indication, which leads to them having higher asciminib exposure. This decreases the safety margin with respect to off-target activities of asciminib. The strongest off-target interaction of asciminib was with the 5-lipoxygenase with a safety margin of 10. However, 5-lipoxygenase inhibitors are anti-inflammatory drugs, which show anti-tumoural properties in humans, and no adverse reactions are expected. 5-HT2B serotonin receptor antagonism of asciminib has a safety margin of 15 with respect to the clinical plasma concentrations. Also in this case no adverse reactions are expected in patients as nonselective 5HT2B antagonists are not known for adverse events in the clinic.

Due to a different dosing in patients with Ph+ CML-CP harbouring the T315I mutation, there are additional safety margins relevant for the SmPC. The occurrence of moderate cardiovascular effects (increased heart rate, decreased systolic pressure, decreased mean arterial pressure, and decreased arterial pulse pressure) after a single 60 mg/kg dosing to dogs was noted at AUC exposures 1.7-fold higher than those in patients treated with asciminib at 200 mg b.i.d. The safety margin regarding cardiac channel activity exceeds 30 also with this dosing.

4.2. Pharmacokinetics

Not applicable

4.3. Toxicology

No new toxicology studies have been submitted, which is acceptable. Due to a different dosing in the newly proposed indication (200 mg b.i.d.), additional safety margins have been calculated.

Pancreatic effects (serum amylase and lipase increases, acinar cell lesions) occurred in dogs at AUC exposures below those achieved in patients at the RD or 200 mg twice daily.

Elevations in liver enzymes and/or bilirubin were observed in rats, dogs and monkeys. Histopathological hepatic changes (centrilobular hepatocyte hypertrophy, slight bile duct hyperplasia, increased individual hepatocyte necrosis and diffuse hepatocellular hypertrophy) were seen in rats and monkeys. These changes occurred at AUC exposures below (rats), equivalent to (dogs) or approximately 2-fold higher than (monkeys) those achieved in patients at the RD of 200 mg twice daily.

Effects on the haematopoietic system (reduction in red blood cell mass, increased splenic or bone marrow pigment and increased reticulocytes) were consistent with a mild and regenerative, extravascular, haemolytic anaemia in all species. These changes occurred at AUC exposures below (rats), equivalent to (dogs) or approximately 2-fold higher than (monkeys) those achieved in patients at the RD of 200 mg twice daily.

Minimal mucosal hypertrophy/hyperplasia (increase in thickness of the mucosa with frequent elongation of villi) was present in the duodenum of rats at AUC exposures 4-fold higher than those achieved in patients at the RD of 200 mg twice daily.

Minimal or slight hypertrophy of the adrenal gland and mild to moderate decreased vacuolation in the zona fasciculata occurred at AUC exposures below (monkeys) or 2-fold higher than (rats) those achieved in patients at the RD of 200 mg twice daily, respectively.

In a 2-year rat carcinogenicity study, benign Sertoli cell tumours in the ovaries were observed in female rats at the highest dose of 66 mg/kg/day. AUC exposures to asciminib in female rats at this dose were generally equivalent to those achieved in patients at the RD of 200 mg twice daily.

In embryo-foetal development studies, a slight increase in foetal malformations (anasarca and cardiac malformations) and increased visceral and skeletal variants were observed in rats. Increased incidence of resorptions indicative of embryo-foetal mortality and a low incidence of cardiac malformations indicative of teratogenicity were observed in rabbits. In rats, at the foetal no observed adverse effect level (NOAEL) of 25 mg/kg/day, the AUC exposures were below those achieved in patients at the RD of 200 mg twice daily. In rabbits, at the foetal NOAEL of 15 mg/kg/day, the AUC exposures were below those achieved in patients at the RD of 200 mg twice daily.

In the rat fertility study, asciminib did not affect reproductive function in male and female rats. A slight effect on male sperm motility and sperm count was observed at doses of 200 mg/kg/day, likely at AUC exposures 2-fold higher than those achieved in patients at the RD of 200 mg twice daily.

In mice, asciminib showed dose-dependent phototoxic effects starting at 200 mg/kg/day. At the NOAEL of 60 mg/kg/day, exposure based on C_{max} in plasma was 2-fold higher than the exposure in patients at the RD of 200 mg twice daily.

4.3.1. Ecotoxicity/environmental risk assessment

The MAH provided a detailed Phase I & Phase II assessment for the active ingredient asciminib.

Based on the provided data set a risk to the sewage treatment plant (STP), surface water, groundwater, sediment, soil and secondary poisoning is not anticipated. Furthermore, based on the results of the water-sediment study (OECD 308) asciminib hydrochloride has to be classified as very persistent in the environment but is considered not to be persistent, bioaccumulative, and toxic (PBT), nor very persistent and very bioaccumulative (vPvB).

Table 2 Screening

Substance (INN/Invented Name):	asciminib hydrochloride		
CAS-number (if available):	2119669-71-3		
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	log D_{ow} = 3.7 at pH 4 log D_{ow} = 3.9 at pH 7 log D_{ow} = 3.9 at pH 9	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.9 at pH 7	not B
	BCF	3.7 L/kg_{ww}	not B
Persistence	DT50 Values are derived from the OECD 308 study below and have been recalculated to 12°C	284 d	vP
Toxicity	$NOEC_{aquatic}$ CMR	0.93 mg/L CMR	not T (aquatic) T
PBT-statement :	The active substance is considered to be not PBT, nor vPvB		

Table 3 Phase I

Phase I

Calculation	Value	Unit	Conclusion
PEC_{sw}, *refined*	**0.026**	**µg/L**	**≥ 0.01 threshold: Y**
Other concerns (e.g. chemical class)	**-**	**-**	**N**

Table 4 Phase II – Physical-chemical properties and fate

Phase II - Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc,\ soil\ 1}$ = 3,601 L/kg$_{oc}$	List all values
		$K_{oc,\ soil\ 2}$ = 6,365 L/kg$_{oc}$	
Soil 1 = *Clay loam*		$K_{oc,\ soil\ 3}$ = 8,253 L/kg$_{oc}$	
Soil 2 = *Sandy silt loam*			
Soil 3 = *Loamy sand*		$K_{oc,\ sludge\ 1}$ = 2,856 L/kg$_{oc}$	
Sludge 1 = *Tilburg*		$K_{oc,\ sludge\ 2}$ = 2,700 L/kg$_{oc}$	
Sludge 2 = *Aa & Maas*			
Ready Biodegradability Test	OECD 301B	3 % (28 d)	
		not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 3.9 / 8 d	DT50s at 20°C
		$DT_{50,\ whole\ system}$ = 78 / 133 d	1 / 2
Sediment 1 = *Clay*		CO_2 = 0.4 / 0.2%	at test end
Sediment 2 = *Sand*		NER = 49.9 / 63.3%	at test end
		Transformation products >10% = *Y*, TP1 (max) = 34 %	at day 2, sed 2
		TP2 (max) = 13 %	identity: N-{4-[chlorodi(fluoro)methoxy]phenyl}-6-(3-oxopyrrolidin-1-yl)-5-(1H-pyrazol-5-yl)pyridine-3-carboxamide
			TP2 at day 31, sed 2, not identified

Table 5 Phase IIa effect studies

Phase IIa effect studies					
Study type	Test protocol	Result	Value	Unit	Remarks
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	**OECD 201**	**NOEC**	**3,500**	**µg/L**	**growth rate (free base)**
***Daphnia magna*, Reproduction Test**	**OECD 211**	**NOEC**	**1800**	**µg/L**	**age of first reproduction (free base)**
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	**OECD 210**	**NOEC**	**930**	**µg/L**	**post-hatch survival (free base)**
Activated Sludge, Respiration Inhibition Test	**OECD 209**	**NOEC**	**8,360**	**µg/L**	**solubility limit**

Table 6 Phase IIb studies

Phase IIb studies					
Sediment dwelling organism/ *Chironomus riparius*	**OECD 218**	**NOEC**	**2,280**	**mg/kg$_{dw}$**	**emergence, normalised to 10% o.c.**

Phase IIb Secondary poisoning					
Bioaccumulation/ *Oncorhynchus mykiss* Test 1 = 0,44 µg/L Test 2 = 5,2 µg/L	OECD 305	 BCF$_{kgL}$ BCF$_{kgL}$	 1.5 3.7	 L/kg$_{ww}$ L/kg$_{ww}$	Growth corrected and lipid normalised (5%)
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**		**Conclusion**
STP	0.26 µg/L	836 µg/L	0.000311		No risk
Surface water	0.026 µg/L	93 µg/L	0.00028		No risk
Groundwater	0.0065 µg/L	9.3 µg/L	0.0007		No risk
Sediment	21.6 µg/kgdw	22.8 mg/kgdw	0.0009		No risk
Secondary Poisoning	0.0026 µg/L	-	-		PNEC and risk assessment calculation not necessary

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

4.4. Overall discussion and conclusions on non-clinical aspects

4.4.1. Discussion

Asciminib activity in cells expressing T315I-mutant BCR::ABL1 and in mice bearing nilotinib- resistant KCL-22 tumours harbouring the T315I mutation support the use of asciminib in the newly proposed indication (treatment of adult patients with Ph+ CML-CP harbouring the T315I mutation).

Patients with Ph+ CML-CP harbouring the T315I mutation receive a different (higher) dose than those within the approved indication, which leads to them having higher asciminib exposure. This decreases the safety margin with respect to off-target activities of asciminib. The strongest off-target interaction of asciminib was with the 5-lipoxygenase with a safety margin of 10. However, no adverse reactions are expected in the clinic. Due to a different dosing in patients with Ph+ CML-CP harbouring the T315I mutation, additional safety margins have been introduced in Section 5.3 of the SmPC for toxicological effects. The calculations of safety margins are agreed upon.

4.4.2. Conclusions

The submission is approvable from the non-clinical point of view.

5. Clinical aspects

Introduction

5.1.1. GCP aspects

The clinical trial X2101 was performed in accordance with GCP as claimed by the MAH.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trial included in this dossier (see section 0).

5.1.2. Tabular overview of clinical trials

Table 7: Tabular overview of main clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
X2101 CABL001X2101	Phase I First-in-human multi-cohort study Final CSR, completed LPLV: 14-Mar-2023	Single agent **Arm 1** (CML-CP/): asciminib 10 mg b.i.d. to 200 mg b.i.d; 80 mg q.d. to 200 mg q.d.	Single agent **Arm 1** (CML-CP/): asciminib 10 mg b.i.d. to 200 mg b.i.d; 80 mg q.d. to 200 mg q.d.	Overall study N=326 (CML-CP/-AP/-BP or Ph+ ALL) **Arm 1: Asciminib monotherapy for patients with CML-CP not harboring the T315I mutation N=115** Starting dose: 10 mg b.i.d. (n=1), 20 mg b.i.d. (n=13), 40 mg b.i.d. (n=30), 80 mg b.i.d. (n=8), 150 mg b.i.d. (n=5), 160 mg b.i.d. (n=3), 200 mg b.i.d. (10), 80 mg q.d. (n=17), 120 mg q.d. (n=17), and 200 mg q.d. (n=11) **Arm 1: Asciminib monotherapy for patients with CML-CP harboring the T315I mutation N=70** Starting dose: 20 mg b.i.d. (n=1), 40 mg b.i.d. (n=1), 80 mg b.i.d. (n=4), 80 mg q.d. (n=1), 120 mg q.d. (n=3), and 200 mg q.d. (n=1), 150 mg b.i.d. (n=5), 160 mg b.i.d. (n=6), and 200 mg b.i.d. (48) **Arm 1: CML-AP N=15**

Supportive Study A2004 CABL001A2004	Phase 4 (NIS) End of data abstraction date: 15-Nov-2022	RWD retrospective, non-interventional chart review study that analyzed abstracted data from patients with CML harboring the T315I mutation who participated in the ongoing asciminib market access program (MAP)	Enrolled patients received at least 1 dose of asciminib between 01-Nov-2018 and 30-Apr-2022 and a maximum of 13 months of data abstraction after asciminib treatement was allowed.	Adult patients with CML-CP/-AP/-BP harboring the T315I mutation, who were either resistant to, intolerant to, or contraindicated for available treatments. Overall study N=31 (CML-CP/-AP/-BP) Median average daily dose at index date was 400 mg (range: 40 to 400 mg)

5.2. Clinical pharmacology

5.2.1. Pharmacokinetics

Introduction

The only new data submitted in relation to clinical pharmacology were those supporting the line extension for the 100 mg film coated tablet strength, specifically comparative *in vitro* dissolution. These were submitted in module 3 (see Quality section).

The application for extension of indication to CML chronic phase with T315I mutation at a dose of 200 mg b.i.d. was not supported by any new PK data or analyses but based on PK and modelling data already available and submitted for the initial MAA or with variations submitted since then. Accordingly, the MAH has stated "No new information is provided in support of the current application" in several chapters of the summary of clinical pharmacology (SCP).

In the initial Marketing Authorisation Application (MAA), due to the focus on the targeted indication for CML patients without the T315I mutation at 40 mg b.i.d. dose, (some of) the T315I-mutation-specific PK and modelling data were not explicitly mentioned in the assessment reports.

Accordingly, herein, data already submitted and assessed are retrieved from the prior assessment reports/EPAR as relevant and "new" data not previously discussed are included for the underlying extension of indication.

Absorption / Food effect

Based on simulations in PBPK report R2001088, the effect of a low-fat (0.6-0.7-fold) and high-fat (0.3-0.37-fold) meal on Cmax and AUC was comparable at a 200mg, an 80 mg and a 40 mg single dose, and similar to the effect observed in study E2101 with 40 mg in healthy volunteers.

Bioequivalence

New information generated in support of this application included the comparative dissolution testing of a new 100 mg dose strength consisting of the asciminib HCl drug substance in FCT formulation. The proposed 100 mg FCT dose strength is qualitatively the same and is quantitatively dose proportional to the currently approved 40 mg FCT with respect to the active and inactive ingredients.

Comparative dissolution testing was performed in dissolution media at pH of 1.2, 3.0, 4.5, and 6.8 and two-step dissolution in FaSSGF and FaSSIF to simulate physiological conditions of the GI tract.

In dissolution media, similar dissolution behavior was demonstrated in both:

- 5 x 40 mg FCTs compared to 2 x 100 mg FCTs to make a total dose of 200 mg.
- Or 4 x 40 mg FCTs compared to the 1 x 100 mg FCT combined with 1 x 20 mg FCT and 1 x 40 mg FCT to make a total dose of 160 mg.

In two-step dissolution in FaSSGF and FaSSIF, similar dissolution behavior was demonstrated among 5x 40 mg FCTs compared to 2x 100 mg FCTs to make a total dose of 200 mg.

Based on the available data and justification, a waiver for a bioequivalence study for the 100 mg dose strength is applied for. Please refer to Quality section.

Elimination

Accumulation for the 200 mg b.i.d. dosing was observed at steady state C2D1 with a geo-mean ratio (Racc %CV) of 2.09 (28%), range 1.09-3.80.

Dose proportionality and time dependency

In CML-CP patients with T315I mutation in study X2101, dose-proportionality was observed for AUClast, AUCtau and Cmax, both after single and multiple doses for the b.i.d. regimen. AUCtau in b.i.d. regimen was 12 hours.

Pharmacokinetics in the target population

Study X2101 was the first in human Phase I study with asciminib in patients with CML-CP/AP or Ph+ ALL, including patients with CML-CP/AP harbouring the T315I mutation. The study was a multicentre, open-label, 5-arm, dose escalation study to define the MTD/ RDE, safety, tolerability, assess the PK profile and provide preliminary evidence of efficacy of asciminib.

Actual dose levels for T315I mutation (n=79) subgroup were: b.i.d. 20 (n=1), 40 (n=1), 80 (n=4), 150 (n=7), 160 (n=8), 200 mg (n=52); QD 80 (n=1), 120 (n=4), 200 mg (n=1).

Out of 62 CML-CP/AP patients in the 200 mg b.i.d. cohort the T315I mutation was present in 48 CML-CP and 4 CML-AP patients. Data for the patients with accelerated phase were not presented.

Full PK sampling was performed on C1D1, C1D15, C2D1. Pre-dose samples were also taken on C1D2, C1D8, C1D15, C1D22, C2D1, C2D2, C3-C6D1.

There was no apparent difference in PK between the patients with CML-CP T315I compared to the total patient population. The summary table (Table 8) includes the 200 mg b.i.d. dose, both for CMP-CP/-AP without and CML-CP with the T315I mutation.

Table 8 Summary of asciminib PK parameters for the 200 mg b.i.d. regimen across studies in patients with CML (all and with T315I mutation)

Dose/Study	Cmax (ng/mL)	Tmax (hr)[1]	AUC0-12hr (ng*hr/mL)	AUClast (ng*hr/mL)	CL/F (L/hr)	Ctrough (ng/ml)	Racc
All CML-CP/-AP							
Cycle 1 Day 1							
200 mg b.i.d.	n = 61 3464.70 (33.60)	n = 61 2.03 (0.95; 7.28)	n = 2 18159.5 (27.82)	n = 61 14869.9 (33.42)	n = 2 11.01 (27.82)		
Cycle 2 Day 1			AUCtau (ng*hr/mL)				
200 mg b.i.d.	n = 54 5641.84 (39.86)	n = 54 2.00 (0.90; 7.03)	n = 34 37547.0 (41.00)	n = 54 29924.6 (41.27)	n = 34 5.33 (41.00)	N = 55 2715.38 (57.65)	n = 29 2.11 (27.03)
Patients with CML-CP with confirmed T315I mutation							
Cycle 1 Day 1							
200 mg b.i.d.	n = 48 3450.79 (34.27)	n = 48 2.05 (0.95; 7.28)	-	n = 48 14835.9 (34.96)	n = 2 11.01 (27.82)		-
Cycle 2 Day 1			AUCtau (ng*hr/mL)		-		-
200 mg b.i.d.	n = 43 5479.64 (41.83)	n = 43 2.00 (0.90; 7.03)	n = 28 37733.6 (45.12)	n = 43 29753.9 (43.65)	n = 28 5.30 (45.12)	n = 44 2799.71 (59.86)	n = 24 2.09 (27.72)

n= number of subjects with corresponding evaluable PK parameters; PK: pharmacokinetics.
[1]PK parameters data are presented as geometric mean (geomean %CV) except Tmax presented as median (range).

The exposure-response report ABL001A summarised exposure parameters simulated for the T315I population on basis of the data from study X2101 (**Error! Reference source not found.**)

Table 9 Summary of simulated exposure parameters by study day for 200 mg b.i.d.

Study day	Daily AUC (ng.h/mL)	Daily Cmax (ng/mL)	Daily Cmin (ng/mL)
Day 1	47170 [27877 - 90519]	1936 [761, 3785]	1361 [502 - 3375]
Steady state	98253[47838 - 205113]	5241[2549 - 10440]	2933 [1186 - 6727]

Data reported as median of the median and 5th-95th percentiles for the 100 replicates of 100 subjects each

In CML-CP patients with T315I mutation in Study X2101 the inter-subject geoCV% in steady-state with 200 mg b.i.d. was 45.1% and 41.8% for AUC0-12 and Cmax, respectively.

Special populations

No new information to support the asciminib PK in special populations was submitted.

Renal impairment

PBPK modelling (report DMPK-R2000208) estimated Cmax and AUC for 40 mg SD in mild/moderate/severe RI based on observed data from renal impairment study A2105 with 40 mg SD in severe RI subjects. The model was applied in PBPK model DMPK-R2001088 (both reports submitted for initial MAA) to simulate Cmax and AUC for 200 mg SD in mild/moderate/severe RI based on observed data from study A2105.

Hepatic impairment

PBPK modelling (report DMPK-R2000208) estimated Cmax and AUC for 40 mg SD in mild/moderate/severe HI based on observed data from hepatic impairment study A2103. The model was applied in PBPK model DMPK-R2001088 (both reports submitted for initial MAA) to simulate Cmax and AUC for 200 mg SD in mild/moderate/severe HI based on observed data from study A2103.

Elderly

According to the CSR of study X2101, from the patients with T315I mutation 4/70 patients were ≥75 (max. 86) years of age, all at the 200 mg b.i.d. dose.

Paediatric population

According to the MAH, the PK of asciminib is currently under investigation in the ongoing paediatric study CABL001I12201 with Ph+ CML-CP not harbouring the T315I mutation, previously treated with one or more TKIs.

The MAH initially concluded and proposed:

- There was no apparent difference in the PK of asciminib in patients with compared to healthy subjects and in female compared to male patients.
- No dose adjustment of asciminib based on body weight, for Asian patients with CML or elderly is recommended.
- Caution should be exercised in subjects with severe hepatic and renal impairment receiving asciminib 200 mg b.i.d. No dose adjustment is necessary in subjects with hepatic and renal impairment.
- Heavy smoking, known to induce UGTs gene expression, had no effect on the PK of asciminib.

Pharmacokinetic interaction studies

No new data was generated and submitted for this submission.

In the clinical DDI studies submitted for MAA only single or multiple doses of 40 mg asciminib were used. Two recent studies investigated asciminib 80 mg QD as transporter inhibitor on atorvastatin and with asciminib 200 mg SD as substrate for CYP3A4 induction by phenytoin.

The EPAR states: "A PBPK model for asciminib was developed and validated (Study 2000208) as a CYP3A4, UGT and BCRP substrate and perpetrator of CYP enzymes for the dose of 40 mg asciminib to predict the effect of food, and hepatic or renal impairment. This model was also applied (Study 2001088) to predict DDI scenarios which has not been tested clinically […]."

This PBPK model was used to predict different interactions including at 200 mg b.i.d. asciminib. The PBPK model reports (DMPK R2001088, DMPK R2300226 and DMPK R2301078) and now submitted SCP provided tables for asciminib as victim and perpetrator under multiple 200 mg b.i.d. dosing, as basis for new text inclusion in the SmPC section 4.5.

5.2.2. Pharmacodynamics

Primary and secondary pharmacology

Primary pharmacology

In the current submission, previous preclinical data was summarised. In the KCL-22 BCR::ABL1 T315I mutation xenograft model, a 4-fold higher dose (30 mg/kg b.i.d. vs. 7.5 mg/kg b.i.d.) was required to achieve a regression of >50% in tumour volume compared to the wild-type KCL-22 xenograft model [RD-2020-00314], [RD-2013-50145].

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

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

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

Secondary pharmacology

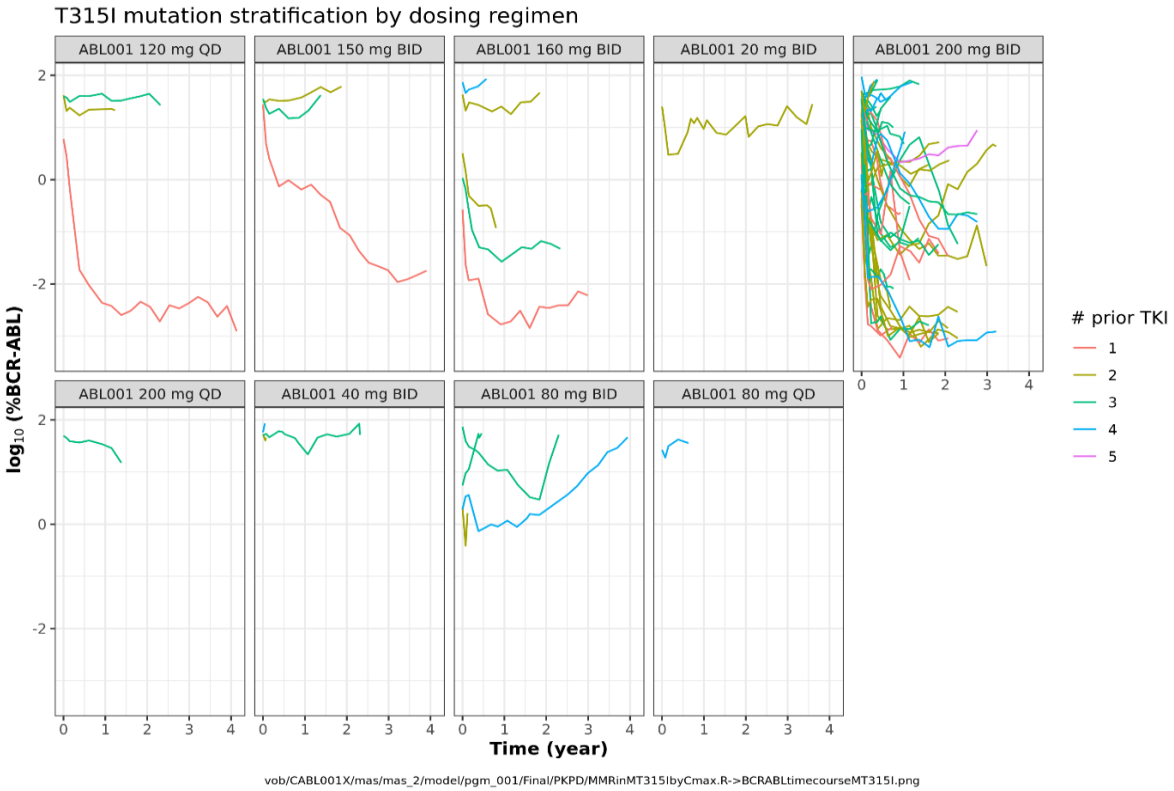
The QT/QTc concentration-effect analysis submitted at initial MAA had demonstrated that the therapeutic doses of single agent asciminib did not have a clinically relevant effect on cardiac repolarization with an estimated mean increase of QTcF < 10 ms up to 10582 ng/mL, which is 2-fold the geo-mean Cmax at 200 mg b.i.d.

As some asymptomatic QTc prolongations and AEs related to QTc prolongation were observed in study X2101, and as it was believed that there are limited clinical data and safety margins at asciminib 200 mg b.i.d. and at the highest clinically relevant exposure, it is now newly recommended to avoid drugs known to cause Torsade de Pointes when administering asciminib at the 200 mg b.i.d. dose.

5.2.3. Pharmacokinetics/pharmacodynamics (PK/PD)

From study X2101 and based on the initially submitted ERR, the time-course of BCR-ABL in CML-CP patients with T315I mutation stratified by dosing regimens and colour coded by prior TKI treatments is shown in Figure 1 Time-course of observed log10-transformed BCR::ABL in patients with T315I mutation stratified by dosing regimens and number of prior TKI treatment. At doses <200 mg b.i.d., most of T315I patients did not experience a decrease in BCR-ABL below -1 $\log_{10}$, or equivalently, 0.1% except those who had one prior TKI treatment. Consistent with non-T315I-patients, the number of prior TKI treatment appears to also have an effect in this group of patients.

Figure 1 Time-course of observed log10-transformed BCR::ABL in patients with T315I mutation stratified by dosing regimens and number of prior TKI treatment



The Emax model revealed EC_{90} values of 31225ng*h/mL, 2493 ng/mL and 792 ng/mL for AUC, Cmax, and Cmin, respectively.

Table 10 Simulated MMR rate for T315I mutation and any prior TKI treatments

Category	24-wk MMR rate (%)	48-wk MMR rate (%)
120 mg b.i.d.	19.3 ± 3.7	22.9 ± 4.0
160 mg b.i.d.	20.2 ± 3.9	23.8 ± 3.8
200 mg b.i.d.	20.7 ± 4.2	23.7 ± 4.5

Data reported as mean ± standard deviation of the median MMR over the 100 replicates.

5.2.4. Dose selection and therapeutic window

Asciminib 280 mg b.i.d. was the highest dose tested in a small number of patients with Ph+ ALL and CML-BP. Even though the MTD was not reached at this dose, no additional dose escalation was attempted, hence the available data does not support a wider safety margin than 280 mg b.i.d.

5.2.5. Overall discussion and conclusions on clinical pharmacology

5.2.5.1. Discussion

Pharmacokinetics

The only new data supporting the line extension for the 100 mg film coated tablet strength, specifically comparative *in vitro* dissolution, were submitted in module 3. No module 2.7.1 was included. The new strength and the previous 40 mg strength are qualitatively the same and quantitatively dose

proportional. Based on comparative dissolution tests at the relevant pH conditions between 1.2 and 6.8 and in FaSSGF and FaSSIF to simulate physiological conditions of the GI tract, the MAH applies for a strength waiver for the new 100 mg strength film coated tablet. To summarise, the justification for biowaiver is acceptable. Please refer to the Quality section for assessment of dissolution.

The application for extension of indication to CML chronic phase with T315I mutation at a dose of 200 mg b.i.d. is not supported by any new data or analyses but based on PK and modelling data already available and submitted for the initial MAA or with variations submitted since then.

Accordingly, herein, data already assessed are retrieved from the prior assessment reports as relevant and only "new" data of relevance are discussed for the underlying EoI.

PK in the target population

In the T315I subgroup, dose-proportionality was observed for AUClast, AUCtau and Cmax, both after single and multiple doses up to 200 mg b.i.d. This is slightly different to the observations in the full study population (CML-CP/AP patients including T315I) where exposure increased slightly over-proportional in b.i.d. regimens between 80-200mg.

Accumulation at the 200 mg b.i.d. dose was about 2-fold (both in the T315I subgroup and the full population), which is higher than observed with the 40 mg b.i.d. (1.65-fold) and the 80 mg QD (1.3-fold) regimens.

PK parameters for the patients with T315I mutations at 200 mg b.i.d. were not different to those of the full PK group of study X2101, which is not too surprising since most of the patients on 200 mg b.i.d. providing PK samples had the T315I mutation (48 of 61 at C1D1 and 43 of 54 at C2D1). Cmax was 5480 ng/ml, AUCtau 37734 ng*hr/ml, Cmin 2780 ng/ml and CL/F 5.3 l/hr in the T315I subgroup.

In the exposure-response report it was stated that exposure metrics were derived from the popPK model, but AUCss was approximately 30% higher than observed (comparing observed daily AUC Cycle 2 Day 1 for patients with CML-CP with confirmed T315I mutation (i.e. 2 x 37733.6 ng*hr/mL) versus daily AUC steady state (i.e. 98253 ng*hr/mL). This discrepancy was justified with the high variability of asciminib PK and not considered clinically meaningful by the MAH. In addition, VPCs stratified by dose (including 200mg) were provided for the popPK model applied and showed a mostly adequate fit of the model.

Inter-subject variability was moderate with ~42-45% for AUC and Cmax at the proposed 200 mg b.i.d. regimen.

Special populations

The dedicated renal impairment study A2105 had revealed 8% higher Cmax and 56% higher AUC for 40 mg single-dose in HV with severe RI. Based on this for the approved 40 mg b.i.d. dose no dose reductions were recommended. Based on the PBPK model results, the MAH proposed no dose adjustments for any severity of RI but recommended cautionary administration in patients with severe RI also for the 200 mg b.i.d. dose.

However, the PBPK model is not considered qualified for extrapolation to higher doses (in the original model, the observed exposures for 40 mg dose were overpredicted in the HV group and underpredicted in the severe renal impairment group, leading to underestimation of effect of renal impairment). The adjusted value of fu,p is not considered justified. In addition, many assumptions will be needed for the extrapolation which cannot be verified. Therefore, no conclusions can be drawn from the PBPK modelling results on potential dose recommendations for different groups of renal impairment. As no conclusions

can be drawn from the PBPK model with respect to dose recommendations for renal impairment, no statement based on PBPK was included in the SmPC.

During review, it was discussed that in absence of further clinical data supporting extrapolation to outside the studied CML-CP T315I population on 200 mg b.i.d. from study X2101, the CML-CP T315I patient group with renal impairment should be limited to the same extent as in study X2101, i.e. patients with creatinine > 1.5xULN should be excluded (as stipulated in exclusion criterion 6) and the SmPC should be amended accordingly in all concerned sections. This was not agreed by the MAH. However, in view of the safety responses, the CHMP eventually requested to amend the SmPC to highlight that no clinical data are available in patients with severe renal impairment with the commitment of further investigation and monitoring, which was accepted by the MAH.

The dedicated hepatic impairment study A2103 had revealed 29% higher Cmax and 66% higher AUC for 40 mg single-dose in HV with Child-Pugh C. Based on this for the approved 40 mg b.i.d. dose no dose reductions were recommended, considering that a MTD had not been reached at 280 mg b.i.d. during development. Based on the results from the PBPK model, the MAH proposed no dose adjustments for any severity of HI but recommended cautionary administration in patients with severe HI also for the 200 mg b.i.d. dose.

However, the PBPK model is not considered qualified for extrapolation to higher doses (in the original model, for the 40 mg dose, the observed exposures revealed an increase of 66% for severe HI compared to normal HI, whereas the model only predicted a 28% increase in exposure. The adjusted value for fu,p is not considered justified). In addition, many assumptions will be needed for the extrapolation which cannot be verified. Therefore, no conclusions can be drawn from the PBPK modelling results on potential dose recommendations for different groups of hepatic impairment. As no conclusions can be drawn from the PBPK model with respect to dose recommendations for renal impairment all statements based on PBPK in the SmPC were not included.

During review it was discussed that in absence of further clinical data supporting extrapolation to outside the studied CML-CP T315I population on 200 mg b.i.d. from study X2101, the CML-CP T315I patient group with hepatic impairment should be limited to the same extent as in study X2101, i.e. patients with hepatic function based on liver function tests as stipulated in exclusion criterion 6 should be excluded and the SmPC should be amended accordingly in all concerned sections. This was not agreed by the MAH. Subsequently, in view of the safety responses, the CHMP requested to amend the SmPC to highlight that no clinical data in patients with severe hepatic impairment are available, with a commitment of further investigation and monitoring, which was accepted by the MAH.

In addition, the MAH had provided another comparison of popPK modelled exposure for severe renal and hepatic impaired subjects with that estimated from few patients with CML-BP or ALL who had been treated at 280 mg b.i.d. dose in the initial study X2101. It was acknowledged that even a higher dose of 280 mg b.i.d. had been administered to date and this daily dose of 560 mg was hence 40% higher than the applied dose of 200 mg b.i.d. Notably, in study X2101 at 280 mg b.i.d. C2D1 C_{trough} was measured with 4165 ng/ml which was hence ~53% higher than in the PK data set for 200 mg b.i.d. (2715 ng/ml).

According to the study X2101 CSR this highest dose seemed well tolerable with a relative dose intensity of >90% in 5 of 6 CP-BP/ALL patients and one patient even taken 280 mg b.i.d. (with slight interruptions) for nearly 2.5 years, which was also considered supportive for final conclusions.

Of cause, PK effects caused by severely impaired hepatic and renal elimination capacities cannot be directly extrapolated from exposure increases with higher doses in "normal" cancer patients. However, based on the clinical safety experience with even a higher dose, under consideration of intense additional monitoring of safety per dose in upcoming PSURs and with the request for SmPC amendment,

it was deemed acceptable that no additional dedicated PK studies for the 200 mg b.i.d. dose were currently requested to establish final dose recommendations for patients with hepatic and renal impairment – and no contraindications were introduced - to give experienced oncologists the immediate opportunity to individually decide to cautiously treat an otherwise indicated CML patient with T315I mutation.

However, in case any safety suspicion arises based on the postmarketing data such studies may still be requested.

According to the MAH, the PK of asciminib is currently under investigation in the ongoing paediatric study CABL001I12201 with Ph+ CML-CP not harbouring the T315I mutation, previously treated with one or more TKIs.

Interactions

No new *in vitro* DDI studies were submitted within this variation. However, as clinical plasma concentrations are higher with the new dosing of 200 mg b.i.d. as compared to the previously approved 40 mg b.i.d., the clinical relevance of drug interactions has been re-assessed.

Asciminib is an inhibitor and an inducer of CYP1A2 and CYP3A4. Using the mechanistic static model, the Applicant has calculated the net effect AUCR for 200 mg b.i.d. as 0.42 and 2.85, respectively, which warrants further investigation as per ICH M12 (AUCR outside the 0.8-1.25 range).

Asciminib inhibits CYP2C8, CYP2C9, CYP2C19 and UGT1A1. The respective AUCR values have been calculated as 1.75, 2.36, 1.38 and 3.01, all warranting further investigation as per ICH M12. The Applicant was thus requested to conduct clinical studies to assess the impact of 200 mg b.i.d. asciminib treatment on CYP1A2, CYP3A4, CYP2C8, CYP2C9, CYP2C19 and UGT1A1 substrates.

According to ICH M12, the estimation of the clinical relevance of transporter interactions is based on in vitro data (IC_{50} or K_i). At 200 mg b.i.d., asciminib inhibits BCRP, P-gp, OAT3, MATE1 and MATE2-K to a relevant extent as per ICH M12 (the assessor used $C_{max,u}$ of 0.3375 µM based on mean C_{max} at steady-state of 5642 ng/mL as reported in the Non-clinical Overview of the current variation and f_u of 2.7%). Given only minor renal elimination of asciminib, no clinically meaningful DDIs involving OAT3, MATE1 and MATE2-K are expected. The Applicant did not provide the unbound maximal hepatic inlet plasma concentration at steady-state following 200 mg b.i.d. dosing, but given $C_{max,u}$ at hepatic inlet after 80 mg QD of 0.253 µM reported in SCP of the initial submission (which is lower than that expected at 200 mg b.i.d.), DDIs with OATP1B1 and OATP1B3 are clinically relevant and should be further investigated. ICH M12 does not cover OCT1 but any information on possible OCT1 interactions mentioned in the SmPC were to be scientifically justified. Thus, the MAH was also requested to conduct clinical studies to assess the impact of 200 mg b.i.d. asciminib treatment on BCRP, P-gp, OATP1B1 and OATP1B3 substrates. The MAH argued against the necessity of new DDI studies.

All *in silico* and clinical data submitted here were previously presented and assessed. As such, especially the PBPK model (reports 2270328 and 2300226) -derived estimations for x-fold changes (per specific dose) by drug interactions were already assessed and concluded as follows in MAA and in variation II/08 in 2023: "*The platform is not qualified for the intended purpose and no additional clinical PK data for the discussed drug interactions were presented. Many assumptions and limited clinical data impaired the validity of the used PBPK model. Therefore, no conclusions derived by PBPK modelling should be listed in the SmPC*." Accordingly, no model-derived data were included in section 4.5 and 5.2.

It is, of cause, of particular importance that the 200 mg b.i.d. dosing will probably result in stronger interactions than previously established for the 40 mg b.i.d. dose (or for the parallel further EoI procedure in newly-diagnosed CML including also the 80 mg QD dose). Therefore, especially drugs with a narrow therapeutic index like warfarin (CYP2C9 substrate) and digoxin (P-gp substrate) need further

review, therefore the text initially proposed for section 4.5 stating specific %-fold changes fully derived from PBPK model estimations was not acceptable. Accordingly, the section was revised and the specific PBPK-derived information deleted.

Meanwhile 2 additional clinical DDI studies were performed, as outcome of variation II/08, for CYP3A4 induction by phenytoin on 200 mg SD asciminib and for inhibition by 80 mg QD asciminib on atorvastatin (CYP3A4, OATP1B1, OATP1B3, P-gp, and at least partly of BCRP) and CP-1 as OATPB1 substrate. The results have been assessed recently in variation EMA/VR/0000248179 and the PI is now updated with the finally approved information. Furthermore, the MAH informed about another ongoing DDI study asciminib at 80 mg QD at steady-state on the single dose PK of rosuvastatin (BCRP substrate) and digoxin (P-gp substrate).

From the calculations (and predictions) of DDI potential from *in vitro* data it is obvious that for several interactions the investigation of their clinical relevance for the 200 mg b.i.d. dose would have been more informative than with 40 mg and 80 mg.

Considering the available dataset, the CML-CP/AP T315I cohort at 200 mg b.i.d. was introduced in the protocol with Amendment 4 and 33 patients with T315I mutation were enrolled. With regard to potential for drug interactions, amendment 9 revised the requirements for concomitant medications so that out of the 62 T315I patients, 29 were enrolled under the new requirements. Even if the following was based on a limited data set, the MAH was asked to clarify whether these patients took concomitant medication that was still prohibited for the first 33 patients. If so, and PK sampling was still ongoing, the PK of these patients was to be compared and potential differences between subgroups discussed with regard to underlying DDI. However, all the DDIs in question were related to asciminib as precipitant, so that no PK changes of substrates could have been obtained.

In addition, potential differences in safety aspects (e.g. TEAEs, dose interruptions or reductions) were to be provided and discussed (see also safety assessment below). Special attention on coagulation-related aspects was relevant due to the mechanism of action regarding the cardiovascular risk (including one case of fatal stroke) for concomitant medications of statins and warfarin. It was clarified that there were no patients with T315I mutation on treatment with asciminib 200 mg b.i.d. who received warfarin. Thus, the impact of asciminib 200 mg b.i.d. on warfarin and other oral Vit K antagonists remains unknown. The data (safety and especially PK) available for concomitant administration of statins are currently limited and too variable to allow conclusions on the effect size of asciminib as precipitant on BCRP/OATP1B substrates like statins and clinical effects. The applicant agreed to address these issues in the next PSURs and to summarise data available from postmarketing sources for the 40 mg b.i.d., 80mg QD and 200 mg b.i.d. doses, both combined and separately, and to discuss these issues in this context (see also safety section).

To enlighten the current data further, in view of clinical safety and considering harmonisation of DDI labelling recommendations especially for the new high 200 mg b.i.d. dose, the MAH was asked to justify the stricter requirements in the US FDA label *vs.* the proposals for the EU SmPC regarding

1. CYP3A4 substrates (**FDA**: avoid together with 200 mg b.i.d.; **EU**: caution for NTI substrates at all doses),

2. CYP2C9 substrates (**FDA**: avoid at all doses, reduce substrate dose at 80 mg daily dose, consider non-2C9 substrate alternative at 200 mg b.i.d.; **EU**: caution at 40 mg b.i.d., avoid sensitive and NTI substrates at 200 mg b.i.d.or use alternative, or reduce substrate dose),

3. OATP1B, BCRP substrates (**FDA**: avoid rosuvastatin and atorvastatin at all doses; **EU**: caution at all doses).

The MAH clarified that FDA's conclusions for DDI information were based on the same data as provided to EMA. The current proposal for the EU SmPC section 4.5 is considered acceptable with its recommendations for specific interactions. Nevertheless, especially for the new 200 mg b.i.d. dose as well as the 80 mg QD dose having been approved just recently it is relevant that any emerging safety information from post-marketing will be thoroughly evaluated.

Pharmacodynamics

Preclinical data had shown that about 4-13-fold higher concentrations are necessary in models at the T315I mutant compared to wildtype CML. These concentrations could be achieved in patients at the 200 mg b.i.d. dose where the geo-mean minimal concentrations were about 2-fold higher than the IC50 at the T315I mutant. At doses <200 mg b.i.d., most of T315I patients did not experience a decrease in BCR-ABL below -1 $\log_{10}$, or equivalently 0.1%, except those who had only one prior TKI treatment.

Overall, based on the data from study X2101 at the proposed dose regimens of asciminib as single agent the risk for QTcF prolongation above the clinically relevant threshold of 10msec is low. However, a warning was already described in the SmPC and PL for caution to be exercised when concomitant drugs known to cause Torsade de Pointes are given. The SmPC was updated to avoid coadministration with drugs known to cause Torsade de Pointes with 200 mg b.i.d. asciminib, which is endorsed.

5.2.5.2. Conclusions

Dissolution data were submitted to support a waiver for the line extension of a 100 mg film coated tablet. These were acceptable. See Quality section.

No new clinical pharmacology data were submitted for the extension of indication in CML-CP patients with the T315I mutation at an asciminib dose of 200 mg b.i.d. This is deemed problematic with regard to potential DDIs as the available PK data are considered unsatisfactory for appropriate extrapolation to the 200 mg b.i.d. dose. Therefore, considering the limited PK data and the rarity of the underlying disease set, the MAH has committed to monitor specifically and discuss postmarketing safety data for patients with hepatic and renal impairment in the next PSURs, as well as specific drug interactions concerning cardiovascular risk separated by doses / dose regimens.

The conclusions for patients with severe hepatic or renal impairment were finally derived in agreement with clinical safety considerations as no satisfactory PK data are available for the 200 mg b.i.d. dose and no definite dose recommendations can be given. Therefore, the recommendations in the SmPC were amended to clearly address this missing clinical experience.

From a clinical pharmacology point of view the extension of indication is approvable.

5.3. Clinical efficacy

5.3.1. Dose response study(ies)

No new data on dose-response were submitted.

See clinical AR section 2.3.2 and 2.4:

Preclinical data had shown that about 4-13-fold higher concentrations are necessary in models at the T315I mutant compared to wildtype CML. These concentrations could be achieved in patients at the 200 mg b.i.d. dose where the geo-mean minimal concentrations were about 2-fold higher than the IC50 at

the T315I mutant. At doses <200 mg b.i.d., most of T315I patients did not experience a decrease in BCR-ABL below -1 $\log_{10}$, or equivalently, 0.1% except those who had one prior TKI treatment.

5.3.2. Main study

CABL001X2101: A phase I, multicenter, open-label study of oral ABL001 in patients with chronic myelogenous leukemia (CML) or Philadelphia Chromosome-positive acute lymphoblastic leukemia (Ph+ ALL)

Study design

Study X2101 was a non-randomised, uncontrolled, open-label, multi-cohort, multi-centre first-in-human (FIH) Phase I, dose escalation study to define the MTD/ RDE, to characterize safety and tolerability, to assess the PK profile, and to assess the preliminary efficacy of asciminib given as single agent or in combination with either nilotinib or imatinib or dasatinib in patients with CML or Ph+ ALL. The study was submitted as supportive evidence in the initial marketing application dossier and respective parts (in patients not harbouring T315I mutation) were assessed, later aspects of the study were assessed for safety and the final CSR was submitted (seq 0028) for variation II/0017.

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

- **Arm 1: asciminib as single agent in CML-CP and accelerated phase (AP) patients (including the cohort of patients harboring the T315I mutation)**
- Arm 2: asciminib in combination with nilotinib in CML-CP and AP patients
- Arm 3: asciminib in combination with imatinib in CML-CP and AP patients
- Arm 4: asciminib in combination with dasatinib in CML-CP and AP patients
- Arm 5: asciminib as single agent in CML blast phase (BP) and Ph+ acute lymphoblastic leukemia (ALL) patients

Figure 2: Study schema for X2101

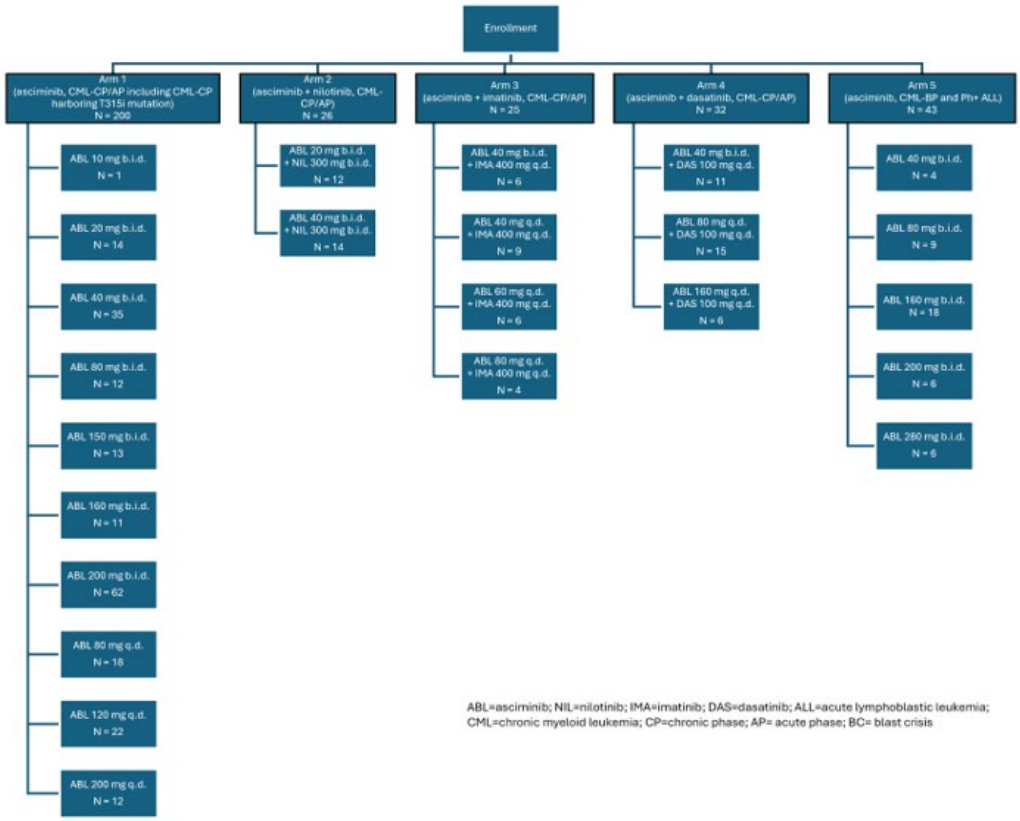
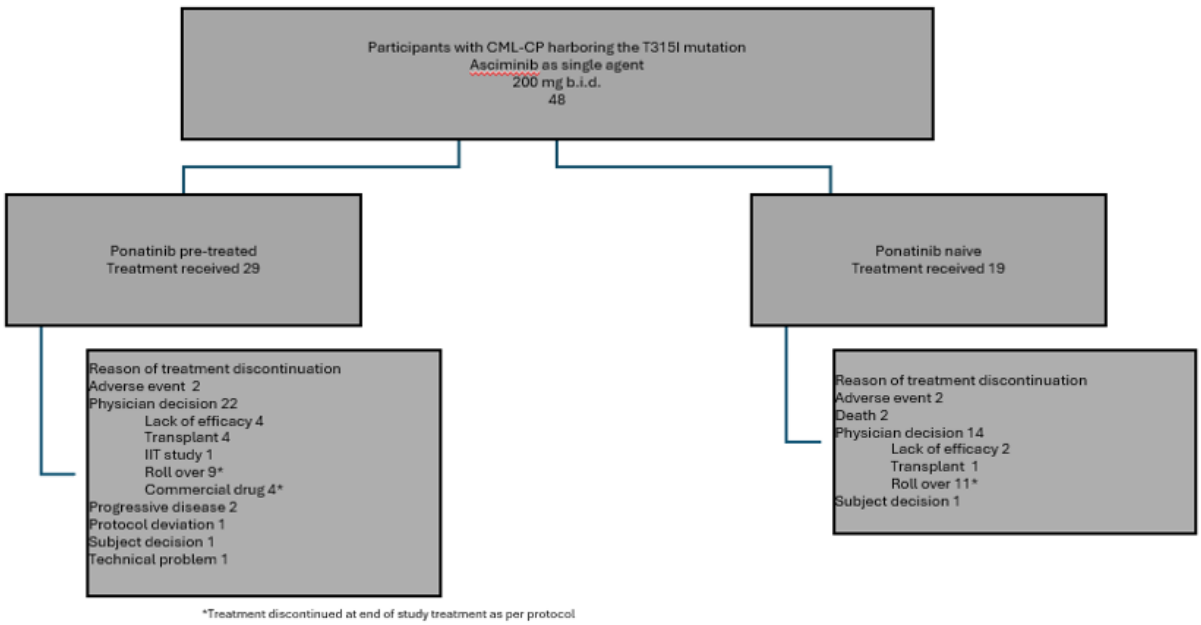


Figure 3 Participant flow of patients with CML-CP harbouring the T315I mutation treated with asciminib 200 mg b.i.d. (Study X2101)



The primary objective of X2101 was to determine the MTD and/or the RDE of asciminib as single agent or in combination with other TKIs. The assessment of the overall safety profile, as well as the antileukemic activity were part of the secondary objectives. The primary analysis was performed when

all patients in Arms 1 and 5 had been treated for at least 6 cycles of 28 days of treatment and had their 24-week efficacy evaluation performed or had discontinued treatment earlier.

The study was amended multiple times. Important in respect to the target population are amendments 4 and 9. With amendment 4 (06.01.2015) patients with CML harboring the T315I "gatekeeper mutation," who exhibited relapsed disease associated with the presence of a T315I mutation after therapy with at least one TKI, were allowed.

With protocol amendment 9 (30.08.2018) an expansion cohort of the 200 mg b.i.d. dose in Arm 1 was incorporated to further assess asciminib as a single agent treatment in CML-CP/-AP patients harboring the T315I mutation and this is the population in the scope of this application. Finally, 70 CML-CP patients harbouring the T315I mutation were enrolled in the study.

Study assessments

Molecular response was assessed based on levels of BCR::ABL1 transcripts, which was determined by RQ-PCR testing of peripheral blood and analyzed at a Novartis designated laboratory with validated PCR technology that had a sensitivity of at least 4.5 logs. The percent ratio of BCR::ABL1 transcripts versus control gene transcripts converted to International Standards (IS) was calculated for each sample. NB: "MMR" is defined as MR3- BCR::ABL1 $\leq$ 0.1% (IS).

For patients enrolled in dose escalation cohorts, BCR::ABL1 using RQ-PCR was monitored at screening, on Day 1 of Cycles 2, 3, 6, 9, 13 and every 3 cycles afterwards during the study treatment, and at the end of treatment visit. For patients enrolled in dose expansion cohorts, BCR::ABL1 using RQ-PCR was monitored at screening, on Day 1 of Cycles 2, 3, 4, 7, 10, 13 and every 3 cycles afterwards during the study treatment, and at the end of treatment visit.

Mutational analysis was performed at baseline, for an unconfirmed loss of response and/or as needed. The mutational analysis was performed at a Novartis designated laboratory using Sanger sequencing assay to determine the BCR::ABL1 mutations including T315I.

Bone marrow analysis and cytogenetics: A minimum of 20 metaphases were required to be examined in each bone marrow sample. Cytogenetic response (CyR) was assessed as the percentage of Ph+ metaphases in the bone marrow. Assessment was performed at screening and when a patient's BCR::ABL1 ratio rose to >1% (equivalent to loss of CCyR), or when a patient lost CHR. In addition, after screening, assessment was performed in patients who were not in CCyR at: Cycles 3, 6, 9, 13 and every 3 cycles thereafter for patients enrolled in dose escalation cohorts- Cycle 4, 7, 10, 13 and every 3 cycles thereafter for patients enrolled in dose expansion cohorts.

After screening, bone marrow aspirate for cytogenetic response was not required for patients unless a patient lost CCyR and/or CHR. After Cycle 13, cytogenetic assessments (via bone marrow aspirate) were performed as clinically indicated.

Treatment

Arm 1: Asciminib monotherapy, cohort of patients with CML-CP harboring the T315I mutation (N=70).

Starting dose: 20 mg b.i.d. (n=1), 40 mg b.i.d. (n=1), 80 mg b.i.d. (n=4), 80 mg q.d. (n=1), 120 mg q.d. (n=3), and 200 mg q.d. (n=1), 150 mg b.i.d. (n=5), 160 mg b.i.d. (n=6), and 200 mg b.i.d. (48).

Asciminib was administered twice daily (b.i.d.) in the fasted state (food was not allowed for at least 2 hours prior and 1 hour after administration) approximately 12 hours apart. Asciminib was supplied as capsules at dose strengths of 5 mg, 20 mg and 50 mg and as tablets of 20 mg, 40 mg and 50 mg (tablets were introduced with protocol amendment 5 (dated 26-Jun-2015).

Randomisation

No randomisation.

Blinding

No blinding.

Patient population

In this international study patients were enrolled in Australia, EU (France, Germany, Italy, Netherlands, Spain), Asia (Japan, South Korea, Singapore) and North America (United States).

Patients eligible for inclusion in this study had to meet all of the following criteria:

1. Male or female patients ≥ 18 years of age who presented one of the following:

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

- Patients with Ph+ CML in the CP or AP who were previously treated with at least two different TKIs prior to study entry and had relapsed, were refractory to or intolerant of TKIs as determined by Investigators, or

- Patients with CML in the CP or AP who exhibited relapsed disease associated with the presence of the T315I "gatekeeper mutation" after at least one TKI were also eligible provided that no other effective therapy exists (criteria introduced with protocol amendment 4). There was no restriction on the number of prior therapies administered to patients, and patients with status of post bone marrow transplant were eligible provided they met the inclusion/exclusion criteria.

Objectives and estimands

Primary objective

Arm 1: To determine the MTD and/or RDE (s) of asciminib as single agent in patients with CML-CP/-AP. As planned as phase 1 study primary endpoint in this was incidence of dose limiting toxicities (DLTs) during the first cycle of study treatment.

Estimands for the primary objective

Not applicable.

Statistical methods for estimation and sensitivity analysis on primary estimand<s>

Not applicable.

Secondary objectives

The secondary endpoints in Study X2101 for the T315I population were in respect to efficacy included: MMR rate (i.e. MR3 - BCR::ABL1 ≤ 0.1% (IS)) by 24 weeks of treatment and MMR by and at selected time points (including Week 24, Week 48, and Week 96), hematologic, cytogenetic (MCyR, PCyR etc.), and MR (BCR::ABL transcript level), as well as time to MMR and duration of MMR.

Molecular response was assessed based on levels of BCR::ABL1 transcripts which was determined by RQ-PCR testing of peripheral blood and analyzed at a Novartis designated laboratory with validated PCR technology that had a sensitivity for BCR::ABL1 detection of at least 4.5 logs (IS). The percent ratio of BCR::ABL1 transcripts versus control gene transcripts converted to IS was calculated for each sample, MR4 and MR4.5 are further secondary endpoints.

Estimands for the secondary objectives

No prospective definition of estimands was retrieved.

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

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

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

A dose-determining analysis set (DDS) for the primary endpoint was defined, it excluded patients from the expansion cohorts.

Results

Participant flow and numbers analysed

Study initiation date: 24-Apr-2014 (first patient first visit)

Study completion date: 14-Mar-2023 (last patient last visit)

Multiple amendments were issued, following amendment 4, 70 CML-CP patients harbouring the T315I mutation were enrolled in the study, 48 patients received 200 mg asciminib b.i.d.

Patient disposition for the CML CP patients with confirmed T315I mutation is given in the table below.

Table 11 Patient disposition by treatment – single agent asciminib in CML CP patients with confirmed T315I mutation at Screening (Study X2101 FAS)

Disposition Reason	Asciminib 200 mg b.i.d. N=48 n (%)	All patients N=70 n (%)
Patients treated		
End of treatment	48 (100)	70 (100)
Primary reason for end of treatment		
Adverse Event	4 (8.3)	6 (8.6)
Death	2 (4.2)	3 (4.3)
Physician Decision	36 (75.0)	47 (67.1)
PTA options*	25 (52.1)	29 (41.4)
Lack of efficacy**	11 (22.9)	18 (25.7)
Progressive Disease	2 (4.2)	4 (5.7)

Disposition Reason	Asciminib 200 mg b.i.d. N=48 n (%)	All patients N=70 n (%)
Patient/Guardian Decision	2 (4.2)	7 (10.0)
Protocol Deviation***	1 (2.1)	1 (1.4)
Technical Problems****	1 (2.1)	2 (2.9)

* includes but not limited to access to reimbursable commercial supply or the roll-over study
** includes transplantation
*** patient discontinued study treatment due to protocol deviation; use of hydroxyurea for disease control
**** patients could not travel to site due to COVID-19 and discontinued treatment
- Percentage is based on N

Deviations from study plan

The study protocol was amended multiple times, important in respect to the target population are amendments 4 and 9.

With amendment 4 (06.01.2015) patients with CML harboring the T315I "gatekeeper mutation," who exhibited relapsed disease associated with the presence of a T315I mutation after therapy with at least one TKI were allowed.

With protocol amendment 9 (30.08.2018) an expansion cohort of the 200 mg b.i.d. dose in Arm 1 was incorporated to further assess asciminib as a single agent treatment in CML-CP/-AP patients harboring the T315I mutation and this is the population in the scope of this application. Finally, 70 CML-CP patients harbouring the T315I mutation were enrolled in the study.

Table15 History of amendments

Version and date	Summary of key changes
Amendment 1 (22-Jan-2014)	This amendment addressed changes requested following post health authority review: • Revised hematologic DLT criteria for patients with CML. • Revised pancreatic DLT criteria • Updated other non-hematologic DLT criteria • Alopecia added as exemption to DLT criteria • Revised monitoring and guidance plan for hematologic and pancreatic toxicities • Included phototoxicity assessment and follow-up plan • Visit evaluation schedule included RSTANCE2101 protocol assessment
Amendment 2 (07-Mar-2014)	This amendment addressed changes requested following administrative correction identified during health authority submission process: • Inclusion criteria: Bullet formatting corrected to reflect intended definition of criteria #1
Amendment 3 (14-Mar-2014)	This amendment addressed changes requested following health authority review: • Visit evaluation schedule table footnote clarified that only Japan patients were required to be hospitalized during Cycle 1 in principle.

Amendment 4 (06-Jan-2015)	This amendment had the following changes: • Introduced the evaluation of the combination of asciminib with nilotinib, to determine the recommended combination regimen for future studies, and to describe the safety and preliminary antitumor activity. Multiple sections were updated based on this change as needed. • To better understand asciminib-mediated therapeutic responses in patients with CML harboring the T315I "gatekeeper mutation," the inclusion criteria 1 was broadened to include those patients who exhibited relapsed disease associated with the presence of a T315I mutation after therapy with at least one TKI. • Inclusion criteria #1 was updated regarding the eligibility of patients with CML harboring the T315I mutation. Clarified that patients with Ph+ ALL who were status post bone marrow transplant were eligible. • Exclusion criteria #1 was updated to modify the wash-out periods for prior therapies. • Exclusion criteria #2 was added to exclude patients who were intolerant to the nilotinib to be enrolled in the combination arm (asciminib + nilotinib). • Exclusion criteria #4 was updated to indicate that at least 4 weeks had to elapse since prophylactic CNS irradiation as part of front-line regimen for ALL. • Exclusion criteria # 6 was updated to allow patients with platelets > 50 10^9/L to be eligible for the study. • Exclusion criteria #7 was updated to add additional medications that, if taken within 1 week of prior to start of treatment and/or for the duration of the treatment would exclude the patient from participation in the trial. • Exclusion criteria #8 was added to indicate exclusions due to the use of hydroxyurea before and during the study treatment. • Exclusion criteria #9 was updated to indicate that the use of grapefruit products excluded patients from participation in the study. • Exclusion criteria #10 was added to exclude patients who were receiving treatment with medications that can prolong QT interval if the treatment cannot be discontinued or switched prior to study treatment. • Exclusion criteria#11 was added to exclude patients with impairment of GI function or GI disease that might alter absorption of study drug. • Exclusion criteria #12 was updated to indicate that alopecia of any grade would not exclude patients from the study. • Exclusion criteria#17 was updated to clarify that baseline QTcB >480 ms would exclude patients only if QTcF was not available. • DLT criteria revised for alopecia. • Clarified intra-patient dose escalation requirements. • Peripheral blood for cytogenetic assessments was added. • aPTT assessment added to coagulation panel as alternative to PTT. • Concomitant medications list revised. • Screening period extended to 28 days. • Added collection of peripheral blood to determine cytogenetics response. • Urinalysis was removed. • For optional biomarker research some additional samples have been added: buccal swab, whole blood sample and newly obtained bone marrow sample.
Amendment 5 (26-Jun-2015)	This amendment had the following changes: • Introduced a new tablet formulation of asciminib in replacement of the solid dispersion capsule. • Updated to clarify women of child bearing potential. • An additional ECG on Day 8 of cycle 1 for only patients who received asciminib in combination with nilotinib was captured to align with nilotinib product safety specifications.

Amendment 6 (14-Oct-2015)	This amendment introduced the following changes: • Introduced the evaluation of additional combinations of asciminib with imatinib or dasatinib to determine the recommended combination regimens for future studies, and to describe the safety and preliminary antitumor activity in CML. Multiple sections were updated based on this change as needed. • Arm 1 – Dose expansion: Sample size for this expansion was increased to a total of approximate 60 patients in order to support the benefit-risk assessment for patients with CML. • Given the aggressive nature of CML-BP, a different dose was required to attain disease responses in this patient population. Therefore, the potential need for a different recommended dose for CML-BP patients were explored along with that for Ph+ ALL patients in the Expansion part of the study. • Study objectives and endpoints were updated. • Inclusion criteria #1 was updated to clarify the number of prior TKIs patients had to be treated prior to study entry. • Dosing regimen of nilotinib was updated. • Exclusion criteria #7 was updated to add additional medications that, if taken within 1 week of prior to start of treatment and/or for the duration of the treatment would exclude the patient from participation in the study. • Exclusion criteria #22 was added to exclude patients with history of or ongoing pulmonary arterial hypertension. • Exclusion criteria #23 the highly contraception methods was updated. • Intra-dose escalation revised. • DLT criteria revised - pleural effusion added and period for DLT observation/assessment added (within the first 28 days (Cycle 1) of study treatment). • Patients enrolled in combination arm could continue asciminib in single agent in case of discontinuation of the combination drug. • List of concomitant medications revised. • Changed schedule of time points for MR and cytogenetics. • Peripheral blood samples for cytogenetics removed. • Relaxed safety assessments beyond cycle 13. • Added additional time points for ECGs (including for patients who had intra-patient dose escalation and were enrolled to receive asciminib +nilotinib). • Pancreas monitoring relaxed and time window specified. • Optional biomarkers - mandatory bone marrow biopsy removed.
Amendment 7 (10-Mar-2016)	This amendment introduced the following changes: • Modified female contraception requirements for patients enrolled to asciminib + imatinib. Female patients of child-bearing potential were required to use highly effective methods of contraception during dosing and for 14 days instead of 3 days after the last dose of study treatment. • Intra-patient dose escalation was allowed after 1 cycle of treatment for Ph+ ALL patients who required increased drug exposures to achieve disease control. • The frequency of abdominal imagining modalities (CT/MRI) performed for early detection of fibrotic change in the pancreas was reduced to baseline screening, C12D1, and End of treatment or as clinically indicated. • Abdominal imagining modalities were broadened to include the use of CT in addition to MRI. • Sodium was added to the Local Lab Parameters Collection Plan as this was previously omitted in error. • PK collection schedules were clarified by replacing footnote that was inadvertently deleted in the previous amendment specifying that 12 hour post dose collections were only required for patients in Japan, as they were housed overnight on intensive PK collection days. • Added outcome required evaluation of AEs.

Amendment 8 (26-Jan-2017)	This amendment introduced the following changes: • Included hepatitis B virus testing as one of the study procedures to identify study patients who could be at risk of hepatitis B reactivation. • Aligned with Tasigna (nilotinib) core data sheet and Investigators Brochure, the required period of female contraception for females of child bearing potential enrolled to Arm 2 (asciminib +nilotinib) was changed from 3 to 14 days. • Clarified fasting condition of asciminib in combination with imatinib. • Optional biomarker testing to study patterns of resistance was removed due to technical infeasibility. • A statement was added to allow collection of PK samples at non-protocol defined time points if determined necessary by the treating physician for patient safety concerns. • Discontinuation from study was been revised and sections added for withdrawal of consent and lost to follow up.
Amendment 9 (03-Aug-2018)	This amendment introduced the following changes: • Expanded the cohort of CML-CP/-AP patients harboring the T315I mutation in Arm 1 to approximately 65 patients to further evaluate the efficacy and safety of asciminib 200 mg b.i.d. in this population. • Dose modification and safety management guidelines were provided for CML-CP/-AP patients harboring the T315I mutation treated at 200 mg b.i.d. (including but not limited to dose level reduction to 160 mg ABL001 b.i.d.). • Details on efficacy analyses planned for the cohort of patients harboring the T315I mutation were added. • PFS was removed. • Criteria for discontinuation of study treatment following >21 days dose delay was updated. • Updated provisional dose levels for asciminib. • Updated monitoring and dose modification guidelines to refer to product labels for imatinib, nilotinib and dasatinib toxicity management. • Updated to clarify events considered for disease progression. • Updated requirements to detect new mutations or new clonal abnormalities in Ph+ cells at any time after start of study treatment. • Peripheral blood collection was removed for the cytogenetic analysis. • AESI were added. • Sample size calculation updated. • Updated on prohibited and permitted CYP substrates when patients were on single agent asciminib. • Updated on the use of substrates of CYP2C8 and CYP2C9 with caution for asciminib combination with nilotinib or imatinib or dasatinib. • Withdrawal of consent section was added/updated to incorporate and reflect the European Economic Area (EEA) General Data Protection Regulation (GDPR) requirements. Following distribution issues with the protocol amendment 9 in the USA, the document was submitted, approved and implemented lately in this country. This delay did not affect the conduct of the study.

Amendment 10 (24-Oct-2019)	This amendment introduced the following changes: • Defined the main endpoint for efficacy analysis (part of the secondary objectives) as the rate of MMR by 24 weeks of treatment. • Clarified that the primary analysis was conducted as soon as all patients in Arm 1 and Arm 5 (asciminib as single agent) had been treated for at least 6 cycles and had their 24-week efficacy evaluation performed or have discontinued the study treatment earlier. This analysis included: • Analysis of primary endpoint, PK and safety and tolerability of asciminib as single agent, driven by the fact that dose escalation for single agent asciminib had been completed and RDE identified. • Analysis of efficacy data for Arms 1 and 5, including the pre-planned sub-group analysis of patients with CML-CP harboring the T315I mutation. • Preliminary analysis of safety and tolerability of asciminib in combination with imatinib, nilotinib or dasatinib (Arms 2, 3 and 4) • Updated provisional dose levels for asciminib when given q.d.. • Removed the required male contraception for patients enrolled in Arms 1, 2, 3 and 5 (evaluating asciminib single agent and in combination with nilotinib and imatinib, respectively). • Included abdominal ultrasound as a method that could be used for detection of anatomic changes in the pancreas and its monitoring in case of a medical contraindication to abdominal CT or MRI. • Allowed the potential for provision of the study drug outside this study through an alternative setting to patients who in the opinion of the investigator were still deriving clinical benefit at the end of the trial. • Clarified that after a study treatment discontinuation, a patient was not allowed to be enrolled in another treatment arm and/or in another trial phase.
Amendment 11 (16-Mar-2022)	This amendment introduced the following: • Defined the end of treatment period, which was considered to be achieved when all patients enrolled had been followed for at least 64 weeks in the study (corresponding approximately to Cycle 16) or had discontinued from the treatment, whichever occurred first and had a PTA option available in the country. • Clarified the end of study declared when all patients enrolled in the study had completed treatment within the study and had performed all applicable study visits. • Introduced the language related to a Public Health Emergency (when it limited or prevented on-site study visits during the Public Health Emergency, such as a pandemic). • Updated the SAE reporting. • Specified the end of use period of the 50 mg capsules. • Added the concept of local regulations or locally approved prescribing information in contraception methods and durations. • Clarified the mutational analysis at end of treatment visit.

Baseline data

Among all CML-CP patients harboring the T315I mutation (N=70), the median age was 53.5 years (min-max: 22-86 years), with 70.0% of patients being 18 to < 65 years old. The majority (74.3%) of patients were male and white (51.4%). The Baseline ECOG performance status was 0 (78.6%) or 1 (21.4%).

In the asciminib 200 mg b.i.d. treatment group (N=48), the median age was 56.5 years (range: 26-86 years), with 66.7% of patients aged 18 to < 65 years. The majority of patients were male (77.1%) and were predominantly white (58.3%). Baseline ECOG performance status was 0 (75.0 %) or 1 (25.0%).

Of the 70 patients harboring the T315I mutation, 5 (7.1%) patients had atypical/p190/unknown transcripts at Screening, and these were not evaluable for the analysis of MMR on the international scale (IS).

Of the 48 patients in the 200 mg b.i.d. treatment group, 3 patients had atypical/p190/unknown transcripts and were not evaluable for the analysis of MMR on the IS. Note that patients with atypical/p190 transcripts were monitored throughout the study and could be evaluated for MMR, but not on the IS.

Demographic and disease characteristic for the T315I cohort and the subgroups by ponatinib pretreatment are presented in the following table:

Table 12 Demographics and disease characteristics by ponatinib pre-treated and ponatinib naive – single agent asciminib 200 mg b.i.d. in CML-CP patients with confirmed T315I mutation (Full analysis set) (Study X2101)

	Ponatinib-pretreated N=29			**Ponatinib-naive N=19**	**All subjects N=48**
				n (%)	**n (%)**
Characteristic	**Intolerant N=9**	**Resistant N=14**	**Other N=6**		
Age (years)					
Median	*67.0*	*54.0*	*55.5*	*49.00*	*56.50*
Range	*33-77*	*38-86*	*30-74*	*26-77*	*26-86.0*
Sex -n (%)					
Male	*7 (77.8)*	*12 (85.7)*	*3 (50.0)*	*15 (78.9)*	*37 (77.1)*
Race -n (%)					
Asian	*0*	*2 (14.3)*	*1 (16.7)*	*9 (47.4)*	*12 (25.0)*
White	*7 (77.8)*	*8 (57.1)*	*3 (50.0)*	*5 (26.3)*	*23 (47.9)*
ECOG performance status -n (%)					
0	*6 (66.7)*	*10 (71.4)*	*5 (83.3)*	*15 (78.9)*	*36 (75.0)*
1	*3 (33.3)*	*4 (28.6)*	*1 (16.7)*	*4 (21.1)*	*12 (25.0)*
Number of prior TKIs-n (%)					
2	*2 (22.2)*	*2 (14.3)*	*2 (33.3)*	*9 (47.4)*	*15 (31.3)*
3	*4 (44.4)*	*8 (57.1)*	*3 (50.0)*	*2 (10.5)*	*17 (35.4)*
4	*3 (33.3)*	*3 (21.4)*	*1 (16.7)*	*0*	*7 (14.6)*
>=5	*0*	*1 (7.1)*	*0*	*0*	*1 (2.1)*
Individual Prior TKIs-n (%)					
Bosutinib	*2 (22.2)*	*1 (7.1)*	*0*	*0*	*3 (6.3)*
Dasatinib	*3 (33.3)*	*11 (78.6)*	*5 (83.3)*	*14 (73.7)*	*33 (68.8)*
Imatinib	*8 (88.9)*	*10 (71.4)*	*2 (33.3)*	*7 (36.8)*	*27 (56.3)*
Nilotinib	*6 (66.7)*	*8 (57.1)*	*4 (66.7)*	*8 (42.1)*	*36 (75.0)*
Ponatinib	*9 (100.0)*	*14 (100.0)*	*6 (100.0)*	*0*	*29 (60.4)*
Radotinib	*0*	*1 (7.1)*	*0*	*3 (15.8)*	*4 (8.3)*
Molecular response at screening					
BCR-ABL >0.1 - 1% IS	*3 (33.3)*	*1 (7.1)*	*1 (16.7)*	*3 (15.8)*	*8 (16.7)*
BCR-ABL >1 - 10% IS	*1 (11.1)*	*3 (21.4)*	*2 (33.3)*	*5 (26.3)*	*11 (22.9)*
BCR-ABL >10% IS	*3 (33.3)*	*9 (64.3)*	*3 (50.0)*	*11 (57.9)*	*26 (54.2)*

Characteristic	Ponatinib-pretreated N=29			Ponatinib-naive N=19 n (%)	All subjects N=48 n (%)
	Intolerant N=9	Resistant N=14	Other N=6		
Atypical/p190/Unknown transcripts	*2 (22.2)*	*1 (7.1)*	*0*	*0*	*3 (6.3)*

Outcomes and estimation

Efficacy analyses were performed on a subset of the FAS (T315I mutation analysis set), which included MMR-evaluable CML-CP patients harboring the T315I mutation who were not in MMR at Screening and were treated with asciminib single agent 200 mg b.i.d. Additional efficacy analyses for this analysis set were performed for the subgroups of ponatinib-naïve and ponatinib pre-treated patients.

Table 13 Duration of exposure to study drug by treatment – single agent asciminib 200 mg b.i.d. in CML-CP patients with confirmed T315I mutation at screening (Safety set) (Study X2101)

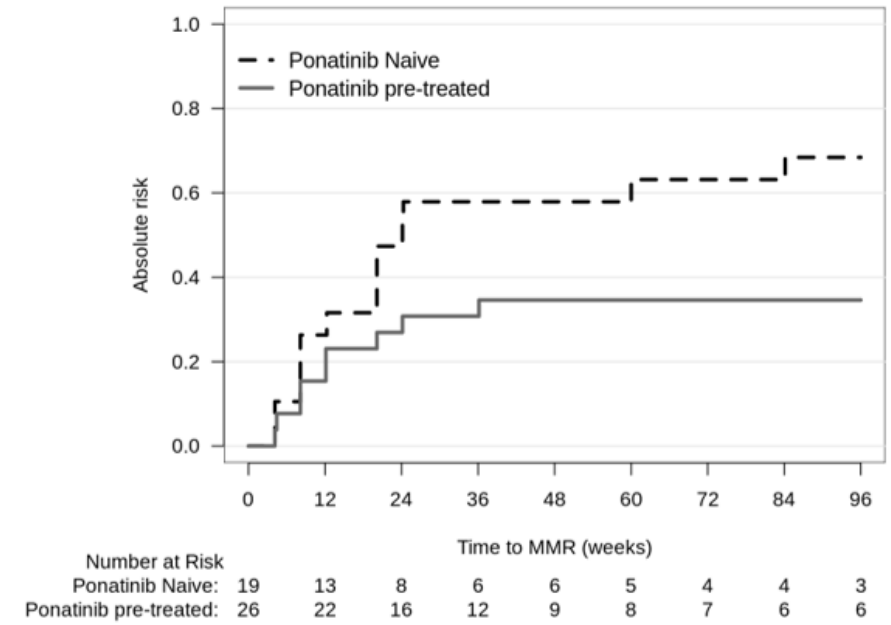
	Ponatinib-pretreated N = 29	Ponatinib-naive N = 19
Duration of exposure (weeks)		
Mean (SD)	*141.4 (99.53)*	*173.4 (96.32)*
Median	*156.0*	*196.0*
Q1-Q3	*36.3-227.3*	*106.0-248.3*
Min-Max	*4-312*	*2-300*
Duration of exposure categories-n (%)		
Less than 4 wks	*0*	*1 (5.3)*
At least 4 wks	*29 (100)*	*18 (94.7)*
At least 8 wks	*28 (96.6)*	*17 (89.5)*
At least 12 wks	*28 (96.6)*	*17 (89.5)*
At least 24 wks	*24 (82.8)*	*16 (84.2)*
At least 48 wks	*20 (69.0)*	*16 (84.2)*
At least 96 wks	*18 (62.1)*	*15 (78.9)*
At least 144 wks	*15 (51.7)*	*12 (63.2)*

Table 14 MMR by time point, by prior ponatinib treatment and overall - single agent asciminib in CML-CP harbouring the T315I mutation and not in MMR at Screening (Study X2101 T315I mutation analysis set)

Response category	Ponatinib Pre-treated N=26 n (%)	Ponatinib Naïve N=19 n (%)	All Patients N=45 n (%)
Overall MMR	**10 (38.5)**	**14 (73.7)**	**24 (53.3)**
MMR by Week 24	8 (30.8)	11 (57.9)	19 (42.2)
(90% Confidence interval)	(16.3 - 48.7)	(36.8 - 77.0)	(27.7 - 57.8)
MMR by Week 48	9 (34.6)	11 (57.9)	20 (44.4)
MMR by Week 96	9 (34.6)	13 (68.4)	22 (48.9)
MMR by Week 216	9 (34.6)	14 (73.7)	23 (51.1)
MMR by Week 264	10 (38.5)	14 (73.7)	24 (53.3)
MMR by Week 312	10 (38.5)	14 (73.7)	24 (53.3)
MMR by Week 360	10 (38.5)	14 (73.7)	24 (53.3)
MMR by Week 432	10 (38.5)	14 (73.7)	24 (53.3)

* Confidence intervals (CI) are based on the Clopper-Pearson method; 95% CI were used for all patients, and 90% CIs for ponatinib pre-treated and ponatinib naïve patients.
BCR::ABL1 % measured at the International Scale.

Figure 4 Cumulative MMR by prior ponatinib treatment – single agent asciminib in CML-CP harboring the T315I mutation and not in MMR at screening (Study X2101 T315I mutation analysis set)



▪ -Treatment discontinuations or deaths are treated as competing events

In Study X2101, the response is reported as durable, with 20 patients out of the 24 responders maintaining the response or improving to a deeper level of response up to the cut-off date. The KM estimated proportion of patients maintaining their MMR for 96 weeks was 86.0% (95% CI: 71.9, 100.0) and remained stable at 86.0% (95% CI: 71.9, 100.0) (reported until 144 weeks).

Pre-defined and post-hoc subgroup analyses

The reported data above are data from the subgroup analyses in patients with CML-CP harbouring the T315I mutation.

Post-hoc subgroup analyses by pretreatment and response to ponatinib are provided in the next table. With all the limitations of the small numbers, the observed MMR rate was higher in ponatinib naïve patients (14/29; 73.7%) as in ponatinib pretreated patients (10/26; 38.5%). The same is observed for deep MR.

In ponatinib resistant patients MMR was reported for 3/13 and deep MMR for 1/13 patients.

The MMR rate and the deep MR rates are impacted by the pretreatment and response/resistance to ponatinib.

Table 15 Molecular response (% IS) of Ponatinib pre-treated patients by reason of discontinuation of ponatinib by each time point - single agent ABL001 200 mg b.i.d. in CML-CP patients with confirmed T315I mutation at screening (Full analysis set)

	Ponatinib pretreated					**All subjects**
Response category				**All ponatinib pretreated Subjects**	**Ponatinib naive**	
	Intolerance	Resistance	Other	N=26		
	N=7	N=13	N=6	n (%)	N=19	N=45
	n (%)	n (%)	n (%)		n (%)	n (%)
Overall Molecular response						
BCR-ABL ≤0.1% IS (MMR)	4 (57.1)	3 (23.1)	3 (50)	10 (38.5)	14 (73.7)	24 (53.3)
BCR-ABL ≤0.01% IS (MR4)	3 (42.9)	1 (7.7)	1 (16.7)	5 (19.2)	9 (47.4)	14 (31.1)
BCR-ABL ≤0.0032% IS (MR4.5)	2 (28.6)	1 (7.7)	1 (16.7)	4 (15.4)	8 (42.1)	12 (26.7)
Molecular response by week 24						
BCR-ABL ≤0.1% IS (MMR)	4 (57.1)	2 (15.4)	2 (33.3)	8 (30.8)	11 (57.9)	19 (42.2)
BCR-ABL ≤0.01% IS (MR4)	2 (28.6)	0	0	2 (7.7)	7 (36.8)	9 (20.00
BCR-ABL ≤0.0032% IS (MR4.5)	1 (14.3)	0	0	1 (3.8)	4 (21.1)	5 (11.1)
Molecular response by week 48						

BCR-ABL ≤0.1% IS (MMR)	4 (57.1)	2 (15.4)	3 (50)	9 (34.6)	11 (57.9)	20 (44.4)
BCR-ABL ≤0.01% IS (MR4)	3 (42.9)	1 (7.7)	1 (16.7)	5 (19.2)	7 (36.8)	12 (26.7)
BCR-ABL ≤0.0032% IS (MR4.5)	2 (28.6)	1 (7.7)	1 (16.7)	4 (15.4)	6 (31.6)	10 (22.2)
Molecular response by week 96						
BCR-ABL ≤0.1% IS (MMR)	4 (57.1)	2 (15.4)	3 (50)	9 (34.6)	13 (68.4)	22 (48.9)
BCR-ABL ≤0.01% IS (MR4)	3 (42.9)	1 (7.7)	1 (16.7)	5 (19.2)	8 (42.1)	13 (28.9)
BCR-ABL ≤0.0032% IS (MR4.5)	2 (28.6)	1 (7.7)	1 (16.7)	4 (15.4)	7 (36.8)	11 (24.4)

5.3.3. Clinical studies in special populations

Not applicable

5.3.4. In vitro biomarker test for patient selection for efficacy

Not applicable

5.3.5. Supportive study

CABL001A2004: Real-world effectiveness of asciminib and treatment patterns in patients with Chronic Myeloid Leukemia with T315I mutation – a chart review study of patients treated in the asciminib Managed Access Program (MAP)

Study design

This non-interventional study (NIS) is a retrospective chart review analyzing existing data for effectiveness and safety from patients participating in the asciminib MAP. MAP started in 2018 enables patients with CML who are resistant or intolerant to available treatments, or in whom available treatments are contraindicated to receive asciminib, if local regulation permits, and if the treating physician deems that the potential benefit outweighs the risk.

Data source: The medical charts at sites were reviewed and data was entered in the electronic data capture (EDC). No additional data were collected beyond what was documented in patient's medical charts from routine medical care.

The index date was defined as the date of start of asciminib treatment (first dose) in the MAP. For medical history, disease (CML) characteristics, treatment patterns, and intolerance to previous TKI, data were extracted for the period starting from CML diagnosis up to the index date, which was named

lookback window. Starting from the index date, data were extracted until a follow-up period defined by 12 months (+1-month window) after start of asciminib, or 1 month after asciminib treatment discontinuation for any reason, or date of the chart review abstraction, or death, whichever comes first.

Study population

Patients with CML who are resistant or intolerant to available treatments, or in whom available treatments are contraindicated to receive asciminib, if local regulation permits, and if the treating physician deems that the potential benefit outweighs the risk, participating in the asciminib MAP (started in 2018).

Inclusion criteria:

1. Diagnosis of CML (chronic phase, accelerated phase or blast crisis).

2. Confirmed presence of T315I mutation prior to asciminib initiation.

3. Patients enrolled in the asciminib MAP and received first dose of asciminib between 01 November 2018 and 30 April 2022. Patients must have received at least one dose of asciminib.

4. Appropriate approval was obtained for the patient chart review including:

• Patient signed the informed consent form (ICF), or,

• ICF waiver was granted by an Institutional review board/ Independent Ethics Committee (IRB/IEC).

Exclusion criteria:

1. Age <18 years old at the time of initiating asciminib treatment.

Randomisation and blinding

Not applicable

Description of trial intervention

Use of ascimitinib in the context of MAP.

Concomitant and rescue therapies

Stem cell transplantation may be an option.

Study assessments

The medical charts at sites were reviewed and data was entered in the electronic data capture (EDC). No additional data were collected beyond what was documented in patient's medical charts from routine medical care.

The index date was defined as the date of start of asciminib treatment (first dose) in the MAP.

Starting from the index date, data were extracted until a follow-up period defined by 12 months (+1-month window) after start of asciminib, or 1 month after asciminib treatment discontinuation for any reason, or date of the chart review abstraction, or death, whichever comes first.

Objectives, endpoints and estimands

Primary Objective

The primary objective is to describe the effectiveness of asciminib assessed by major molecular response (MMR) rates at and by 6 months in CML patients with T315I mutation treated in the asciminib MAP.

Table 16 MR, CCyR, and CHR definition and assessment window

Outcomes	Definitions	Assessment period
MMR	BCR::ABL1 transcript level (on the IS) ≤ 0.1%	At 3 months: Assessment between months 2-4 from index date (Start date = index date + 61 days and End date = index date + 122 days)
CCyR	No Ph+ cells in metaphases, with at least 20 evaluated in the bone marrow. OR <1% BCR::ABL1–positive nuclei of at least 200 nuclei evaluated in blood interphase cell nuclei by FISH	By 3 months: Assessment between months 0-4 from index date (Start date = index date and End date = index date + 122 days) At 6 months: Assessment between months 5-7 from index date (Start date = index date + 152 days and End date = index date + 213 days) By 6 months: Assessment between months 0-7 from index date (Start date = index date and End date = index date + 213 days) At 9 months: Assessment between months 8-10 from index date (Start date = index date + 244 days and End date = index date + 305 days) By 9 months: Assessment between months 0-10 from index date (Start date = index date and End date = index date + 305 days) At 12 months: Assessment between months 11-13 from index date (Start date = index date + 335 days and End date = index date + 396 days) By 12 months: Assessment between months 0-13 from index date (Start date = index date and End date = index date + 396 days)
CHR	Platelet count < 450 $\times 10^9$/L WBC count < 10 $\times 10^9$/L Differential without immature granulocytes and with < 5% basophils, nonpalpable spleen	

Abbreviations: CCyR = complete cytogenetic response; CHR = complete hematologic response; FISH = fluorescence in situ hybridization; IS = international standards; MMR = major molecular response; Ph+ = Philadelphia chromosome positive; WBC = white blood cell

Estimands for the primary objective

Not defined

Secondary objectives

• To describe the effectiveness of asciminib assessed by MMR rates at and by 3, 9 and 12 months

• To describe the effectiveness of asciminib assessed by complete cytogenetic response (CCyR), and complete hematologic response (CHR)

• To describe the demographic, clinical, and disease characteristics of patients enrolled

• To describe the treatment patterns and response to prior TKIs of patients enrolled

• To evaluate intolerance to previous TKIs of patients enrolled

• To describe the safety of asciminib in CML patients with T315I mutation treated in the asciminib MAP

Estimands for the secondary objective

Not defined

Statistical methods for estimation and sensitivity analysis

Planned analyses

Analyses for this study were descriptive in nature (estimation based), and therefore no hypothesis testing was conducted. Continuous data were summarized by mean, standard deviation (SD), median, interquartile range (IQR), 25th and 75th percentiles, minimum, and maximum. Categorical and binary data were presented by frequency counts and percentages. All descriptive analyses were presented along with their 95% CIs wherever appropriate.

Planned subgroup analyses

Subgroup analyses addressed treatment effectiveness analysis based on patients treated/not treated for HSCT at baseline i.e., prior to asciminib index date. The sub-group analysis was conducted based on patients treated for hematopoietic stem-cell transplantation (HSCT) any time prior to starting asciminib treatment in Full Analysis Set (FAS). Patients with missing data at baseline were considered as not treated for HSCT any time prior to index date.

Sample size determination

At the time of feasibility assessment in June 2021, there were approximately 92 potentially eligible patients in the asciminib MAP between 01 November 2018 and 30 April 2022. Assuming 50% of the patients would not be eligible for any reason (e.g., site or patient unwillingness to participate, inability to contact MAP patients, not meeting inclusion/exclusion criteria), it was estimated that approximately 50 patients should be enrolled in the chart review. Further, a sample size of 50 patients would have allowed for a two-sided 95% confidence interval (CI) with a width equal to 0.289 when the sample proportion is 0.50 (maximum width with p=0.50).

Error probabilities, adjustment for multiplicity and interim analyses

N/A

Changes from protocol-specified analyses

Not reported

Data quality assurance

Quality assurance measures were put in place, no reports on audits were retrieved.

- The CSR addresses the limitations of the research method: it is retrospective secondary use of data that is potentially exposed to a certain level of selection bias, so caution is needed when interpreting the results. Data availability in patient charts might be different due to different routine clinical care settings across the different countries.
- Potential selection bias and immortal time bias may impact interpretation of results. For example, chart review may exclude MAP patients who may have died before signing ICF, resulting in overstating the actual outcomes. To minimize impact of the bias, an ICF waiver will be submitted to the IRB/IEC.

- Potential for channeling bias: Patients in a MAP might not be representative of all patients with this mutation.

Results

Changes in the planned conduct of the study

Due to the lower than expected number of potentially eligible patients, the timelines were extended from 31 May 2021 to 30 April 2022.

Participant flow and numbers analysed

A total of 31 patients were enrolled in the study. Of these, 21 (67.7%) patients completed the study (i.e., completed the follow-up period of 396 days).

The reasons for discontinuation for the remaining patients included death (n = 7; 22.6% (causes of death included: fungal infection worsening [n=1], study indication [n=2], relapsed CML/study indication [n=1], pneumonia [n=1], recurrent stroke/death [n=1], and unknown reason [patient discontinued the study due to poor compliance prior to death, n=1]), and physician decision (n =3; 9.7%).

Table 17 Patient disposition (all patients screened)

	Asciminib (N = 31) n (%)
Patients Screened (N)	31
Patients Who Did Not Meet All Eligibility Criteria [1]	0
Patients in Full Analysis Set (FAS) [1] (N1)	31 (100)
Patients Who Completed the Study [2]	21 (67.74) [3]
Patients Discontinued [2]	10 (32.26)
Reason for Discontinuation [2]	
Adverse Event	0
Death	7 (22.58)
Lost to Follow-Up	0
Physician Decision	3 (9.68)
Pregnancy	0
Study Terminated by Sponsor	0
Withdrawal of Informed Consent	0
Guardian Decision	0

Abbreviations: FAS: full analysis set; N: total number of patients screened; n: number of patients in specific category; N1: number of patients in the FAS.
[1] % Calculated using the number of patients screened, as denominator (n/N*100).
[2] % Calculated using the number of patients in the FAS, as denominator (n/N1*100).
[3] Patients completed the follow-up period of 396 days.

Baseline data

A majority of the 31 patients enrolled in Study A2004 were male (74.2%). Most patients were white (32.3%), followed by Asian (25.8%). The median age at CML diagnosis was 47.0 years, and the majority of patients (24 (77.4%)) were diagnosed with CML between the ages of 30 to 65 years. The median age at the start of asciminib was 51.0 years. The median duration between CML diagnosis and study index date (date of asciminib treatment start) was 76.4 months.

At the index date, 12 patients with CML harboring the T315I mutation were already in MMR and 19 patients were not (including 4 patients with missing data).

The 19 patients not in MMR at the index date, i.e. start of asciminib treatment were used for the primary effectiveness analyses. An addendum to the CSR was provided that evaluated the maintenance of response in the 12 patients were in MMR at the index date.

All patients received at least 1 prior TKI, and the majority of patients reported 2 (38.7% of patients) or 3 (32.3% of patients) TKIs and 6 (19.4%) patients reported receiving 4 TKIs prior to asciminib. The remaining patients reported either a single prior TKI (n=2, 6.5%) or 5 prior TKIs (n=1, 3.2%). The most common prior TKIs received were ponatinib (90.3%), imatinib (64.5%), and dasatinib (61.3%), followed by nilotinib (51.6%). All patients in MMR at the index date had received prior ponatinib treatment.

Overall, 22 (71.0%) patients discontinued any prior TKIs due to AEs. During the TKI treatment immediately before asciminib treatment, 14 (45.2%) of 31 patients discontinued their last prior TKIs due to AEs.

With the exception of ponatinib, no previous TKIs were associated with MMR responses in more than 2 patients.

Table 18 Patient disposition, time on treatment, baseline demographics and disease characteristics for patients not in MMR and in MMR in Study A2004

	Not in MMR (or unknown MMR status at baseline) (N=19)	**In MMR (N= 12)**	**Overall (N= 31)**
Patient Disposition			
Patients Screened (N)*	19*	12	31
Patients Who Completed the Study	10	11	21 (67.74)
Patients Discontinued Study	9	1	10 (32.26)
Reason for Discontinuation n (%)			
Adverse Event	0	0	0
Death**	6	1	7 (22.58)
Lost to Follow-Up	0	0	0
Physician Decision	3	0	3 (9.68)
Baseline demographics			
Gender, Male n (%)	14 (73.68)	9 (75.00)	23 (74.19)
Race n (%)			
White	5 (26.32)	5 (41.67)	10 (32.26)
Black or African American	3 (15.79)	0	3 (9.68)
Asian	7 (36.84)	1 (8.33)	8 (25.81)
Other	4 (21.05)	2 (16.67)	6 (19.35)
Missing/Unknown	0	4 (33.33)	4 (12.90)
Country of Residence n (%)			
Australia	0	1 (8.33)	1 (3.23)
Hong Kong	3 (15.79)	0	3 (9.68)
Italy	4 (21.05)	0	4 (12.90)
Netherlands	2 (10.53)	7 (58.33)	9 (29.03)
Pakistan	3 (15.79)	0	3 (9.68)
Spain	0	2 (16.67)	2 (6.45)
United Kingdom	6 (31.58)	2 (16.67)	8 (25.81)
United States	1 (5.26)	0	1 (3.23)
Age at CML Diagnosis (Years)			
Median	46.00	48.50	47.00
Minimum, Maximum	18.00, 67.00	34.00, 74.0	18.0, 74.0
< 30 years n (%)	4 (21.05)	0	4 (12.90)
30-65 years n (%)	14 (73.68)	10 (83.33)	24 (77.42)

	Not in MMR (or unknown MMR status at baseline) (N=19)	In MMR (N= 12)	Overall (N= 31)
>65 years n (%)	1 (5.26)	2 (16.67)	3 (9.68)
Age at the Start Date of asciminib (Years)			
Median	50.00	55.00	51.00
Minimum, Maximum	24.00, 83.00	38.00, 84.00	24.00, 84.00
Disease characteristics			
Time from CML Diagnosis to Study Index Date (Months)			
Median	79.63	71.57	76.38
Minimum, Maximum	9.30, 293.20	20.60, 161.66	9.30, 293.20
Status of CML at Baseline n (%)			
Chronic Phase	17 (89.47)	11 (91.67)	28 (90.32)
Accelerated Phase	1 (5.26)	1 (8.33)	2 (6.45)
Blast Phase	1 (5.26)	0	1 (3.23)
Response Status at asciminib Start Date			
Yes	-	12	12 (38.71)
No	15	-	15 (48.39)
Missing/Unknown	4	-	4 (12.90)
Stem-Cell Transplant Performed			
Yes	2 (10.53)	3 (25.00)	5 (16.13)
No	14 (73.68)	8 (66.67)	22 (70.97)
Missing/Unknown	3 (15.79)	1 (8.33)	4 (12.90)
Time on treatment with asciminib Exposure Duration (days)			
Median	202	359	295
Minimum, Maximum	9, 827	71, 477	9, 827
Subjects who permanently discontinued asciminib during follow-up	8	2	10
Reason for permanent asciminib discontinuation during follow-up			
Adverse Event	-	1 (8.33)	1 (3.23)
Death	3 (15.79)	-	3 (9.68)
Physician Decision	3 (15.79)	-	3 (9.68)
Progression to Blast Phase	1 (5.26)	-	1 (3.23)
Response Not Achieved	-	1 (8.33)	1 (3.23)
Others	1 (5.26)	-	1 (3.23)
Time to asciminib discontinuation (Months)	8	2	10
Median	4.99	3.84	4.94
Minimum, Maximum	0.30 , 27.17	2.69 , 4.99	0.30, 27.17
Number of patients who discontinued ponatinib anytime prior to asciminib	16	11	27
Total number of reasons for permanent discontinuation of ponatinib	23	11	34

	Not in MMR (or unknown MMR status at baseline) (N=19)	In MMR (N= 12)	Overall (N= 31)
Reason for ending ponatinib (anytime prior to asciminib) n (%)			
Lack of Efficacy - Progression to Blast Phase	2 (8.70)	1 (9.09)	3 (8.82)
Lack of Efficacy - Response Not Achieved	8 (34.78)	-	8 (23.53)
Adverse Event	4 (17.39)	8 (72.73)	12 (35.29)
Other	9 (39.13)	2 (18.18)	32.35)

*Patients with unknown status of MMR at index date (n=4) were classified as "Not in MMR" for the purpose of the stratified analyses.

** Causes of death included: fungal infection worsening [n=1], study indication [n=2], relapsed CML/study indication [n=1], pneumonia [n=1], recurrent stroke/death [n=1], and unknown reason [patient discontinued the study due to poor compliance prior to death, n=1].

Table 19 Summary of overall TKIs prior to index date, prior TKIs between CML diagnosis and T315I mutation diagnosis, and prior TKIs between T315I mutation diagnosis and index date (full analysis set)

Statistics	Overall TKIs prior to index date Asciminib (N = 31)	Prior TKIs between CML diagnosis and T315I mutation Asciminib (N = 31)	Prior TKIs between T315I mutation diagnosis and index date Asciminib (N = 31)
Number of TKIs Received[1], n (%)			
1	2 (6.45)	11 (35.48)	18 (58.06)
2	12 (38.71)	10 (32.26)	2 (6.45)
3	10 (32.26)	6 (19.35)	0
4	6 (19.35)	2 (6.45)	0
5	1 (3.23)	1 (3.23)	0
Type of TKIs Received[2], n (%)			
Imatinib	20 (64.52)	20 (64.52)	1 (3.23)
Dasatinib	19 (61.29)	17 (54.84)	1 (3.23)
Nilotinib	16 (51.61)	15 (48.39)	0
Bosutinib	2 (6.45)	2 (6.45)	0
Ponatinib	28 (90.32)	8 (25.81)	20 (64.52)

[1] and [2]%: Calculated using the number of patients in the FAS as the denominator (n/N*100).

The median duration of asciminib treatment exposure was 295 days. Nine (29.0%) patients had an exposure duration of > 12 months during the study.

The average median daily dose of asciminib was 400 mg in all patients and in patients in MMR at the index date, and it was 375.48 mg in patients not in MMR at index date.

Concomitant medication was hydroxyurea in 3 patients and ponatinib in 1 patient who were not responding or for whom no response assessment was documented.

Outcomes and estimation

Of the 19 patients not in MMR, 4 patients (21.1%) achieved MMR by 6 months, and 6 patients (31.6%) had events that precluded MMR assessment (3 patients were not evaluated for MMR by 6 months).

Five patients (26.3%) achieved MMR by 12 months, and 6 patients (31.6%) had events that precluded MMR assessment (1 patient was not evaluated for MMR at 12 months).

MMR was achieved at 6 months and at 12 months by 1 patient (5.3%) at each of these time points (where MMR at X months included the period between X-1 and X+1 months; 11 (57.9%) and 15 (79.0%) patients at 6 and at 12 months, respectively, had events that precluded MMR assessment.

Of the 19 patients not in MMR 2 patients had received prior stem cell transplant, one of these achieved MMR by 3, 6, 9, and 12 months.

Table 20 MMR by and at 6 months and 12 months in patients not in MMR at the Index date (Study A2004 Full analysis set)

	Asciminib (N = 31) 6 months		**Asciminib (N = 31) 12 months**	
	n (%)	**95% CI**	**n (%)**	**95% CI**
Patients already in MMR at Index Date[1]	**12 (38.71)**		**12 (38.71)**	
Patients not in MMR at Index Date[1]	**19 (61.29)**		**19 (61.29)**	
Patients achieving MMR *by* 6 months/12 months[2]	**4 (21.05)**	**6.05, 45.57**	**5 (26.32)**	**9.15, 51.20**
Patients not evaluated for MMR *by* 6 months/12 months[2]	3 (15.79)		1 (5.26)	
Patients evaluated but not achieved MMR *by* 6 months/12 months	6 (31.58)		7 (36.84)	
Events precluding MMR *by* 6 months/12 months[2]	6 (31.58)		6 (31.58)	
Treatment Discontinuation	4 (21.05)		4 (21.05)	
Progression to Blast Phase	1 (5.26)		1 (5.26)	
Hematopoietic Stem-Cell Transplantation	1 (5.26)		1 (5.26)	
Patients achieving MMR *at* 6 months/12 months[2]	**1 (5.26)**	**0.13, 26.03**	**1 (5.26)**	**0.13, 26.03**
Patients not evaluated for MMR *at* 6 months/12 months[2]	6 (31.58)		2 (10.53)	
Patients evaluated but not achieved MMR *at* 6 months/12 months[2]	1 (5.26)		1 (5.26)	
Events precluding MMR *at* 6 months/12 months[2]	11 (57.89)		15 (78.95)	
Treatment Discontinuation	8 (42.11)		12 (63.16)	
Death	1 (5.26)		1 (5.26)	
Progression to Blast Phase	1 (5.26)		1 (5.26)	
Hematopoietic Stem-Cell Transplantation	1 (5.26)		1 (5.26)	

[1] Denominator for % was the total number of patients in the FAS.

[2] Denominator for % was the total number of patients who were not in MMR at index date.

95% CI was calculated using Clopper-Pearson method.

Patients with no available MMR assessment were considered not to be in MMR.

Table 21 Primary analysis MMR at and by and at 6 months (FAS)

	Asciminib (N = 31) n (%)	95% CI
Patients Already in MMR at Index Date[1]	12 (38.71)	
Patients Not in MMR at Index Date[1]	19 (61.29)	
Events Precluding MMR at 6 Months[2]	11 (57.89)	
Treatment Discontinuation	8 (42.11)	
Death	1 (5.26)	
Loss to Follow-Up	0	
Progression to Accelerated Phase	0	
Progression to Blast Phase	1 (5.26)	
Hematopoietic Stem-Cell Transplantation	1 (5.26)	
Last Recorded Clinical Visit or Assessment	0	
Patients Not Evaluated for MMR at 6 Months[2]	6 (31.58)	
Patients Achieving MMR at 6 Months[2]	1 (5.26)	0.13, 26.03
Patients Evaluated but Not Achieved MMR at 6 months[2]	1 (5.26)	
Events Precluding MMR by 6 Months[2]	6 (31.58)	
Treatment Discontinuation	4 (21.05)	
Death	0	
Loss to Follow-Up	0	
Progression to Accelerated Phase	0	
Progression to Blast Phase	1 (5.26)	
Hematopoietic Stem-Cell Transplantation	1 (5.26)	
Last Recorded Clinical Visit or Assessment	0	
Patients Not Evaluated for MMR by 6 Months[2]	3 (15.79)	
Patients Achieving MMR by 6 Months[2]	4 (21.05)	6.05, 45.57
Patients Evaluated but Not Achieved MMR by 6 months#	6 (31.58)	

Abbreviations: CI: confidence interval; n: The number of patients in the specific category; N: Total number of patients in full analysis set.

[1] Denominator for % was the total number of patients in the FAS.

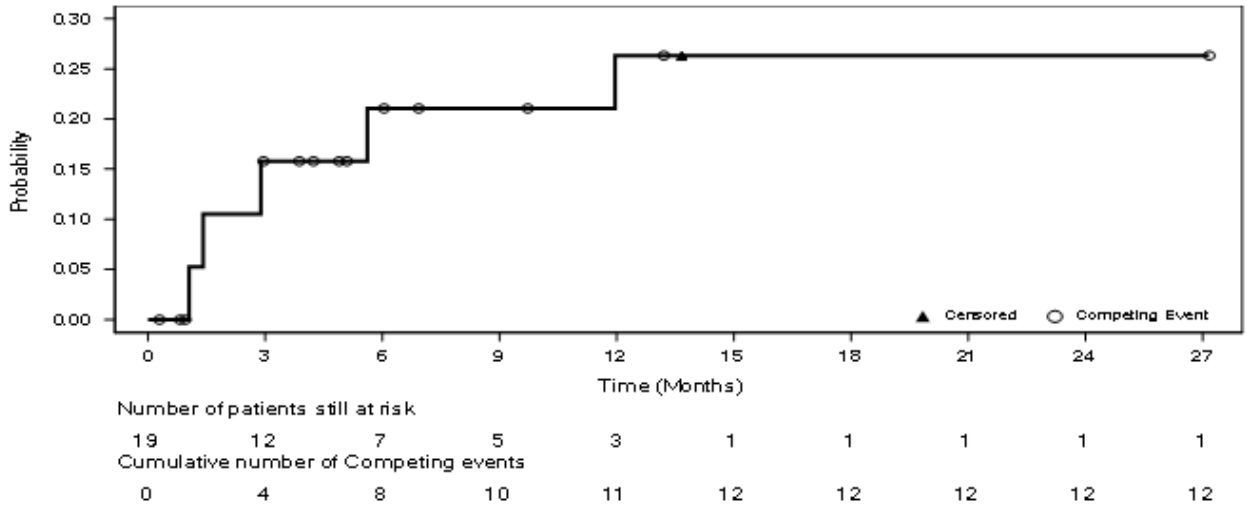
[2] Denominator for % was the total number of patients who were not in MMR at index date.

95% CI was calculated using Clopper-Pearson method.

Patients with no available MMR assessment were considered not to be in MMR.

Cumulative MMR increased for the FAS during the study period, and the number of patients at risk of achieving MMR decreased over time. However, there was not a major increase in the cumulative number of patients achieving MMR during the study.

Figure 5 ***Time to first MMR***



Complete Cytogenetic Response (CCyR)

Seven patients were already in CCyR at the index date, and 24 were not (including 15 who had missing CCyR data).
Of the 24 patients not in CCyR, 2 patients (8.3%) achieved CCyR **by** 6 months and **by** 12 months. None of the 24 patients achieved CCyR at 6 months or at 12 months.

Complete Hematologic Response (CHR)

Nineteen patients (61.3%) were already in CHR at the index date, and 12 patients were not (including 3 patients with missing CHR data).
Of the 12 patients (38.7%) not in CHR at the index date, 3 patients (25.0%) achieved CHR by 6 months and 4 patients (33.3%) achieved CHR by 12 months. One (8.3%) of 12 patients not in CHR at the index date achieved CHR at 6 months, and 2 patients (16.7%) achieved CHR at 12 months.

Among the 12 patients in MMR at the index date, 3 patients had received prior stem cell transplant.

In total, 6 patients (50.0%) were maintaining MMR by 6 months and 2 patients (16.7%) had events that precluded MMR assessment (4 patients were not evaluated for MMR by 6 months).

Ten patients (83.3%) were maintaining MMR by 12 months, and 2 patients (16.7%) had events that precluded MMR assessment (all 12 patients were evaluated for MMR by 12 months). Two patients (16.7%) were maintaining MMR at 6 months, and 2 patients (16.7%) had events that precluded MMR assessment (8 patients were not evaluated for MMR at 6 months). Five patients (41.7%) were maintaining MMR at 12 months, and 6 patients (50.0%) had events that precluded analysis (1 patient was not evaluated for MMR at 12 months).

Most patients (28 of 31) in Study A2004 were pre-treated with ponatinib. All 12 patients in MMR at the index date had received prior ponatinib treatment, and 16 out of the 19 (84.2%) patients not in MMR at index date had received prior ponatinib treatment.

5.3.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

5.3.7. Observational data / data from registries

See section 5.3.5 for description of real-world effectiveness study A2004.

5.3.8. Overall discussion and conclusions on clinical efficacy

5.3.8.1. Discussion

Basic information

The initially applied indication was

> "Scemblix is indicated for the treatment of adult patients with Ph+ CML-CP harbouring the T315I mutation (see section 5.1)."

with the following posology:

> "Ph+ CML-CP harbouring the T315I mutation:
> The recommended dose is 200 mg twice daily at approximately 12-hour intervals."

The applied dose regimen is 200 mg b.i.d., which is 5 times higher than the currently approved dose regimen of 40 mg b.i.d. Preclinical data had shown that about 4-13-fold higher concentrations are necessary in models at the T315I mutant compared to wildtype CML. These concentrations could be achieved in patients at the 200 mg b.i.d. dose where the geo-mean minimal concentrations were about 2-fold higher than the IC50 at the T315I mutant. At doses <200 mg b.i.d., most of T315I patients did not experience a decrease in BCR-ABL below -1 $\log_{10}$, or equivalently, 0.1% except those who had one prior TKI treatment. No new clinical data on dose-response were submitted.

Scientific advice was requested regarding the biowaiver for the new dosage strength of 100 mg, intended for the proposed indication in patients harboring the T315I mutation.

CML is a rare disease with a prevalence 1:17000 in EU and an incidence 1.2 – 1.5:100000.[1]
T315I mutation occurs in 1-5% of CML patients, mostly while on treatment. CML T315I is resistant to all approved TKI, with the exception of ponatinib.

Since 2013, ponatinib is approved for CML with T315I mutation in chronic phase, accelerated phase and blast phase. Approval of ponatinib for CML with T315I mutation in chronic phase was based on a cohort of the PACE Trial, a single-arm, open-label, international, multicentre trial which enrolled 64 patients with CML with T315I mutation in chronic phase (and further 42 patients with CML with T315I mutation in accelerated and blast phase). For the cohort of CML-CP with T315I mutation an MMR (i.e. IS ≤ 0.1 ratio BCR:ABL) of 58% was reported. In 2018, from PACE trial 5 year OS rate of 66% was reported for patients with CML harbouring the T315I mutation.(Cortes, Kim et al. 2018). Later, the OPTIC trial reported a 4-year OS rate for CML-T315I of 86% (ponatinib 45mg group)(Deininger, Apperley et al. 2024). In case of suboptimal response allogeneic stem transplantation should be considered. HSCT is the only treatment option with curative potential.

The initially requested new indication is independent of treatment line, any pre-treatment with ponatinib and covers patients not in MMR and patients in MMR at treatment initiation. Thus, for the evaluation of

[1] https://www.orpha.net/de/disease/detail/521, https://www.onkopedia.com/de/onkopedia/guidelines/chronische-myeloische-leukaemie-cml/@@guideline/html/index.html#:~:text=Die%20Inzidenz%20der%20CML%20betr%C3%A4gt,extrem%20selten%20gestellt%20%5B61%5D

efficacy, different subgroups needed to be addressed to reflect the clinical decisions in view of different prognosis and alternative treatment options:

For the induction of remission, i.e. patients not in MMR e.g.:

- CML-CP with the T315I mutation and ponatinib-naïve
- CML-CP with the T315I mutation and ponatinib-intolerant
- CML-CP with the T315I mutation and relapsed after or refractory to ponatinib

For the maintenance indication, i.e. patients are in MMR after pre-treated with ponatinib (and/or stem cell transplant) e.g.:

- CML-CP with the T315I mutation and ponatinib-intolerant
- CML-CP with the T315I mutation and have other reasons to switch

The application relied on clinical data from the first-in-human study X2101 and on supportive real-world data from a retrospective chart review of data from patients participating in the MAP study A2004.

The subgroup of patients with T315I mutation from study X2101, Arm 1 (monotherapy) included 70 patients, including 45 patients not in MMR at screening and treated with the intended dose of 200 mg bid.

The supportive RWD chart review enrolled 31 patients, 19 patients were not in MMR at enrolment and were treated with the intended dose. 12 patients in MMR at enrolment and were treated with the intended dose.

Several questions were raised to disentangle the populations above in order to describe clearly the subpopulations ponatinib-naïve and ponatinib pre-treated from X2101 and patients not in MMR vs in MMR at index date from A2004.

Study design

Study X2101 was a Phase I, multi-centre, first in human dose escalation study to define the MTD/ RDE, to characterize safety and tolerability, PK profile, and to assess the preliminary efficacy of asciminib. The study was amended multiple times, from amendment 4 (05.01.2015) the inclusion of patients harbouring T315I mutation was allowed. Amendment 9 (30.08.2018) introduced an expansion cohort of the 200 mg b.i.d. dose in Arm 1 to further assess asciminib as a single agent treatment in CML-CP/-AP patients with the T315I mutation being the target population in the scope of this application. Furthermore, it introduced efficacy (molecular response incl. MMR by and at 24 weeks) of asciminib as single agent in CML CP and AP patients with T315I mutation.

Study X2101 was submitted as supportive evidence in the initial marketing application dossier and respective parts (primary objectives -MTD and RDE- efficacy in patients not with T315I mutation) were initially assessed. Later safety aspects of the study were assessed, and the final CSR was submitted (eCTD sequence 0028) for variation II/0017. The efficacy and safety results for the target population with T315I were already included but not the primary focus of the assessment at the time.

The efficacy endpoints MMR, CCyR and CHR are appropriate endpoints for the evaluation of efficacy in CML-CP. Methods for determining MMR (validated PCR technology) are in line with current standards, MR3 (MMR) - BCR::ABL1 $\leq$ 0.1% (IS) was included as measure for the primary endpoint. Deeper molecular response e.g. MR4.5 were included as secondary endpoint.

By design there is no alpha control. Thus, all analyses are descriptive. Due to the open-label, non-comparative nature of the study as well as the multiple amendments of the protocol, it bears noting all

the uncertainties which are typical to this type of studies. By late amendment 10 the main efficacy endpoint was defined as the rate of MMR by 24 weeks of treatment which was a secondary endpoint earlier.

In the T315I cohort asciminib was administered twice daily (b.i.d.) in the fasted state (food was not allowed for at least 2 hours prior and 1 hour after administration) approximately 12 hours apart. Asciminib was supplied as capsules at dose strengths of 5 mg, 20 mg and 50 mg and as tablets of 20 mg, 40 mg and 50 mg.

Study results

In total, 70 CML-CP patients with the T315I mutation were enrolled in the study arm 1 receiving asciminib monotherapy; 48/70 patients with the T315I mutation received the now applied dose regimen of 200 mg b.i.d. **Of these, 45 patients in CML-CP harbouring the T315I mutation were not in MMR at screening and received the new dose regimen of 200 mg b.i.d.; 26 patients were pre-treated with ponatinib and 19 patients were ponatinib-naïve.**

For the study population with CML-CP with the T315I mutation treated with asciminib single agent across treatment cohorts (n=70), the median age was 53.5 years (min-max: 22-86 years) with 70.0% of patients being 18 to < 65 years old. The majority (74.3%) of patients were male and white (51.4%). The ECOG was 0 (78.6%) or 1 (21.4%).

With the responses, baseline characteristics provided for ponatinib-naïve and ponatinib pre-treated side by side to the combined population of 48 patients with the T315I mutation received the now applied dose regimen of 200 mg bid. As expected, the subpopulations show some differences:

Ponatinib naïve patients were younger, had less prior treatment lines than ponatinib pretreated patients. Only 5/19 ponatinib naïve patients were reported as "white". While eligibility criteria require that no other effective therapy exists, the MAH was asked to clarify how this criterion was fulfilled in patients not pre-treated with ponatinib. Reasons for not administering ponatinib were not documented. 9/19 patients originate from Asian countries in which ponatinib was not approved, the others were enrolled in the US and EU.

For ponatinib pre-treated patients the reason for ending ponatinib was intolerance in 9/26 patients and resistance in 14/26 patients, for 6/26 patients the reason could not be retrieved. Higher disease activity at screening was documented for the ponatinib resistant compared to the ponatinib intolerant subgroup.

Duration of exposure was reported with a median of 181.7 and range of 2-312 weeks. Exposure was longer in ponatinib-naïve patients (median 196 weeks) compared to ponatinib pretreated patients (median 156 weeks).

The majority of patients (25/48) ended asciminib treatment due to "Physician decision - PTA options" which included access to commercial supply, roll-over study and other reasons, 11/48 patients ended treatment due to lack of efficacy and 4/48 patients due to adverse events. For the category *Physician decision post-trial access options (PTA options)*, the MAH was asked to clarify the reasons and for how many patients specific reasons applied. Respective listing was provided and listed beside roll-over to extension study or commercial prescription 5 patients which were transferred to stem cell transplantation and further 6 patients with loss of efficacy.

For 11 patients (200 mg bid) included in the roll-over study the duration of treatment till cut-off date (20-Aug-2025) was 117 weeks (range: 3 to 154).

The primary endpoint – MMR (MR3) by week 24 - was reported with 19/45 patients, i.e. 42.2% (95% CI 27.7-57.8%).
The MMR rate at 24 weeks was higher in the subgroup of ponatinib-naïve patients: 11/19 patients, i.e.

57.9% (90% CI 36.8-77%) and lower in the subgroup of ponatinib-pre-treated patients 8/26 patients 30.8% (90% CI 16.3-48.7).

Further 5 patients reached MMR at a later timepoint. Thus, overall cumulative MMR was reported for 24/45 patients, i.e. 53.3%. It was higher in the subgroup of ponatinib-naïve patients 73.7% (14/19 patients) and lower in the subgroup of ponatinib-pre-treated patients 38.5% (10/26 patients).

In terms of duration of MMR, it is reported that the majority of responding patients at least maintained MMR or improved it to a deeper level. With the responses, data on depth of responses in relation to baseline and disease characteristics (including ponatinib- naïve, ponatinib intolerant, relapsed/refractory to ponatinib) was provided. MR 4.5 observed was observed in 8/19 ponatinib naïve patients and 4/16 ponatinib pre-treated patients, these were mostly in ponatinib intolerant disease. In ponatinib resistant patients MMR was reported for 3/13 and deep MMR for 1/13 patients. The MMR rate and the deep MR rates are clearly impacted by the pretreatment and response/resistance to ponatinib.

Exposure of at least 144 weeks was reported for 27/45 patients (56.3%).

Supportive evidence

The appropriateness of the data sources – Phase 1/2 data and supportive RWD – for generation of pivotal evidence was not discussed upfront in the context of scientific advice. As ponatinib was an approved efficacious treatment in CML-CP patients with the T315I mutation and recommended e.g. by ESMO (Hochhaus, 2017 #1013) at the time of starting enrolment of the T315I cohort, it would have been more appropriate to consider a randomised controlled study design comparing asciminib to ponatinib. Results from the OPTIC study (initiated due to safety reasons and resulting in a revised dosage regimen) were assessed by CHMP in 2021 and the opinion was published in March 2022. The severity, rarity of the condition, the safety issues addressed in the post-marketing studies for ponatinib, the well-organized study landscape in CML and the availability of protocol assistance in the context of an orphan development could have been used to enable robust evidence generation pre-approval. Instead, the assessment of the efficacy in **ponatinib naïve** patients in this application is severely hampered by the absence of comparative data.

Indirect comparisons to PACE and OPTIC are presented. For asciminib the cohort with 200 mg b.i.d. was selected, for ponatinib the 45 mg cohort is relevant. Comparison of the baseline characteristics of ponatinib naïve patients (n=19) to PACE 45 mg (n=64) reveal that ponatinib naïve patient cohort in X2101 included more Asian patients and with less pre-treatment (10.5% and 41% had 3 or more TKI). Although the (cumulative) MMR in the 19 asciminib patients is interesting, known baseline differences in pre-treatment preclude a claim of superiority of asciminib. Without available baseline data for the OPTIC study, comparison of crude MMR data from X2101 and OPTIC cannot be interpreted.
In a recent publication of a matching-adjusted indirect comparison superiority of ponatinib (Garcia-Gutierrez, Huang et al. 2024) was reported. The methodology appears more appropriate than comparison of the crude data although the limitations need to be acknowledged. According to the MAH the authors used premature data of X2101. Indeed, this may have resulted in an underestimation of the treatment effect of asciminib, the analysis presented by the company using the publicly available "pre-MAIC and MAIC data from PACE and OPTIC" is, however, also not appropriate for B/R assessment.

Valid indirect comparison relies on the documented similarity of design and patient populations of the treatment options to be compared. In the absence of baseline characteristics for the OPTIC trial, this cannot be verified. Furthermore, the small number of patients in the X2101 dataset questions the robustness of the reported response rates. Outcomes could have been disproportionately influenced by imbalances in patient related factors (such as disease activity at screening, pre-treatment history, region, potentially differing methodology of MMR assessment). The alignment of the patient populations by excluding patients with baseline BCR::ABL ≤1% from X2021 is not sufficient to replace adequate

matching of relevant variables, especially when major differences between datasets exist. In conclusion the presented intertrial comparisons of MMR data in small patient numbers are not sufficiently robust for B/R assessment. As comparative data to ponatinib are lacking, it cannot be assessed from the submitted data whether the size of MMR rate, the depth of responses and the duration of responses is comparable to ponatinib treatment in ponatinib-naïve patients. A recent publication of a matching-adjusted indirect comparison reports superiority of ponatinib (Garcia-Gutierrez, Huang et al. 2024). The benefit in the subpopulation ponatinib-naïve remains uncertain and the indication was restricted to exclude these patients.

Supportive real-world data from the market access program (MAP) named A2004 were submitted. The MAP started in 2018 to enable patients with CML who are resistant or intolerant to available treatments, or in whom available treatments are contraindicated to receive asciminib. For **patients in MMR** after pre-treatment with ponatinib (and/or stem cell transplant) this is the only evidence.

A2004 is a retrospective chart review which collected medical history (disease (CML) characteristics, treatment patterns, and intolerance to previous TKI) prior to initiation of asciminib treatment (index date) and follow-up data for 12 month (+ 1 month window) or 1 month after asciminib treatment. Primary objective was to describe effectiveness in patients with CML harbouring the T315I mutation by MMR (MR3) rates at and by 6 months. The chosen secondary endpoints are in line with other applications. Due to the retrospective approach missing data are even more likely. It was planned to enroll approximately 50 patients based on the feasibility review.

Finally, the study enrolled fewer patients, a total of 31 patients including 12 patients in MMR at asciminib start. Thus, there are only 19 patients in whom the primary endpoint MMR (MR3) can be assessed in a valuable way as initiation of MMR has a different meaning than maintenance of MMR.

For the 31 patients the median age was 53.5 years (min-max: 18-74 years), the majority of patients were male (74.2%) and white (32.3%) or Asian (25.8%). Median time from CML diagnosis to start of asciminib was 76.4 months, all had received prior TKIs (1-5), 28/31 patients had received prior ponatinib and 5 had received stem cell transplant. From the baseline characteristics it appears that the population is heterogenous. Baseline demographic and disease characteristics was requested for patients not in MMR and patients in MMR at index date side by side with the information on the full population. The information was provided. In the subgroup not in MMR the majority was non-white, 17/19 were enrolled in CP, and 2/19 had previous SCT.

Nineteen of 31 patients were not in MMR at the index date. Of the 19 patients not in MMR at the index date, 9/19 discontinued the study prematurely (incl 6 deaths), Six patients (31.6%) had events that precluded MMR assessment, 3 patients were not evaluated for MMR by 6 months and 6 patients were evaluated but did not achieve MMR by 6 months). 4/19 patients (21.1%) achieved MMR by 6 months. All patients who achieved MMR by 6 months were pretreated with ponatinib and one had prior stem cell transplant.

In the subgroup in MMR at index date the majority was white, 11/12 were enrolled in CP, and 3/12 had previous SCT, exposure was longer and 2/10 patients discontinued the study prematurely (no deaths).

Among the 12 patients in MMR at the index date, 6 patients (50.0%) were maintaining MMR by 6 months. Information on depths of MMR at baseline and during asciminib is not available. Thus, the information on maintenance of MMR can hardly be put in context.

The number of missing observations is high for MMR and even higher for the secondary endpoints. Depth of response was not retrieved. Long-term duration of response cannot be analysed due to the limited observation period.

The average median daily dose of asciminib was reported with 400 mg in all patients. Concomitant medication was hydroxyurea in 3 patients and ponatinib in 1 patient. It was clarified that no patients for whom MMR by 6 months is reported received hydroxyurea or ponatinib concomitantly.

The CSR addresses the limitations of the research method: it is retrospective secondary use of data that is potentially exposed to selection bias, heterogeneity in data availability from patient charts across the different countries, potential selection bias and immortal time bias that may impact interpretation of results and that patients in a MAP might not be representative of all patients with this mutation.

This chart review retrospective in nature with all potential implications of patient selection, heterogeneity, missing data in terms of incomplete effectiveness assessment, incomplete dose documentation and incomplete safety assessments. Overall, the value of the supportive chart review is limited also due to the very small number of patients with CML harbouring the T315I mutation not in MMR at index date, due to the high number of missing assessments and the limited observation period. The reported MMR rate under real-world conditions in **patients not in MMR** at treatment initiation can be considered as moderate at best, for evaluation of long-term effectiveness the observation period appears too limited.

5.3.8.2. Conclusions on the clinical efficacy

In general, the level of evidence of pivotal data discussed in this extension of indication procedure is low. This is due to the fact that efficacy claims are based on single pivotal study (study X2101), being a non-randomised, uncontrolled, open-label, multi-cohort, first-in-human Phase 1/2 study. Study X2101 was analysed and fundamentally amended multiple times. All patient populations discussed in this procedure are post-hoc defined subpopulations of this study. No scientific advice on the clinical development in the sought indication was requested.

The initially requested new indication was independent of treatment-line, pre-treatment with ponatinib and MMR status at treatment initiation ("treatment of adult patients with Ph+ CML-CP harbouring the T315I mutation"). Thus, for the evaluation of efficacy different subgroups needed to be addressed to reflect the clinical decisions in view of different prognosis and alternative treatment options. For patients with CML-CP with the T315I mutation not in MMR the subgroups ponatinib-naïve, ponatinib pretreated (including ponatinib-intolerant and ponatinib-resistant) represent different clinical entities. Pre-treated patients in MMR at treatment initiation are a distinct patient group.

Ponatinib naïve patients not in MMR

As ponatinib was an approved efficacious treatment in CML-CP patients with the T315I mutation at the time of starting enrolment of the T315I cohort and recommended e.g. by ESMO, it would have been appropriate to consider a randomised controlled study design comparing asciminib to ponatinib or to focus on patients pre-treated with ponatinib. The severity, rarity of the condition, the safety issues which were addressed in the post-marketing studies for ponatinib, the well-organised study landscape in CML and the availability of scientific advice in the context of an orphan development would have enabled evidence generation pre-approval. Instead, the assessment of the efficacy in **ponatinib-naïve** patients (MMR (MR3) by week 24: 11/19 patients, i.e. 57.9%) was severely hampered by the absence of comparative data.

Indirect comparisons to PACE and OPTIC were presented but were not sufficiently robust for B/R assessment. For asciminib the cohort with 200 mg b.i.d. was selected, for ponatinib the 45 mg cohort is relevant. A recent publication of a matching-adjusted indirect comparison reported superiority of ponatinib (Garcia-Gutierrez, Huang et al. 2024). According to the MAH, the authors used premature data of X2101. Indeed, this may have resulted in an underestimation of the treatment effect of asciminib.

The MAH presented a comparison of the crude MMR rates and an analysis using the publicly available "pre-MAIC and MAIC data from PACE and OPTIC". This is, however, also not appropriate for B/R assessment. Valid indirect comparison relies on the documented similarity of design and patient populations of the treatment options to be compared. In the absence of baseline characteristics for the OPTIC trial, this could not be verified. As comparative data to ponatinib are lacking and numbers are small, it could not be assessed from the submitted data whether the size of MMR rate, the depth of responses and the duration of responses is comparable or inferior to ponatinib treatment in ponatinib-naïve patients. The benefit in the subpopulation ponatinib-naïve remains uncertain.

Ponatinib pre-treated patients not in MMR

Ponatinib pre-treated patients not in MMR with CML-CP harbouring the T315I mutation include subgroups of ponatinib-intolerant and ponatinib-resistant. Currently, for these patients the only efficacious treatment option is stem cell transplantation. As these patients were not in MMR at baseline, MMR by 6 months can be considered as an appropriate main endpoint. Although the numbers are small and the evidence generated in a single arm setting, an MMR rate of 30.8 % (8/26 patients) is considered to be relevant and may be of benefit, in particular for those achieving a deep and or durable MMR.

Ponatinib pre-treated patients in MMR at treatment initiation

For this clinical setting after pre-treatment with ponatinib and/or allogeneic stem cell transplant, the meaning of the endpoint MMR by 24 weeks is not obvious. For a robust assessment, detailed information on the depth of response at baseline and during treatment would be needed. In this application, the only data source was the RWD chart review A2004 with extremely limited strength of evidence: the data source is retrospective secondary use with inherent potential selection bias, with heterogeneity in data availability, potential selection bias and immortal time bias, uncertainty about representativity of the MAP patients, number of missing observations for primary and secondary endpoints, and an observation period of a maximum of 1 year. Evidence was limited to data from 12 patients, including 3/12 following SCT. These data can neither be considered as sufficient nor robust for benefit-risk evaluation.

5.4. Clinical safety

The safety data for this application is derived from the final clinical study report (CSR) of study CABL001X2101 (hereafter referred to as Study X2101), a completed phase I, multicenter, open-label study of oral asciminib in patients with Ph+ CML or Ph+ ALL.

The expansion cohort characterizing the safety, tolerability and efficacy of asciminib as single agent in patients with CML-CP harbouring the T315I mutation are the main results supporting the proposed indication and the five-fold higher posology (200 mg b.i.d.) than in the previously approved indication.

The application also refers to some additional data from the **supportive study CABL001A2004** (hereafter referred to as Study A2004) which is a chart review study of patients treated in the asciminib market access program (MAP). **Study A2004 assessed the real-world effectiveness of asciminib and treatment patterns in patients with Chronic Myeloid Leukemia with T315I mutation.**

Table 22 Overview of Studies or Source data

Study	Study design	Treatments and number of patients	Treatment duration	Study status
X2101	Phase I, multicenter, open-label study in	Total enrolled: 326:	Median=	Completed

Study	Study design	Treatments and number of patients	Treatment duration	Study status
	patients with CML or Ph+ ALL	**CML-CP harboring the T315I mutation: N=70 at the following doses:** 20 mg b.i.d. (n=1), 40 mg b.i.d. (n=1), 80 mg b.i.d. (n=4), 80 mg q.d. (n=1), 120 mg q.d. (n=3), and 200 mg q.d. (n=1). and **Enrichment groups at doses of:** 150 mg b.i.d. (n=5), 160 mg b.i.d. (n=6), and **200 mg b.i.d. (n=48)**	136.6 weeks (range: 2-372 weeks)	
A2004	Retrospective, non-interventional chart review study	31 patients	up to 827 days	Not Applicable

Study X2101

Study X2101 was a Phase I, multi-center, open-label, dose escalation study to define the MTD/ RDE, to characterize safety and tolerability, to assess the pharmacokinetic profile, and to assess the preliminary efficacy of asciminib given as single agent or in combination with either nilotinib or imatinib or dasatinib in patients with CML or Ph+ ALL.

The study had **5 treatment arms**. **Each arm began with a dose escalation part. After determination of the MTD, or the RDE(s), further safety and tolerability was evaluated in an expansion part** [Study X2101 Final Analysis-Section 10]:

Arm 1 (N=200): asciminib as single agent in patients with CML-CP/-AP including CML-CP harboring T315I mutation (this arm includes the total 70 patients harbouring the T315I mutation)

Arm 2 (N=26): asciminib in combination with nilotinib in patients with CML-CP/-AP

Arm 3 (N=25): asciminib in combination with imatinib in patients with CML-CP/-AP

Arm 4 (N=32): asciminib in combination with dasatinib in patients with CML-CP/-AP

(Arm 5 (N=43): asciminib as single agent in patients with CML-BP and Ph+ ALL).

The **primary objective of Phase I trial X2101 was to determine the MTD and/or the RDE of asciminib** has been assessed as single agent or in combination with other TKIs. The assessment of the overall safety profile and tolerability, as well as the antileukemic activity were part of the secondary objectives.

The primary analysis was performed when all patients in Arms 1 and 5 had been treated for at least 6 cycles of 28 days of treatment and had their 24-week efficacy evaluation performed or had discontinued treatment earlier.

The final analysis occurred at the end of the study after last patient last visit (14 Mar 2023) had occurred.

Of note, the impact of COVID-19 pandemic on missed safety assessments was minimal, no safety issues were reported for the impacted patients as assessed by the study team. There were 95 cases (69 patients) of suspected or confirmed SARS-CoV-2 infection in the study up to the cut-off date for this report. Though some visits were missed by patients due to COVID-19 pandemic, there was not more

than one missed visit within a treatment cycle for each patient impacted. Safety assessments were performed at local facility as per visit schedule and/or when required and were transferred to the clinical data base.

Table 23 Summary of the Study X2101 cohort harboring the T315I mutation

Study population pertinent to this SCS	Patients with chronic myeloid leukemia in chronic phase (CML-CP) harboring the T315I mutation.
Safety endpoints pertinent to the SCS	*Primary endpoint:* Incidence of dose limiting toxicities (DLTs) during the first cycle of study treatment *Secondary endpoint:* Adverse events (AEs), serious adverse events (SAEs), changes in laboratory values, vital signs, and electrocardiograms
No of patients enrolled	70 CML-CP patients harboring the T315I mutation were enrolled in Arm 1
Regimen pertinent to the indication	The b.i.d. regimen was explored in patients enrolled in dose escalation and expansion cohorts, and in patients harboring the T315I mutation, was set to 200 mg b.i.d.
Treatment duration	End of treatment was considered to be when all patients enrolled had been followed for at least 64 weeks in the study (corresponding approximately to Cycle 16) or had discontinued from treatment, whichever occurred first and had a PTA option available in the country
Safety assessment pertinent to the SCS	The primary endpoint was the incidence of DLTs in Cycle 1 (each cycle was defined as 28 days). Estimation of the MTD/RDE of the treatment was based upon the estimation of the probability of DLT in Cycle 1 for patients in the DDS. The MTD was defined as the highest drug dosage that is unlikely (< 25% posterior probability) to cause DLT in 33% or more of the treated patients in the first cycle of study treatment under that schedule. Safety was monitored by assessing changes from index date in laboratory values, physical examination including extramedullary involvement of the disease, ECGs, and vital signs as well as collection of the AEs and SAEs at every visit
Statistical methodology	A 2-parameter adaptive BLRM guided by the EWOC principle was used to determine the MTD/RDE for patients in Arm 1 who were harboring the T315I mutation.
Details of the study design are provided in [Study X2101 Final Analysis]	

Study A2004

This retrospective NIS chart review analyzed the existing data for a subset of patients participating in the ongoing asciminib MAP [Study A2004-Section 9.1]. The study population included patients treated in the asciminib MAP with CML who had the T315I mutation and were either resistant or intolerant to prior treatments or in whom other available treatments were contraindicated [Study A2004-Section 9.3].

5.4.1. Safety data collection

Trial X2101

Safety in **trial X2101** was monitored by assessing changes from index date in laboratory values, physical examination including extramedullary involvement of the disease, ECGs, and vital signs as well as collection of the AEs and SAEs at every visit.

Serum and urine pregnancy tests were also performed at screening and other predefined timepoints for all females of childbearing potential. Safety was also assessed by obtaining Eastern Cooperative

Oncology Group (ECOG) performance status, abdominal imaging, and conducting ophthalmologic examinations [Study X2101 Final Analysis-Section 9.5.4].

For each specified AESI, the number and percentage of patients with at least one event of the AESI occurring during on-treatment period were summarized.

Pooling of safety data was not an option for the purposes of this submission, as one interventional trial (Study X2101) provides the main prospective safety data evaluation for the target population of patients with Ph+ CML-CP harboring the T315I mutation.

Coding dictionary versions: For Study X2101, AEs were coded using MedDRA version 25.1 for final analysis.

Cut-off date: For Study X2101, the final analysis occurred at the end of the study after LPLV on data lock (14-Mar-2023) had occurred.

Trial A2004

With respect to the supportive retrospective **study A2004** the information provided regarding the mode and quality of the safety assessment remains not sufficient to evaluate the validity of this data.

5.4.2. Patient exposure

Main study – Study X2101

Overall, the median duration of exposure to asciminib single agent in **70 patients with CML-CP harboring the T315I mutation** at the Final Analysis data cut-off was **136.6 weeks** (min-max: 2 to 372 weeks), an increase of 56 weeks from 80.8 weeks (min-max: 2 to 242 weeks) at the Primary Analysis data cut-off.

The **median duration of exposure to asciminib in 200 mg b.i.d. cohort** increased to **181.7 weeks** (min-max: 2 to 312 weeks) at Final Analysis data cut-off from 69.8 weeks (min-max: 2 to 175 weeks) at the Primary Analysis data cut-off [Study X2101 Primary Analysis-Section 12.1.3.1].

Of the 70 patients, 59 (84.3%) patients were exposed to asciminib for at least 24 weeks, and 34 (48.6%) patients were exposed to asciminib for at least 144 weeks.

Table 24 Duration of exposure to study drug by treatment – single agent asciminib in CML-CP harboring the T315I mutation at screening (Safety Set) - Study X2101

	Asciminib 150 mg b.i.d. N=5	**Asciminib 160 mg b.i.d. N=6**	**Asciminib 200 mg b.i.d. N=48**	**All Subjects N=70**
Duration of exposure (wks)				
Mean (SD)	180.0 (168.67)	103.6 (104.22)	154.1 (99.04)	146.2 (104.85)
Median	98.0	69.4	181.7	136.6
Q1-Q3	80.0-348.4	30.1-153.7	46.6-240.0	40.9-237.1
Min-Max	2-372	11-288	2-312	2-372
Duration of exposure categories-n (%)				
Less than 4 wks	1 (20.0)	0	1 (2.1)	2 (2.9)
At least 4 wks	4 (80.0)	6 (100)	47 (97.9)	68 (97.1)
At least 8 wks	4 (80.0)	6 (100)	45 (93.8)	65 (92.9)
At least 12 wks	4 (80.0)	5 (83.3)	45 (93.8)	64 (91.4)
At least 24 wks	4 (80.0)	5 (83.3)	40 (83.3)	59 (84.3)
At least 48 wks	4 (80.0)	3 (50.0)	36 (75.0)	51 (72.9)

	Asciminib 150 mg b.i.d. N=5	Asciminib 160 mg b.i.d. N=6	Asciminib 200 mg b.i.d. N=48	All Subjects N=70
At least 96 wks	3 (60.0)	3 (50.0)	33 (68.8)	45 (64.3)
At least 144 wks	2 (40.0)	2 (33.3)	27 (56.3)	34 (48.6)

Amongst the 70 patients with CML-CP harboring the T315I mutation, median total daily dose of asciminib received was 361.5 mg, which was highly variable (min - max: 70 - 400 mg) due to the range of doses tested.

In the largest cohort 200 mg b.i.d., the median total daily dose of asciminib received was 398.2 mg (see table below).

Table 25 Dose of study drug received – single agent asciminib in CML-CP harboring the T315I mutation at screening (Safety set) - Study X2101

	Asciminib 150 mg b.i.d. N=5	Asciminib 160 mg b.i.d. N=6	Asciminib 200 mg b.i.d. N=48	All Subjects N=70
Total number of subjects receiving study drug-n (%)	5 (100)	6 (100)	48 (100)	70 (100)
Cumulative dose (mg)				
Mean (SD)	405880.0 (369843.07)	219546.7 (235411.86)	382256.3 (254265.74)	339015.1 (254559.73)
Median	244520.0	113960.0	400800.0	295600.0
Q1-Q3	184100.0-774620.0	77040.0-343040.0	101760.0-596960.0	101600.0-554800.0
Min-Max	3300-822860	24320-644960	4400-834000	2860-834000
Dose intensity (mg/day)				
Mean (SD)	323.8 (20.95)	310.0 (66.05)	363.5 (62.16)	333.6 (82.46)
Median	317.6	320.0	398.2	361.5
Q1-Q3	316.0-328.8	318.8-354.7	342.7-399.9	311.1-399.6
Min-Max	300-356	182-365	171-400	70-400
Relative dose intensity				
Mean (SD)	1.1 (0.07)	1.0 (0.21)	0.9 (0.16)	1.1 (0.83)
Median	1.1	1.0	1.0	1.0
Q1-Q3	1.1-1.1	1.0-1.1	0.9-1.0	0.9-1.0
Min-Max	1-1	1-1	0-1	0-7
Relative dose intensity categories-n (%)				
<=75%	0	1 (16.7)	6 (12.5)	8 (11.4)
>75-90%	0	0	8 (16.7)	8 (11.4)
>90-110%	4 (80.0)	3 (50.0)	**34 (70.8)**	42 (60.0)
>110%	1 (20.0)	2 (33.3)	0	12 (17.1)

Dose intensity and relative dose intensity include days of zero dose in the calculation.

Supportive study – Study A2004

Table 26 Extent of exposure – Study A2004

Characteristic (Unit)	Category	Statistics	Asciminib (N=31)
Exposure Duration (days)		n	31
		Mean (SD)	267.9 (172.41)
		25thPercentile	129.0
		Median	295.0

Characteristic (Unit)	Category	Statistics	Asciminib (N=31)
		75thPercentile	386.0
		IQR	257.0
		Minimum, Maximum	9, 827
Exposure Duration (months)	≤3 months	n (%)	6 (19.35)
	>3 months and ≤6 months	n (%)	5 (16.13)
	>6 months and ≤9 months	n (%)	3 (9.68)
	>9 months and ≤12 months	n (%)	8 (25.81)
	>12 months	n (%)	9 (29.03)

Exposure duration (days) = Exposure end date - Index date + 1; index date was defined as the date of start of asciminib treatment (first dose).Exposure duration was summarized for all patients including those still ongoing asciminib treatment at the time of end of follow-up.

5.4.3. Adverse events

Common adverse events

All patients with CML-CP harboring the T315I mutation (n=70), treated with any dose of asciminib single agent had at least one AE regardless of study treatment relationship. An overview of on-treatment AEs, SAEs, AEs leading to discontinuation, AEs requiring dose adjustments/interruptions, and additional therapy is provided in Table 27.

Regardless of the longer duration of exposure since the Primary Analysis data cut-off (136.6 weeks vs. 80.8 weeks) there was no relevant change in the severity of the AEs (grade ≥3 58.6% vs 61.4%) and the frequency of SAEs (30.0% vs 37.1%), AEs leading to dose adjustment/interruption (34.3% vs 40.0%) and AEs leading to treatment discontinuation, which increased from 8.6% at the Primary Analysis data cut-off to 11.4% at the Final Analysis data cut-off.

Table 27 Overview of adverse events – single agent asciminib in CML-CP harboring the T315I mutation at screening (Safety set) - Study X2101

	Asciminib	**All**
	200 mg b.i.d.	**subjects**
	N=48	**N=70**
Category	**n (%)**	**n (%)**
Adverse events	48 (100)	70 (100)
Treatment-related	42 (87.5)	62 (88.6)
AEs with grade >=3	29 (60.4)	43 (61.4)
Treatment-related	18 (37.5)	26 (37.1)
SAEs	14 (29.2)	26 (37.1)
Treatment-related	2 (4.2)	5 (7.1)
Fatal SAEs	3 (6.3)	4 (5.7)
AEs leading to discontinuation	5 (10.4)	8 (11.4)
Treatment-related	2 (4.2)	3 (4.3)
AEs leading to dose adjustment/interruption	21 (43.8)	28 (40.0)
AEs requiring additional therapy	39 (81.3)	59 (84.3)

Numbers(n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.1, CTCAE version 4.03.

Adverse events by system organ class

Main Study - Study X2101

In the 200 mg b.i.d. cohort, AEs that occurred most frequently (≥ 40% of patients with CML-CP harboring the T315I mutation) were in the following system organ classes (SOCs):

- musculoskeletal and connective tissue disorders (58.3%),
- investigations, infections and infestations (56.3% each),
- GI disorders, general disorders and administration site conditions (50.0% each),
- skin and subcutaneous disorders and nervous system disorders (47.9% each).

Table 28 Adverse events, regardless of study treatment relationship, by primary system organ class and treatment – single agent asciminib in CML-CP harboring the T315I mutation at screening (Safety set) – Study X2101

	Asciminib		**All**	
	200 mg b.i.d.		**patients**	
	N=48		**N=70**	
	All grades	**Grade >=3**	**All grades**	**Grade >=3**
Body System or Organ Class	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of patients with at least one event	48 (100)	29 (60.4)	70 (100)	43 (61.4)
Musculoskeletal and connective tissue disorders	28 (58.3)	3 (6.3)	42 (60.0)	5 (7.1)
Investigations	27 (56.3)	18 (37.5)	41 (58.6)	23 (32.9)
Infections and infestations	27 (56.3)	8 (16.7)	40 (57.1)	9 (12.9)
Gastrointestinal disorders	24 (50.0)	6 (12.5)	38 (54.3)	6 (8.6)
Skin and subcutaneous tissue disorders	23 (47.9)	0	35 (50.0)	0
General disorders and administration site conditions	24 (50.0)	5 (10.4)	33 (47.1)	6 (8.6)
Nervous system disorders	23 (47.9)	5 (10.4)	33 (47.1)	7 (10.0)
Metabolism and nutrition disorders	18 (37.5)	3 (6.3)	28 (40.0)	7 (10.0)
Respiratory, thoracic and mediastinal disorders	19 (39.6)	3 (6.3)	24 (34.3)	5 (7.1)
Blood and lymphatic system disorders	17 (35.4)	9 (18.8)	23 (32.9)	2 (2.9)
Eye disorders	13 (27.1)	2 (4.2)	19 (27.1)	9 (12.9)
Vascular disorders	14 (29.2)	6 (12.5)	19 (27.1)	1 (1.4)
Injury, poisoning and procedural complications	13 (27.1)	1 (2.1)	17 (24.3)	2 (2.9)
Psychiatric disorders	8 (16.7)	0	15 (21.4)	6 (8.6)
Cardiac disorders	6 (12.5)	4 (8.3)	12 (17.1)	3 (4.3)
Hepatobiliary disorders	4 (8.3)	1 (2.1)	8 (11.4)	1 (1.4)
Renal and urinary disorders	7 (14.6)	1 (2.1)	8 (11.4)	0
Ear and labyrinth disorders	5 (10.4)	0	7 (10.0)	0
Reproductive system and breast disorders	6 (12.5)	0	7 (10.0)	1 (1.4)
Immune system disorders	2 (4.2)	1 (2.1)	2 (2.9)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (4.2)	0	2 (2.9)	0
Endocrine disorders	1 (2.1)	0	1 (1.4)	0
Product issues	0	0	1 (1.4)	
Numbers (n) represent counts of patients. A patient with multiple severity grades for a SOC is only counted under the maximum grade. MedDRA version 25.1 , CTCAE version 4.03.				

Supportive study – Study A2004

A total of 65 non-serious AEs were reported by 17 (54.84%) patients during the study. The majority of the reported non-serious AEs were of Grade 1 toxicity in 12 (38.71%) patients and were not considered related to asciminib in 13 (41.94%) patients. Among the majority of the non-serious AEs, the asciminib dose was not changed in 16 (51.61%) patients. Study drug interruption was reported in 4 (12.90%) patients and one patient (3.23%) reported withdrawal of the study drug. Of 65 reported nonserious events, 47 events were considered recovered/resolved, and 16 events were considered not recovered/not resolved.

Adverse events by preferred term

Main study - Study X2101

Table 29 Adverse events, regardless of study treatment relationship by preferred term and treatment (reported in at least 10% of all patients) – single agent asciminib in CML-CP with T315I mutation at screening (Safety set) – Study X2101

	Asciminib		**All**	
	200 mg b.i.d.		**subjects**	
	N=48		**N=70**	
	All grades	**Grade >=3**	**All grades**	**Grade >=3**
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of subjects with at least one event	48 (100)	29 (60.4)	70 (100)	43 (61.4)
Diarrhoea	13 (27.1)	1 (2.1)	18 (25.7)	1 (1.4)
Fatigue	15 (31.3)	1 (2.1)	18 (25.7)	1 (1.4)
Arthralgia	10 (20.8)	0	17 (24.3)	1 (1.4)
Headache	10 (20.8)	1 (2.1)	17 (24.3)	1 (1.4)
Nausea	13 (27.1)	0	16 (22.9)	0
Alanine aminotransferase increased	10 (20.8)	4 (8.3)	15 (21.4)	6 (8.6)
Lipase increased	14 (29.2)	10 (20.8)	15 (21.4)	11 (15.7)
COVID-19	11 (22.9)	1 (2.1)	13 (18.6)	1 (1.4)
Cough	11 (22.9)	0	13 (18.6)	0
Pain in extremity	7 (14.6)	0	13 (18.6)	0
Rash	6 (12.5)	0	13 (18.6)	0
Vomiting	10 (20.8)	3 (6.3)	13 (18.6)	3 (4.3)
Aspartate aminotransferase increased	7 (14.6)	1 (2.1)	12 (17.1)	4 (5.7)
Pyrexia	6 (12.5)	0	12 (17.1)	0
Constipation	6 (12.5)	0	11 (15.7)	0
Hypertension	7 (14.6)	4 (8.3)	11 (15.7)	6 (8.6)
Thrombocytopenia	8 (16.7)	7 (14.6)	11 (15.7)	8 (11.4)
Back pain	7 (14.6)	1 (2.1)	10 (14.3)	1 (1.4)
Pruritus	6 (12.5)	0	10 (14.3)	0
Hyperuricaemia	6 (12.5)	0	9 (12.9)	0
Hypophosphataemia	3 (6.3)	1 (2.1)	9 (12.9)	3 (4.3)
Myalgia	4 (8.3)	0	9 (12.9)	1 (1.4)
Abdominal pain	7 (14.6)	3 (6.3)	8 (11.4)	3 (4.3)
Anaemia	5 (10.4)	3 (6.3)	8 (11.4)	6 (8.6)
Amylase increased	6 (12.5)	2 (4.2)	7 (10.0)	2 (2.9)
Dizziness	4 (8.3)	0	7 (10.0)	1 (1.4)
Dyspnoea	3 (6.3)	0	7 (10.0)	0
Gamma-glutamyl transferase increased	4 (8.3)	2 (4.2)	7 (10.0)	3 (4.3)
Musculoskeletal pain	7 (14.6)	0	7 (10.0)	0
Neutropenia	5 (10.4)	3 (6.3)	7 (10.0)	5 (7.1)
Non-cardiac chest pain	5 (10.4)	1 (2.1)	7 (10.0)	1 (1.4)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.1, CTCAE version 4.03.

Treatment-related AEs

Regardless of the longer duration of exposure to asciminib since the Primary Analysis data cut-off, overall, there was no relevant change in the incidence of study treatment-related AEs (88.6% at Final Analysis data cut-off vs. 87.1% at Primary Analysis data cut-off).

In the 200 mg b.i.d. cohort, 42/48 (87.5%) patients (1 additional patient since the Primary Analysis data cut-off) reported treatment-related AEs.

The most frequent (≥ 10% of patients) treatment-related AEs were lipase increased (22.9%), nausea (18.8%), fatigue and diarrhea (14.6% each), arthralgia, ALT increased, and thrombocytopenia (12.5% each), pruritus, headache, amylase increased, vomiting, and musculoskeletal pain (10.4% each).

5.4.4. Adverse event of special interest, serious adverse events and deaths, other significant events

AEs of special interest and other significant events

The safety profile of asciminib was established based on the Phase III registration Study A2301 and Study X2101.

<u>The current AESI related to asciminib are the following:</u>

- Acute pancreatitis (including isolated pancreatic enzyme elevations)
- Myelosuppression
- Hypersensitivity
- Hepatotoxicity (including hepatic enzyme elevations)
- Hepatitis B virus reactivation
- Reproductive toxicity
- GI toxicity
- Phototoxicity
- QTc prolongation
- Cardiac failure
- Edema and fluid retention
- Ischemic heart disease
- Central nervous system (CNS) conditions
- Haemorrhage
- Arterial occlusive events (AOE)

<u>Main study - Study X2101</u>

An overview of AESI reported in patients with CML-CP harboring the T315I mutation treated with asciminib single agent is provided in Table 30. Each AESI reported in the 200 mg b.i.d. cohort is further discussed below.

Regardless of the longer duration of exposure since the Primary Analysis data cut-off (136.6 weeks vs. 80.8 weeks), there was no relevant increase (≥10% difference) in the incidence of AESIs under any safety topic.

Table 30 Adverse events of special interest by treatment – single agent asciminib in CML-CP harboring the T315I mutation at screening (Safety set) – Study X2101

	Asciminib 200 mg b.i.d. N=48		**All subjects N=70**	
	All grades	**Grade >=3**	**All grades**	**Grade >=3**
Safety topic	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Acute pancreatitis (including isolated pancreatic enzyme elevations)	15 (31.3)	11 (22.9)	17 (24.3)	12 (17.1)
Pancreatic toxicity (clinical events)	1 (2.1)	0	1 (1.4)	0
Myelosuppression*	14 (29.2)	10 (20.8)	22 (31.4)	15 (21.4)
Thrombocytopenia	10 (20.8)	8 (16.7)	15 (21.4)	9 (12.9)
Leucopenia	8 (16.7)	6 (12.5)	12 (17.1)	10 (14.3)
Neutropenia	8 (16.7)	6 (12.5)	12 (17.1)	10 (14.3)
Erythropenia	5 (10.4)	3 (6.3)	8 (11.4)	6 (8.6)
Cytopenias affecting more than one lineage	1 (2.1)	1 (2.1)	1 (1.4)	1 (1.4)
QTc prolongation	1 (2.1)	1 (2.1)	1 (1.4)	1 (1.4)
Hepatotoxicity (including laboratory terms)	15 (31.3)	6 (12.5)	24 (34.3)	9 (12.9)
Arterial-occlusive events (AOEs)**	6 (12.5)	3 (6.3)	10 (14.3)	6 (8.6)
Ischemic heart and CNS conditions***	7 (14.6)	3 (6.3)	11 (15.7)	6 (8.6)
Ischemic heart disease	5 (10.4)	2 (4.2)	8 (11.4)	4 (5.7)
Ischemic CNS vascular conditions	4 (8.3)	2 (4.2)	5 (7.1)	3 (4.3)
Hypersensitivity	16 (33.3)	1 (2.1)	26 (37.1)	1 (1.4)
GI toxicity	24 (50.0)	5 (10.4)	37 (52.9)	5 (7.1)
Edema and fluid retention	9 (18.8)	3 (6.3)	13 (18.6)	4 (5.7)
Hemorrhage	10 (20.8)	1 (2.1)	12 (17.1)	1 (1.4)
Phototoxicity	1 (2.1)	0	2 (2.9)	0
Cardiac failure (clinical events)	1 (2.1)	1 (2.1)	1 (1.4)	1 (1.4)
Hepatitis B virus reactivation	0	0	1 (1.4)	0

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
*Myelosuppression includes Erythropenia, Leucopenia, Neutropenia, Thrombocytopenia, cytopenias affecting more than one lineage.
** Arterial-occlusive events (AOEs) were added an AESI category after the Primary Analysis data cut-off.
***Ischemic heart and CNS conditions includes 'ischemic CNS vascular conditions' and 'ischemic heart disease'
MedDRA version 25.1, CTCAE version 4.03, Case Retrieval Strategy version released 2022-11-17

Arterial-occlusive events (AOEs)

In the 200 mg b.i.d. cohort, arterial occlusive events were reported in 6/48 (12.5%) patients; majority of them were CTCAE grade 1 or 2. Grade 3 events were reported in 2/48 (4.2%) patients, and grade 4

events were reported in 1 (2.1%) patient. The most frequent AEs reported (all grades, ≥ 4% of all patients) by PT were Cerebrovascular accident (6.3%) and Peripheral arterial occlusive disease (4.2%).

Arterial occlusive event of coronary artery disease suspected to be related to study treatment was reported in 1 (2.1%) patient. SAEs were reported in 4 (8.3%) patients. No patient required dose adjustment or temporary interruption. No patient had AOEs that led to treatment-discontinuation. Concomitant medication or therapy was required in 4 (8.3%) patients. One patient had AOEs with fatal outcome: one event for cerebrovascular accident and myocardial infarction. AOEs did not resolve in 5 (10.4%) patients at the time of data cut-off date.

Gastrointestinal toxicity

In the 200 mg b.i.d. cohort, GI toxicity events (nausea, diarrhea, vomiting, constipation, abdominal pain, non-cardiac chest pain) were reported in 24/48 (50.0%) patients (1 additional patient since Primary Analysis data cut-off); majority of them were of CTC grade 1 or 2. Grade 3 events were reported in 5/48 (10.4%) patients, and no grade 4 event was reported. The most frequent AEs were (all grades, ≥10% of patients) by PT were Nausea and Diarrhea (27.1% each), Vomiting (20.8%), Constipation (12.5%), Abdominal pain (14.6%), and non-cardiac chest pain (10.4%).

GI toxicity events suspected to be related to study treatment were reported in 14 (29.2%) patients. Serious adverse events were reported in 3 (6.3%) patients.

Dose adjustment was required in 2 (4.2%) patients and interruption in 1 (2.1%) patient. None of these events led to treatment discontinuation or were fatal. Concomitant medication or therapy was required in 10 (20.8%) patients. Most of these AEs resolved or were resolving at the time of data cut-off date.

Hypersensitivity

In the 200 mg b.i.d. cohort, hypersensitivity events were reported in 16/48 (33.3%) patients (4 additional patients since the Primary Analysis data cut-off); all except one of them are of CTC grade 1 or 2. Grade 3 iodine allergy was reported in one patient and was considered serious and not related to asciminib which is the only SAE reported. Individual PTs were infrequent with no AE reported in ≥10% of patients except for Rash in 6 (12.5%) patients. Hypersensitivity events suspected to be related to study treatment were reported in 10 (20.8%) patients.

None of these events required dose adjustment/interruption, led to treatment discontinuation or fatal. Concomitant medication was required for 5 (10.4%) patients (3 additional patients since the Primary Analysis data cut-off); 2 had rash and 1 each had eczema, iodine allergy and urticaria as PT. Majority of these AEs resolved at the time of data cut-off date for this report.

Pancreatic toxicity including acute pancreatitis and pancreatic enzyme elevations

In the 200 mg b.i.d. cohort, AEs pertaining to the definition of acute pancreatitis (including isolated pancreatic enzyme elevations) events were reported in 15/48 (31.3%) patients (3 additional patients since the Primary Analysis data cut-off), with grade 3/4 events reported in 11/48 (22.9%) patients (2 additional patients since the Primary Analysis data cut-off).

Lipase increase (29.2%; grade 3/4: 20.8%), and amylase increased (12.5%; grade 3/4: 4.2%) were the most frequent PTs reported (all grades; in ≥10% of patients). Majority of these events (25.0% of patients) were suspected to be treatment related. None of these events were serious or fatal.

Dose adjustment and interruption were required in 5 (10.4%) and 8 (16.7%) patients, respectively. One patient discontinued treatment due to increased lipase levels. Concomitant medication or therapy was required for pancreatitis in 1 patient (2.1%). Most of the AEs resolved or were resolved at the time of Final Analysis data cut-off.

Of note, AE(s) pertaining to the definition of acute pancreatitis (clinical events; all grades) were reported in 1/70 (1.4%) patient; grade 2 pancreatitis, which was resolving at the Final Analysis data cut-off.

Hepatotoxicity (including laboratory terms)

In the 200 mg b.i.d. cohort, AEs pertaining to the definition of hepatotoxicity were reported in 15/48 (31.3%) patients (3 additional patients since Primary Analysis data cut-off); majority of them are of CTC grade 1 or 2. Grade 3 events reported in 6/48 (12.5%) patients (1 additional patient since Primary Analysis data cut-off) and no grade 4 event was reported. Increased ALT (20.8%; grade 3: 8.3%) and Increased AST (14.6%; grade 3: 2.1%) were the most frequent PTs reported (all grades; in ≥ 10% of patients). Seven (14.6%) patients had an event suspected to be treatment-related. None of these events were serious, led to treatment-discontinuation or fatal. Dose adjustment and interruption were required in 2 (4.2%) patients each. Concomitant medication or therapy was required in 2 (4.2%) patients.

Myelosuppression (including thrombocytopenia, erythropenia, leucopenia, and other cytopenias)

In the 200 mg b.i.d. cohort, AEs pertaining to the definition of myelosuppression were reported in 14/48 (29.2%) patients (3 additional patients since Primary Analysis data cut-off), with grade 3/4 events reported in 10/48 (20.8%) patients (1 additional patient since Primary Analysis data cut-off). Thrombocytopenia (16.7%; grade 3/4: 10.4%), Anemia (10.4%; grade 3/4: 4.2%), and Neutropenia (10.4%; grade 3/4: 6.3%) were the most frequent PTs reported in ≥ 10% of patients. The majority of these events (18.8% of patients) were suspected to be treatment related. None of these events was serious or fatal. Dose adjustment and interruption was required in 3 (6.3%) patients each. One patient discontinued treatment due to neutrophil count decreased, platelet count decreased, and pancytopenia. Concomitant medication or therapy was required in 5 (10.4) patients (1 additional patient since Primary Analysis data was cut off). The majority of these AEs were resolved or were resolved at the time of Final Analysis data cut-off.

Edema and fluid retention

In the 200 mg b.i.d. cohort, AEs pertaining to the definition of edema and fluid retention were reported in 9/48 (18.8%) patients (2 additional patients since Primary Analysis data cut-off); grade 3 events were reported in 3/48 (6.3%) patients, and no grade 4 event was reported. Individual PTs were infrequent with no AE reported in ≥10% of patients except for Oedema peripheral in 5 (10.4%) patients. One patient had peripheral edema which was suspected to be treatment related. One patient had an SAE of pleural effusion (Grade 3), which was resolved and not related to asciminib. None of these events required dose adjustment, led to treatment-discontinuation, or were fatal. One patient with pleural effusion required dose interruption. Concomitant medication or therapy was required in 5 (10.4%) of patients (1 additional patient since Primary Analysis data cut-off). In the majority of patients, these AEs were resolved.

Hemorrhage

In the 200 mg b.i.d. cohort, AEs pertaining to the definition of hemorrhage were reported in 10/48 (20.8%) patients (2 additional patients since Primary Analysis data cut-off); all except one of them are of CTC grade 1 or 2. One patient had grade 3 SAE of post procedural hemorrhage, which was resolved at the cut-off date. No grade 4 events were reported.

Except for Epistaxis (6.3%; 3 patients), all other individual PTs (all grades) were infrequently reported in <5% of patients. Skin hemorrhage was the treatment-related event reported in 1/48 (2.1%) patient. None of these events required dose adjustment/interruption, led to treatment-discontinuation or were fatal. Concomitant medication or therapy was required in 3 (6.3%) of patients (1 additional patient since Primary Analysis data cut-off). All these AEs were resolved at the time of data cut-off date.

Ischemic heart and CNS conditions

In the 200 mg b.i.d. cohort, AEs pertaining to the definition of ischemic heart and CNS conditions were reported in 7/48 (14.6%) patients (4 additional patients since Primary Analysis data cut-off); most of them are of CTC grade 1 or 2. Grade 3 AEs were reported in 2 (4.2%) patients, and grade 4 AE was reported in 1 (2.1%) patient.

Increased blood creatine phosphokinase was reported in 2 (4.2%) patients, of which 1 (2.1%) was suspected to be treatment related. Coronary artery disease was reported in 1 patient that was suspected to be treatment related. Serious adverse events were reported in 4 (8.3%) patients (3 additional patients since Primary Analysis data cut-off). None of these events required dose adjustment/interruption or led to treatment discontinuation.

Fatal AEs of cerebrovascular accident and myocardial infarction were reported in 1 (2.1%) patient. Concomitant medication or therapy was required by 4 patients (8.3%) since the Primary Analysis data cut-off.

Phototoxicity

In the 200 mg b.i.d. cohort, 1/48 (2.1%) patient reported with grade 1 photosensitivity reaction, which was not serious and suspected to be treatment related. No action was taken with treatment, and the event was resolved at the time of data cut-off date.

QTc prolongation

In the 200 mg b.i.d. cohort, 1/48 (2.1%) patient reported with grade 3 ventricular tachycardia, which was considered a serious event and treated with concomitant medication. No action was taken with treatment, and the event was resolved at the time of data cut-off date for the final analysis of Study X2101. No additional cases of QTc prolongation were observed since the Primary Analysis data cut-off.

Cardiac failure (clinical events)

In the 200 mg b.i.d. cohort, 1/48 (2.1%) patient reported congestive hepatopathy and Grade 3 ejection fraction decreased, which were not serious and not suspected of being treatment related. No action was taken with asciminib. Congestive hepatopathy resolved whereas ejection fraction decreased did not at the time of data cut-off date for this report. No additional cases of cardiac failure were observed since the Primary Analysis data cut-off.

Serious adverse events

Main study - Study X2101

In patients with CML-CP harboring the T315I mutation, regardless of the longer duration of exposure to asciminib since the Primary Analysis data cut-off (136.6 weeks vs. 80.8 weeks), there was no relevant change in the frequency of SAEs (26/70; 37.1% at Final Analysis vs. 21/70; 30.0% at Primary Analysis). Overall, grade ≥ 3 SAEs (regardless of study treatment relationship) were reported in 18/70 (25.7%) patients with CML-CP harboring the T315I mutation.

Table 31 Serious adverse events, regardless of study treatment relationship, by preferred term and treatment (reported in at least 2 patients overall) – single agent asciminib in patients with CML-CP harboring the T315I mutation at screening (Safety set) - Study X2101

	Asciminib		**All**	
	200 mg b.i.d.		**subjects**	
	N=48		**N=70**	
	All grades	**Grade >=3**	**All grades**	**Grade >=3**
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of subjects with at least one event	14 (29.2)	11 (22.9)	26 (37.1)	18 (25.7)
Abdominal pain	2 (4.2)	2 (4.2)	2 (2.9)	2 (2.9)
Acute coronary syndrome	1 (2.1)	0	2 (2.9)	1 (1.4)
COVID-19	2 (4.2)	1 (2.1)	2 (2.9)	1 (1.4)
COVID-19 pneumonia	2 (4.2)	2 (4.2)	2 (2.9)	2 (2.9)
Cerebrovascular accident	2 (4.2)	1 (2.1)	2 (2.9)	1 (1.4)
Pneumonia	2 (4.2)	2 (4.2)	2 (2.9)	2 (2.9)
Vomiting	2 (4.2)	2 (4.2)	2 (2.9)	2 (2.9)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.1, CTCAE version 4.03.

Supportive study – Study A2004

In total, 21 SAEs were reported in 9 of 31 patients (29.0%) during asciminib treatment. The most common seriousness criteria was hospitalization (8 [25.8%] patients).

Deaths

Main study - Study X2101

A total of 4 on-treatment deaths were reported during the study. At the primary Analysis cut-off, overall, 2/70 (2.9%) patients with CML-CP harboring the T315I mutation died on-treatment (within 30 days after last dose of study treatment) with asciminib single agent. Of these, 1 death was due to underlying disease, and the other was due to suicide (80 mg b.i.d. cohort; with depression being SAE contributing to death), which was not related to study treatment [Study X2101 Primary Analysis -Section 12.3.3.3]. The causes of additional on-treatment deaths since Primary Analysis data cut-off were COVID-19 pneumonia and myocardial infarction, each in one patient: both in the asciminib 200 mg b.i.d. cohort. Neither of these two fatal events was considered to be related to study treatment.

Supportive study – Study A2004

Overall, four of 31 patients died due to reported SAEs during the study; a fungal infection (1 [3.2%] patient) and CML (1 [3.2%] patients) led to death while on treatment. Two patients died after discontinuing asciminib: the SAEs of cerebrovascular accident (1 [3.2%] patient) and pneumonia (1 [3.2%] patient) led to death however, none of the patients discontinued the study due to these SAEs (one patient with pneumonia discontinued the study drug at the physician's discretion before the death, while another patient who had a cerebrovascular accident discontinued the study drug permanently on the same day of death).

5.4.5. Discontinuation due to adverse events

Table 32 Adverse events leading to study treatment discontinuation, regardless of study treatment relationship by preferred term and treatment – single agent asciminib in CML-CP harboring the T315I mutation at screening (Safety set) – Study X2101

	Asciminib 200 mg b.i.d. N=48	**All subjects N=70**
Preferred Term	**n (%)**	**n (%)**
Number of subjects with at least one event	5 (10.4)	8 (11.4)
COVID-19 pneumonia	2 (4.2)	2 (2.9)
Acute coronary syndrome	0	1 (1.4)
Cholecystitis acute	0	1 (1.4)
Completed suicide	0	1 (1.4)
Lipase increased	1 (2.1)	1 (1.4)
Neutrophil count decreased	1 (2.1)	1 (1.4)
Pancytopenia	1 (2.1)	1 (1.4)
Platelet count decreased	1 (2.1)	1 (1.4)
Thrombocytosis	1 (2.1)	1 (1.4)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.1, CTCAE version 4.03.

Adverse events requiring dose adjustment and/or interruption

Main study - Study X2101

Overall, 28 (40.0%) patients with CML-CP harboring the T315I mutation had at least one AE requiring dose adjustment/interruption; 21 (30.0%) of patients had treatment-related AEs.

In the 200 mg b.i.d. cohort, 15/48 (31.3%) patients had at least one treatment-related AE requiring dose adjustment/interruption. Lipase increase (14.6%) and thrombocytopenia (6.3%) were the most frequent AEs reported in at least 5% of patients.

Adverse events requiring significant additional therapy

Main study - Study X2101

Overall, 59 (84.3%) patients with CML-CP harboring the T315I mutation had at least one AE requiring additional therapy.

In the 200 mg b.i.d. cohort, 39 (81.3%) patients required additional therapy. Nausea, COVID-19, arthralgia, and cough (10.4% each) were the most frequent AE reported in ≥ 10% of patients.

5.4.6. Safety in special populations

Intrinsic factors

No intrinsic factors were evaluated in Trial X2101.

Extrinsic factors

No extrinsic factors were evaluated in Trial X2101.

With respect to safety in special populations no new information has been generated in support of this application. Considering that the investigated target population includes only 48 subjects this is plausible Also, no additional extrinsic or intrinsic factors were evaluated and can be discussed.

However, with reported to the elderly population this is an important lack of information since it remains completely unknown whether the reported safety risks are similar in subjects older than 65 years.

5.4.7. Immunological events

No information provided.

5.4.8. Safety related to drug-drug interactions and other interactions

The following interactions and potential risk are currently described in the SmPC section 4.5:

Medicinal products with known risk of torsades de pointes

Caution should be exercised during concomitant administration of asciminib and medicinal products with known risk of torsades de pointes, including, but not limited to, bepridil, chloroquine, clarithromycin, halofantrine, haloperidol, methadone, moxifloxacin or pimozide.

Medicinal products that may decrease asciminib plasma concentrations

Strong CYP3A4 inducers

Co-administration of a strong CYP3A4 inducer (rifampicin) decreased asciminib AUCinf by 15% and increased Cmax by 9% in healthy subjects receiving a single asciminib dose of 40 mg.

Caution should be exercised during concomitant administration of asciminib with strong CYP3A4 inducers, including, but not limited to, carbamazepine, phenobarbital, phenytoin or St. John's wort (Hypericum perforatum), which may result in lower efficacy of asciminib.

Medicinal products that may have their plasma concentrations altered by asciminib CYP3A4 substrates with narrow therapeutic index

Co-administration of asciminib with a CYP3A4 substrate (midazolam) increased midazolam AUCinf and Cmax by 28% and 11%, respectively, in healthy subjects receiving asciminib 40 mg twice daily. Caution should be exercised during concomitant administration of asciminib with CYP3A4 substrates known to have a narrow therapeutic index, including, but not limited to, the CYP3A4 substrates fentanyl, alfentanil, dihydroergotamine or ergotamine (see section 5.2). Dose adjustment of asciminib is not required.

CYP2C9 substrates

Co-administration of asciminib with a CYP2C9 substrate (warfarin) increased S-warfarin AUCinf and Cmax by 41% and 8%, respectively, in healthy subjects receiving asciminib 40 mg twice daily. Caution should be exercised during concomitant administration of asciminib with CYP2C9 substrates known to have a narrow therapeutic index, including, but not limited to, phenytoin or warfarin (see section 5.2). Dose adjustment of asciminib is not required.

OATP1B, BCRP substrates or substrates of both transporters

Based on physiologically based pharmacokinetic (PBPK) modelling, caution should be exercised during concomitant administration of asciminib with substrates of OATP1B, BCRP or both transporters, including, but not limited to sulfasalazine, methotrexate, pravastatin, atorvastatin, pitavastatin, rosuvastatin and simvastatin. No clinical drug interaction study was performed.

P-gp substrates of narrow therapeutic index

Based on PBPK modelling, caution should be exercised during concomitant administration of asciminib with P-gp substrates known to have a narrow therapeutic index, including, but not limited to digoxin, dabigatran and colchicine (see section 5.2). Dose adjustment of asciminib is not required.

5.4.9. Vital signs and laboratory findings

Laboratory findings

HAEMATOLOGY

Main study - Study X2101

In the 200 mg b.i.d. cohort, the worst post-baseline hematology laboratory parameter values during the study were mostly grade 1 or 2. The most frequent post-baseline abnormalities of any grade noted were decreased hemoglobin (68.8%), and decreased lymphocytes (56.3%). Decreased platelets and decreased neutrophils (14.6% each) were the most frequent grade 3/4 abnormality post-baseline noted in > 10% of patients.

CLINICAL CHEMISTRY

Main study - Study X2101

Table 33 Worst post-baseline biochemistry abnormalities based on CTC grades by treatment – single agent asciminib in CML-CP harboring the T315I mutation at screening (Safety Set) – Study X2101

	Asciminib 200 mg b.i.d. N=48		**All subjects N=70**	
	All grades n (%)	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Alanine Aminotransferase (U/L), Serum - increase	28 (58.3)	4 (8.3)	40 (57.1)	6 (8.6)
Albumin (g/L), Serum - decrease	7 (14.6)	0	13 (18.6)	1 (1.4)
Alkaline Phosphatase (U/L), Serum - increase	11 (22.9)	0	20 (28.6)	0
Amylase (U/L), Serum - increase	16 (33.3)	6 (12.5)	23 (32.9)	7 (10.0)
Aspartate Aminotransferase (U/L), Serum - increase	23 (47.9)	1 (2.1)	31 (44.3)	4 (5.7)
Bilirubin (umol/L), Serum - increase	12 (25.0)	0	21 (30.0)	1 (1.4)
Calcium Corrected (mmol/L), Serum - decrease	24 (50.0)	0	32 (45.7)	0
Calcium Corrected (mmol/L), Serum - increase	4 (8.3)	0	6 (8.6)	0
Cholesterol (mmol/L), Serum - increase	15 (31.3)	0	24 (34.3)	0
Creatinine (umol/L), Plasma/Serum - increase	19 (39.6)	0	26 (37.1)	0
Gamma Glutamyl Transferase (GGT) (U/L), Serum - increase	26 (54.2)	6 (12.5)	38 (54.3)	7 (10.0)
Lipase, Pancreatic (U/L), Serum - increase	25 (52.1)	12 (25.0)	31 (44.3)	14 (20.0)
Magnesium (mmol/L), Serum - decrease	8 (16.7)	0	17 (24.3)	0

	Asciminib 200 mg b.i.d. N=48		All subjects N=70	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Magnesium (mmol/L), Serum - increase	11 (22.9)	1 (2.1)	20 (28.6)	3 (4.3)
Phosphate (mmol/L), Serum - decrease	25 (52.1)	4 (8.3)	36 (51.4)	7 (10.0)
Potassium (mmol/L), Plasma/Serum - decrease	4 (8.3)	1 (2.1)	6 (8.6)	1 (1.4)
Potassium (mmol/L), Plasma/Serum - increase	24 (50.0)	1 (2.1)	31 (44.3)	2 (2.9)
Sodium (mmol/L), Plasma/Serum - decrease	15 (31.3)	1 (2.1)	21 (30.0)	3 (4.3)
Sodium (mmol/L), Plasma/Serum - increase	6 (12.5)	0	9 (12.9)	1 (1.4)
Triglycerides (mmol/L), Plasma/Serum - increase	34 (70.8)	1 (2.1)	51 (72.9)	3 (4.3)
Urate (umol/L), Serum - increase	25 (52.1)	4 (8.3)	38 (54.3)	5 (7.1)

Numbers (n) represent counts of subjects. 'All grades' represents subjects with any grade 1, 2, 3 or 4 post-baseline.Grades based on CTCAE version 4.03.

The most frequent post-baseline abnormalities of any grade noted were increased triglycerides (70.8%), increased alanine aminotransferase (ALT) (58.3%), increased gamma-glutamyl transferase (GGT) (54.2%), increased lipase, increased urate and decreased phosphate (52.1% each), decreased calcium and increased potassium (50.0% each).

Increased lipase (25.0%), increased GGT and increased amylase (12.5% each) were the most frequent grade 3/4 abnormality post-baseline noted in ≥ 10% of patients.

In the 200 mg b.i.d. cohort, elevation in transaminases (ALT or Aspartate aminotransferase [AST]) > 3 x upper limit of normal (ULN) post-baseline was noted in 8/48 (16.7%) patients (1 additional patient since the Primary Analysis data cut-off for Study X2101.

Total bilirubin > 2 x ULN was reported in 1/48 (2.1%) patient.

One patient had concurrent elevations of ALT or AST > 3 x ULN and total bilirubin > 2 x ULN and alkaline phosphatase < 2 x ULN meeting the Hy's law biochemical criteria since the Primary Analysis data cut-off for Study X2101.

Vital signs, physical findings, and other observations related to safety

Vital signs

Main study - Study X2101

In the 200 mg b.i.d. cohort, no clinically meaningful changes in vital signs from index date were noted. The most frequent (≥ 10% of patients) notable change observed was increased pulse rate (≥ 100 bpm and increase of > 25%) in 8/48 (16.7%) patients, increased weight (≥10%) in 9/48 (18.8%) patients. Notable systolic blood pressure (≥ 180 mm Hg and increase ≥ 20 mm Hg) and diastolic pressure (≥ 105 mm Hg and increase ≥ 15 mm Hg) were reported in 6/48 (12.5%) and 2/48 (4.2%), patients respectively.

All notable vital signs are reported in the Study X2101 Final Analysis.

Electrocardiograms

Main study - Study X2101

QTcF increase > 60 ms from baseline and absolute QTcF > 500 ms, were observed in 2/48 (4.2%) patients each. No additional patients had absolute QTcF > 500 ms since the primary Analysis cut-off. An increase > 30 ms to ≤ 60 ms from index date in QTcF was reported in 5/48 (10.4%) patients.

Table 34 ECG notable values by treatment-single agent asciminib in CML-CP harboring the T315I mutation at screening (Safety Set) – Study X2101

ECG parameter **Notable criteria**	**Asciminib 200 mg b.i.d** **N=48** **n/m (%)**	**All Subjects** **N=70** **n/m (%)**
QTcF (ms)		
Increase >30 to <=60 ms	5/48 (10.4)	8/70 (11.4)
Increase >60 ms	2/48 (4.2)	2/70 (2.9)
New >450 to <=480 ms	3/45 (6.7)	6/66 (9.1)
New >480 to <=500 ms	2/48 (4.2)	2/70 (2.9)
New >500 ms	2/48 (4.2)	2/70 (2.9)
QT (ms)		
Increase >30 to <=60 ms	19/48 (39.6)	29/70 (41.4)
Increase >60 ms	2/48 (4.2)	4/70 (5.7)
New >450 to <=480 ms	5/45 (11.1)	9/65 (13.8)
New >480 to <=500 ms	3/48 (6.3)	4/70 (5.7)
New >500 ms	1/48 (2.1)	2/70 (2.9)
PR (ms)		
Increase >25% and PR >200 ms	0/42	0/61
New >200 ms	2/42 (4.8)	2/61 (3.3)
QRS (ms)		
Increase >25% and QRS >120 ms	1/45 (2.2)	2/66 (3.0)
New >120 ms	3/45 (6.7)	4/66 (6.1)
HR (bpm)		
Increase >25% and HR >100 bpm	1/46 (2.2)	1/68 (1.5)
Decrease >25% and HR <50 bpm	1/48 (2.1)	2/67 (3.0)

n: Number of subjects at risk who met the criterion at least once post baseline.
m: Number of subjects at risk.

5.4.10. Post marketing experience

In the most recent PSUR covering the period from 29-Apr-2023 to 28-Oct-2023, there has been no change in the risk profile and missing information. It will continue to be reviewed in next PSURs. The assessment of the safety topics of interest in the most recent PSUR is consistent with assessment of the clinical study data. According to the MAH's statement, no new safety signals and/or substantial changes to the safety profile of the drug were identified based on the review of the post marketing experience data. However, this information is only correct for the approved 40 mg b.i.d. asciminib dose, while the now applied 200 mg b.i.d. dose is five-fold higher and an increase in toxicity can be reasonable presumed.

As an example, with the 200 mg b.i.d. dose, a significant increase in arterial occlusive and pancreatic events was observed in the very limited population available to date, the relevance of the available post-marketing for the T315I population seemed limited.

5.4.11. In vitro biomarker test for patient selection for safety

Not applicable.

5.4.12. Overall discussion and conclusions on clinical safety

Discussion

Scemblix (40 mg bid) is currently approved in the EU for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors.

In this variation procedure, the MAH applied for an **extension of indication in the CML subpopulation of adult CML patients with T315I mutation**. This mutation is resistant to treatment with other CML-TKIs with the exception of Iclusig (ponatinib), the only TKI-treatment option which has shown efficacy in this CML subpopulation, but with a non-negligible safety profile characterised by a very high-rate cardiovascular adverse events, which are probably dose-dependent.

For the new indication **a five-fold higher posology (200 mg b.i.d) asciminib is currently applied**, compared with the 40 mg b.i.d asciminib dose currently in the approved late-line indication. Therefore, it can be expected that dose-dependent safety risks are probably more pronounced and more frequent than in the approved CML population.

The **safety evaluation of asciminib in the new indication is based nearly exclusively on the data from the T315I positive adults with Ph+ CML-CP in the Phase I/II trial (Study X2101).** Some supportive safety information in the T315I target population was submitted from 31 subjects from a retrospective Phase 4 study A2004. However, impact of this trial's data for the overall safety assessment appears to be very low not only due to the retrospective and explorative mode of evaluation. Whether this database in the absence of a head-to-head comparison with the approved comparator Iclusig is sufficient to approve the applied indication may be challenged in principle. It is worth noting that with ~ 4000 patients with this mutation in the EU, a comparative trial against the approved comparator Iclusig would likely have been feasible.

Exposure: The recommended dose for the CML target population harbouring the T315I mutation is 200 mg twice daily at approximately 12-hour intervals. The median duration of exposure to asciminib single agent in 70 patients with CML-CP harbouring the T315I mutation in Trial X2101 was 136.6 weeks at data cut-off for this application. **Insofar, the length of follow-up is seen as sufficient.** However, it appears critical that **only 48/70 (68%) patients with CML-CP harbouring the T315I mutation in trial X2101 received the applied posology**. Moreover, **only 34 (48%) of the subjects who received 200 mg b.i.d. were able to reach a relative dose intensity of >90%.**

These findings indicate that safety profile of the applied posology can be assessed reliably only from 34/70 patients in the target population, which is very limited. Potential differences with respect to the established safety profile of the approved 40 mg b.i.d. dose are not reliably evaluable from the currently available data. Moreover, this may indicate a significantly lower tolerability compared with the approved dose of 40 mg b.i.d. since adverse events were the most frequent reason for dose interruption of asciminib in 26/70 (37.1%) patients. **In consequence, it is probable that the presented safety profile does not fully reflect the safety risks of the now applied posology as mentioned in a special warning in the SmPC section 4.4.**

With the responses, the MAH has provided the requested safety tables allowing a direct comparison between the safety profile of the approved 40 mg b.i.d. dose and the applied 200 mg b.i.d. posology for the T315I subpopulation. It is acknowledged that the overall safety profile may be considered similar in terms of total as well as drug related TEAES, SAE, Grad≥3 events and fatal SAEs. However, for GI toxicity and hepatotoxicity (inc. lab) higher event rates (>10% incidence rate difference) occurred in the 200 mg b.i.d. compared to the 40 mg b.i.d. pool data. Similarly, frequencies of musculoskeletal and connective tissue disorders were significantly more frequent in the 200 mg b.i.d. treated population.

Additional information clarified also that ponatinib pre-treatment appears not to decrease tolerability of asciminib after ponatinib in the small groups investigated. The incidence as well as severity of AEs in the 29 ponatinib-pretreated and the 19 ponatinib-naïve subjects was rather similar. However, the incidence as well as severity of AEs in both groups is likely to be affected by the variable extent based on pre-treatment with other TKIs which might have biased the result.

AEs that occurred **most frequently** (≥ 40% of patients) were in the **system organ classes** (SOCs) of musculoskeletal and connective tissue disorders (58.3%), investigations, infections and infestations (56.3% each), GI disorders, general disorders and administration site conditions (50.0% each) and skin and subcutaneous disorders and nervous system disorders (47.9% each).

The **most frequent AEs by PT** reported in ≥ 20% of patients were **fatigue (31.3%)**, **lipase increase (29.2%), diarrhoea and nausea (27.1% each),** COVID-19 and cough (22.9% each), **arthralgia, headache, vomiting, and ALT increased (20.8% each).**

It is noted that between the 80.8 weeks-and the 136.6 weeks cut off no relevant change in the severity of the AEs (grade ≥3 58.6% vs 61.4%), the **frequency of SAEs (30.0% vs 37.1%)** and the **AEs leading to dose adjustment/interruption (34.3% vs 40.0%)** nor with respect to the **AEs leading to treatment discontinuation (8.6% vs 11.4%)** occurred.

The **most frequent (≥ 10% of patients) treatment-related AEs** were lipase increased (22.9%), nausea (18.8%), fatigue and diarrhea (14.6% each), arthralgia, ALT increased, and thrombocytopenia (12.5% each), pruritus, headache, amylase increased, vomiting, and musculoskeletal pain (10.4% each).

A total of **4 on-treatment deaths** were reported during study X2101; the reasons were reported as underlying disease, suicide with depression, COVID-19 pneumonia and **myocardial infarction**. The last two were in the asciminib 200 mg b.i.d. cohort (2/48). Neither of these two fatal events was considered to be related to study treatment. In the supportive study A2004, in total 4**/**31 (13%) patients died. Two while on treatment (underlying disease and fungal infection) and two after discontinuing asciminib (**SAEs of cerebrovascular accident** and pneumonia led to death) however, none of the patients discontinued the study due to these SAEs.

In trial X2101, **grade ≥ 3 SAEs (regardless of study treatment relationship)** were reported in 18/70 (25.7%) patients with CML-CP harboring the T315I mutation. It appears that most of these events occurred in the 200 mg b.i.d. cohort, 14/48 (29.2%) patients had SAEs and most (11/48; 22.9%) had grade ≥ 3 SAEs. Similarly, in the supportive study A2004, 21 SAEs were reported in 9 of 31 patients (29.0%) during 200 mg b.i.d. asciminib treatment. The most common seriousness criteria was hospitalization (8 [25.8%] patients). Out the 21 SAEs, fatal outcome was reported for 4 (12.9%) patients. The majority of these 21 SAEs, 19 SAEs were not related to asciminib treatment retrospectively.

Compared with the 40 mg b.i.d. population in trial A2301 the ≥3 grade SAEs were more frequent in the T315I population, as shown by an incidence rate of 15.4%. Overall, the number of individual SAEs in both studies was too low to conclude on any trends.

With respect to the **adverse event of special interest** the following adverse events were identified from the non-clinical and previous clinical data in asciminib's clinical development program: acute

pancreatitis (including isolated pancreatic enzyme elevations), myelosuppression, hypersensitivity, hepatotoxicity (including hepatic enzyme elevations), hepatitis B virus reactivation, reproductive toxicity, GI toxicity, phototoxicity, QTc prolongation, cardiac failure, edema and fluid retention, ischemic heart disease , central nervous system (CNS) conditions, haemorrhage and arterial occlusive events (AOE).

Arterial-occlusive events (AOEs)'/cardiovascular events: In the 200 mg b.i.d. cohort, arterial occlusive events were reported in 6/48 (12.5%) patients; Grade 3 events were reported in 2/48 (4.2%) patients, and one had a grade 4 event. In terms of PTs, cerebrovascular accident (6.3%) and peripheral arterial occlusive disease (4.2%) were most frequent.

AEs pertaining to the definition of ischemic heart and CNS conditions also caused due to disturbance in the arterio-vascular system were reported in 7/48 (14.6%) patients and increased with 4 additional patients since Primary Analysis data cut-off Grade≥ 3 AEs were reported in 2 (4.2%) patients and grade 4 AE was reported in 1 (2.1%) patient. The MAH reported two additional patients on the 200 mg b.i.d. dose with SAEs of AOE and one additional patient developed SAE event of "peripheral ischaemia".

Two **fatal AEs** of cerebrovascular accident and myocardial infarction were reported each in 1 (2.1%) patient. Considering the very small number of patients exposed, this important risk remains not fully evaluable, but an increase of frequency with the 200 mg b.i.d. dose appears probable.

Although the observed incidence of ischemic heart and CNS condition events may also be explained in these patients at least partially by multiple other confounding factors/underlying conditions (including ponatinib pretreatment), the impact of asciminib in the development of these events remains uncertain in particular, since the mechanism behind the increased AOE rate with ponatinib is unknown.

Considering the experience with the high rates of thromboembolic complication revealed after longer exposure with high dose ponatinib, this possibly dose related risk remains an important uncertainty regarding the safety of the applied high dose 200 mg b.i.d. dose particularly since it contributes to the observed fatal outcome in two patients in this small subgroup.

Tyrosine Kinase Inhibitors (TKIs) as asciminib can have significant impacts on **cardiac function**, including potential cardiotoxicity. These impacts range from hypertension and arrhythmias to heart failure and reduced left ventricular ejection fraction (LVEF). The mechanisms behind these effects are complex, incompletely understood and involve both on-target and off-target effects of TKIs on cardiac cells.

In the pivotal trial for the approved indication, **QTc prolongation** related events were reported in 4 patients in the asciminib group. Appropriate warnings regarding QT prolongation and combination with drugs known to cause Torsade de Pointes have been included in the SmPC. In the pivotal population, 1/48 (2.1%) patient had a grade 3 SAE of ventricular tachycardia event, which was though probably not related according to the provided clarification and the issue that hERG inhibition provides an estimated safety margin > 30-fold even when compared to free Cmax exposure even in subjects at therapeutic dose of 200 mg b.i.d.

Pancreatic toxicity appears to be a dose-dependent, drug related class risk for most CML TKIs. The pancreas was identified as a toxicity target organ in nonclinical studies. The mechanism of action of pancreatitis is not completely understood at this time but also known for other TKIs. In the 200 mg b.i.d. cohort, pancreatic enzyme elevations (including acute pancreatitis) occurred in 15/48 (31.3%) patients, compared with 13/156 (8.3 %) with the 40 mg b.i.d. posology in the third line population. Difference in toxicity become even more pronounced, if the grade 3/4 events are analysed: 200mg: 22.9% versus 40 mg: 3.8%. Although none of these events were serious or fatal, long-term consequences (pancreatic destruction/diabetes mellitus etc) are probable and since not all events resolved chronic pancreatitis may develop. This remains a clear safety risk for the applied 200 mg b.i.d. posology, which has led to treatment discontinuation and is further monitored as detailed in the RMP.

Hepatotoxicity with the 200 mg b.i.d. cohort, AEs pertaining to the definition of hepatotoxicity were reported in 15/48 (31.3%) patients. Grade 3 events reported in 6/48 (12.5%) patients and no grade 4 event was reported. Elevation in transaminases (ALT or Aspartate aminotransferase [AST]) > 3 x upper limit of normal (ULN) post-baseline were noted in 8/48 (16.7%) patients. Compared with the outcome for the 40 mg b.i.d. dose, the incidence was again significantly higher as shown by 3.8 % for ALT/AST > 3 x ULN and for total bilirubin > 2 x ULN, which was reported in 1/48 (2.1%) patient (40 mg bid: 0.6) in trial A2301.

Thus, a significant increase regarding hepatotoxicity in terms of ALT/AST and bilirubin elevations was observed with the 200 mg b.i.d. dose compared with the 40 mg b.i.d. dose. More clarification regarding the clinical relevance of the risk is expected from further post-marketing data sources and should be provided as part of future PSURs.

Gastrointestinal toxicity events (nausea, diarrhoea, vomiting, constipation, abdominal pain, non-cardiac chest pain) were reported in 24/48 (50.0%) patients [5/48 (10.4%) assessed as drug related]. Grade 3 events were reported in 5/48 (10.4%) patients of whom 3 (6.3%) were classified as SAEs. Compared with the 80mg dose (GI TEAS; 31.4%), the limited data indicate a higher GI toxicity which can be expected.

Oedema and fluid retention: In the 200 mg b.i.d. cohort, AEs pertaining to the definition of oedema and fluid retention were reported in 9/48 (18.8%) patients (most common PT: peripheral); grade 3 events were reported in 3/48 (6.3%) patients, and no grade 4 event was reported. **Hypersensitivity events** not further differentiated were reported in 16/48 (33.3%) patients (drug related: 10/48; 20.8%), the only Grade 3 SAE event reported was a jodid allergy not related to asciminib.

Myelosuppression-related events are very common during TKI treatment and are considered to be due to the combined effect of suppression of the leukemic clone and inhibition of non-leukemic haematopoiesis. In the 200 mg b.i.d. cohort, AEs pertaining to the definition of myelosuppression were reported in 14/48 (29.2%) patients (3 additional patients since Primary Analysis data cut-off), with grade 3/4 events reported in 10/48 (20.8%) patients (1 additional patient since Primary Analysis data cut-off). Thrombocytopenia (16.7%; grade 3/4: 10.4%) was the most frequent event in this SOC, but AEs pertaining to the definition of haemorrhage were reported in 10/48 (20.8%) patients ((one SAE haemorrhage). One patient discontinued treatment due to neutrophil count decreased, platelet count decreased, and pancytopenia.

In the significantly larger and less heterogenous CML population (TD: 80 mg) of the pivotal trial A2301 for the approved indication, myelotoxic events were reported more frequent with 37.8% for the asciminib treated subjects, which appears counterintuitive considering the total daily dose (TD) of 400 mg.

Myelosuppression related events appear generally reversible and manageable with appropriate monitoring, and dose interruption/modification as clinical practise recommends. Moreover, it needs to be considered that some of these adverse events may be caused also by the disease itself.

In the 200 mg b.i.d. cohort, **haemorrhage** events were reported in 10/48 (20.8%) patients. One patient had grade 3 SAE of post procedural haemorrhage, which resolved at the cut-off date. No grade 4 events were reported. None of these events required dose adjustment/interruption, led to treatment discontinuation or were fatal. All these AEs was resolved at the time of data cut-off date for this report.

Assessing **treatment discontinuation due to AE's** in the T315I -CML it is important to consider that patients pretreated with ponatinib have no treatment alternative beside transplantation (HSCT). This means that these patients generally may be prepared to accept a higher degree of toxicity compared with subjects with other treatment alternatives. Among 48 patients in the 200 mg b.i.d. cohort, 5 (10.4%) patients had AEs that led to treatment discontinuation. While two subjects had COVID-19 pneumonia, pancytopenia, thrombocytosis, increase lipase, neutrophil count decreased, platelet count

decreased in one patient each, were suspected to be treatment-related. 15/48 (31.3%) patients had at least one treatment-related AE requiring dose adjustment/interruption. Lipase increase (14.6%) and thrombocytopenia (6.3%) were the most frequent AEs reported in at least 5% of patients. This outcome confirms the importance of pancreatic adverse events in the intended treatment. Whether increases of hyperglycaemia and development of diabetes mellitus events reflect long term consequences of chronic pancreatitis as consequence of TKI treatment remains uncertain.

With respect to **safety in special populations**, no new information has been generated in support of this application. Considering that the investigated target population includes only 48 phase I trial subjects no analyses of extrinsic or intrinsic factors were performed. However, particularly for the elderly population this is an important lack of information. It remains completely unknown whether the reported safety risks are similar in subjects older than 65 years and how gender and body weight will affect tolerability of the 200 mg b.i.d. dose.

There is a still limited safety data in patients with **renal impairment** treated with the 40 mg b.i.d. dose, in fact, no patient with severe renal impairment was included in the asciminib studies. Therefore, treatment with the new five-fold higher dose in patients with mild to moderate renal impairment should be done cautiously until reliable data is available.

From the available results of the dedicated **hepatic impairment** study with 40 mg SD having investigated the impact of mild, moderate and severe hepatic impairment on the PK of asciminib, the MAH recommended no dose adjustment in patents with hepatic impairment of any severity and dose. For the five-fold higher dose of 200 mg b.i.d. for the T315I-CML subpopulation, further explanations were included in section 4.2 of the SmPC to justify the lack of dose adjustment for hepatic and renal impaired patients.

It is acknowledged that based on the data from Study X2101, including the very limited experience from one patient in whom the highest investigated dose of 280 mg b.i.d. had been administered up to a period of 2.5 years, and the expected benefit of asciminib in the very rare population with T315I mutation with limited therapeutic options, a contraindication is currently not warranted in subjects with mild, moderate and severe renal or hepatic impairment for the asciminib 200 mg b.i.d. on the grounds of safety. Thus, the proposed dosing recommendations regarding the renal and hepatic impairment populations in sections 4.2, 4.4 and 5.2 of the proposed EU SmPC are acceptable. A warning has been included in the product information highlighting that, due to missing clinical experience, no final dose recommendations can be given for severely organ impaired populations, as detailed in the discussion in the PK section above.

The impact of asciminib on warfarin and other oral Vitamin K antagonists (at 200 mg b.i.d.) remains unknown. The data (safety and especially PK) available for concomitant administration of statins are currently limited and too variable to allow conclusions on the effect size of asciminib as precipitant on BCRP/OATP1B substrates like statins and clinical effects. The MAH committed to address these issues in the next PSURs and to summarise data available from postmarketing sources for the doses, both combined and separately, and to discuss these issues in this context (see also PK section above).

No new safety signals and/or substantial changes to the safety profile of the drug were identified based on the review of the **post marketing experience data**. However, this information is only robust for the approved 40 mg b.i.d. asciminib dose, while only 33 cases were identified since approval of the now applied 200 mg b.i.d. dose in the US. Considering the five-fold higher dose, an increase in toxicity can be reasonable presumed but is not evident from the limited data at present. Since regarding the 200 mg b.i.d. dose a signal of a significant increase in arterial occlusive and pancreatic events appears possible, the relevance of the available post-marketing for the T315I population is currently low. Further evaluation of post-marketing data should reflect and report potential differences in the PSURs.

Adverse drug reactions (ADRs) in the SmPC

With respect to ADRs in the proposed SmPC the MAH propose the following table in SmPC section 4.8:

Table 35 SmPC Table 2 Adverse reactions observed with asciminib in clinical studies

System organ class	**Frequency category**	**Adverse reaction**
Infections and infestations	Very common	Upper respiratory tract infection[1]
	Common	Lower respiratory tract infection[2], influenza
Blood and lymphatic system disorders	Very common	Thrombocytopenia[3], neutropenia[4], anaemia[5]
	Uncommon	Febrile neutropenia, pancytopenia
Immune system disorders	Uncommon	Hypersensitivity
Endocrine disorders	Common	Hypothyroidism[6]
Metabolism and nutrition disorders	Very common	Dyslipidaemia[7]
	Common	Decreased appetite, hyperglycaemia
Nervous system disorders	Very common	Headache, dizziness
Eye disorders	Common	Dry eye, vision blurred
Cardiac disorders	Common	Palpitations
Vascular disorders	Very common	Hypertension[8]
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Pleural effusion, dyspnoea, non-cardiac chest pain
Gastrointestinal disorders	Very common	Pancreatic enzymes increased[9], vomiting, diarrhoea, nausea, abdominal pain[10], constipation
	Common	Pancreatitis[11]
Hepatobiliary disorders	Very common	Hepatic enzyme increased[12]
	Common	Blood bilirubin increased[13]
Skin and subcutaneous tissue disorders	Very common	Rash[14], pruritus
	Common	Urticaria
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[15], arthralgia
General disorders and administration site conditions	Very common	Fatigue[16]
	Common	Oedema[17], pyrexia[18]
Investigations	Common	Blood creatine phosphokinase increased
	Uncommon	Electrocardiogram QT prolonged

1	Upper respiratory tract infection includes: upper respiratory tract infection, nasopharyngitis, pharyngitis and rhinitis.
2	Lower respiratory tract infections include: pneumonia, bronchitis and tracheobronchitis.
3	Thrombocytopenia includes: thrombocytopenia and platelet count decreased.
4	Neutropenia includes: neutropenia and neutrophil count decreased.
5	Anaemia includes: anaemia, haemoglobin decreased and normocytic anaemia.
6	Dyslipidaemia includes: hypertriglyceridaemia, blood cholesterol increased, hypercholesterolaemia, blood triglycerides increased, hyperlipidaemia and dyslipidaemia.
7	Hypertension includes: hypertension and blood pressure increased.
8	Pancreatic enzymes increased includes: lipase increased, amylase increased and hyperlipasaemia.
9	Abdominal pain includes: abdominal pain and abdominal pain upper.
10	Pancreatitis includes: pancreatitis and pancreatitis acute.
11	Hepatic enzymes increased includes: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, transaminases increased and hypertransaminasaemia.
12	Blood bilirubin increased includes: blood bilirubin increased, bilirubin conjugated increased and hyperbilirubinaemia.
13	Rash includes: rash, rash maculopapular and rash pruritic.
14	Musculoskeletal pain includes: pain in extremity, back pain, myalgia, bone pain, musculoskeletal pain, neck pain, musculoskeletal chest pain and musculoskeletal discomfort.
15	Fatigue includes: fatigue and asthenia.
16	Oedema includes: oedema and oedema peripheral.
17	Pyrexia includes: pyrexia and body temperature increased.

Conclusions on clinical safety

Overall, results presented indicate that the treatment of asciminib 200 mg b.i.d. in patients with CML CP harbouring the T315I mutation is probably more toxic than at the 40mg dose but might be tolerable for patients with no other treatment alternative beside HSCT.

Asciminib's safety profile in general is characterised by a significant gastrointestinal toxicity, particularly pancreatic and hepatic toxicity, myelotoxicity and arterio-occlusive events (including fatal events).

However, the level of tolerability relies upon limited data from the phase I trial X2101 and remains uncertain since safety evaluation of the five-fold higher dose (compared with that currently approved) is based only on outcome in 48 subjects of whom only 34 had the needed treatment intensity of >90 % to establish reliably durable efficacy.

A warning regarding this uncertainty has been included in the SmPC and PL. Similarly, those events for which the current data may indicate a higher risk have been explicitly mentioned in the product information to inform patients, to increase the treating physician's vigilance for such events and to adapt the patient's monitoring for such events.

6. Risk management plan

The MAH submitted an updated RMP version 3.0 (sign-off 14 February 2025) with this application. Addressing the request from the list of questions, the MAH submitted updated RMP version 3.1 (sign-off 25 September 2025) and version 7.0 (signed off 19 January 2026).

Only significant changes are addressed in this AR.

Rationale for submitting an updated RMP:

This EU Risk Management Plan (RMP) update was prepared to support the new indication of use of asciminib for the treatment of adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP) (hereafter referred to as Ph + CML-CP) with the T315I mutation who are resistant to, intolerant to or ineligible for ponatinib.

Summary of significant changes in the RMP:

- Updated the proposed expanded indication of use of asciminib and dosage in adult patients with Ph + CML-CP with T315I mutation who are resistant to, intolerant to or ineligible for ponatinib.
- Updated epidemiology details for Ph + CML-CP with T315I mutation.
- Post-marketing experience data was updated from the PSUR (reporting interval: 29-Oct-2023 to 28-Apr-2024).
- Exposure and safety data from CABL001X2101 First-In-Human study (X2101, FIH) has been added to support the proposed expanded indication.
- Included evaluation of the safety profile of the 200 mg b.i.d. dose within the PSURs as other routine pharmacovigilance activity.
- Data across the sections of the document is aligned with the proposed Summary of Product Characteristics (SmPC).

6.1. Safety specification

The MAH updated this part of the RMP with the relevant data on patients with T315I mutation treated with 200 mg dose per each relevant safety concern.

The MAH also updated the important potential risk of reproductive toxicity with cumulative data on experience of foetal outcomes in human pregnancy with maternal exposure and birth type reported across the indications. These data were assessed in the most recent PSUSA procedure. No new or significant information has been identified based on the presented data.

6.1.1. Proposed safety specification

No changes of the safety specification were proposed.

Table 36 Summary of safety concerns in the proposed RMP

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

6.1.2. Discussion on proposed safety specification

Only 48 subjects of the 70 subjects with CML CP harbouring the T315I mutation are in the safety database. Moreover, of these 48 subjects only 34 subjects had a treatment intensity of >90 % normally needed to establish efficacy and reflect the safety of the 200 mg b.i.d. dose. It should be acknowledged, that data provided with this application are very limited which significantly hamper the assessment of events reported in low frequencies.

There are issues raised on arterial occlusive events, ischemic heart and CNS conditions and cardiotoxicity as a class effect of TK inhibitors.

Considering that no such risks have been identified in both 40 mg b.i.d. and 200 mg b.i.d. dosing populations, current data does not suggest any issue that would have a significant impact on benefit-risk profile of this medicinal product. Thus, no new safety concern is proposed.

Collection of additional safety data to further characterise the safety risks associated with the dose of 200 mg b.i.d. compared to that known for the approved 40 mg b.i.d. dose in the post-marketing setting as proposed in the pharmacovigilance plan will be valuable.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

Routine pharmacovigilance activities beyond ADRs reporting and signal detection

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

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

- Arterial occlusive events (including ischemic heart and CNS conditions plus arterial embolic and thrombotic events).
- Evaluation of the safety profile of the 200 mg b.i.d. dose

6.2.2. Discussion on the Pharmacovigilance Plan

The MAH has proposed the following changes of the routine pharmacovigilance activities:

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

- ~~Hyperglycemia~~

The Applicant did not propose any changes to the additional pharmacovigilance activities.

1.1.1.1. Routine pharmacovigilance activities

The MAH removed hyperglycemia from the list of issues closely monitored within PSURs. This was agreed upon during the most recent PSUSA procedure, in relation to the monitoring of patients treated with 40 mg dose of asciminib.

In addition to the arterial occlusive events and considering that the 200 mg dose represents a 5-fold dose of asciminib compared to the currently approved 40 mg dose, the MAH agreed to evaluate its safety profile separately within the PSURs.

1.1.1.2. Additional pharmacovigilance activities

No study has been proposed by the Applicant. This is acknowledged. Instead, the safety profile of the 200 mg b.i.d. dose will be further evaluated post-marketing via routine pharmacovigilance and reported within PSURs.

6.3. Plans for post-authorisation efficacy studies

None proposed.

6.4. Risk minimisation measures

Proposed risk minimisation measures

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

Safety concerns	Routine risk minimization activities
	monitored for signs and symptoms of acute pancreatitis (including isolated pancreatic enzyme elevations). More frequent monitoring should be performed in patients with a history of pancreatitis. If lipase and amylase elevation are accompanied by abdominal symptoms, treatment should be temporarily withheld and appropriate diagnostic tests should be considered to exclude pancreatitis. Based on the severity of lipase and amylase elevation, the dose should be reduced, temporarily withheld or permanently discontinued. **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product
Myelosuppression	**Routine risk communication** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC Section 4.4 includes following recommendations: Complete blood counts should be performed every 2 weeks for the first 3 months of treatment and then monthly thereafter, or as clinically indicated. Patients should be monitored for signs and symptoms of myelosuppression. Based on the severity of thrombocytopenia and/or neutropenia, the dose should be reduced, temporarily withheld or permanently discontinued. **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product
QTc prolongation	**Routine risk communication** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.5 SmPC Section 4.8 SmPC Section 5.1 PL Section 2 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC Section 4.4 includes following recommendations: It is recommended that an ECG is performed prior to the start of treatment with asciminib and monitored during treatment as clinically indicated. Hypokalaemia and hypomagnesaemia should be corrected prior to asciminib administration and monitored during treatment as clinically indicated. Caution should be exercised when administering asciminib **at 40 mg twice daily** concomitantly with medicinal products known to cause Torsades de Pointes. **Concomitant administration of asciminib at 200 mg twice daily with medicinal products with a known risk of *torsades de pointes* should be avoided.** **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product
Important potential risks	
Hepatotoxicity	**Routine risk communication** SmPC Section 4.2

Safety concerns	Routine risk minimization activities
	SmPC Section 4.8 SmPC Section 5.2 PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product
Hepatitis B virus infection reactivation	**Routine risk communication** SmPC Section 4.4 PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC Section 4.4 includes following recommendations: Patients should be tested for HBV infection before the start of treatment with asciminib. Hepatitis B virus carriers who require treatment with asciminib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product
Reproductive toxicity	**Routine risk communication** SmPC Section 4.6 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**

Safety concerns	Routine risk minimization activities
	SmPC Section 4.2 states that no dose adjustment is required in patients with mild, moderate or severe renal impairment. **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product
Use in patients with hepatic impairment	**Routine risk communication** SmPC Section 4.2 SmPC Section 5.2 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC Section 4.2 states that no dose adjustment is required in patients with mild, moderate or severe hepatic impairment. **Other routine risk minimization measures beyond the Product Information** Legal status: Medical prescription only product

Discussion on the risk minimisation measures

Routine risk minimisation measures

Routine risk minimization activities as described in Part V.1 are considered sufficient to manage the safety concerns of the medicinal product provided the MAH implements the changes requested by the CHMP.

Additional risk minimisation measures

Not applicable

Patients engagement on the risk minimisation activities

Not applicable

6.5. RMP Summary and RMP Annexes overall conclusion

The RMP Part VI and the RMP Annexes should be amended in line with other changes of the RMP.

6.6. Overall conclusion on the Risk Management Plan

☒ The PRAC and CHMP consider that the updated risk management plan version 7.0 is acceptable.

7. Pharmacovigilance

Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.1. Periodic Safety Update Reports submission requirements

The scientific opinion holder shall submit periodic safety update reports for this product in alignment with the requirements for the centrally authorised product as set out in the list of Union reference dates (EURD list) and any subsequent updates published on the European medicines web-portal.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

SmPC section 4.1 justification

The initially requested new indication was independent of treatment-line, pre-treatment with ponatinib and MMR status at treatment initiation ("treatment of adult patients with Ph+ CML-CP harbouring the T315I mutation").

The indication was finally restricted to patients resistant to, intolerant to or ineligible for ponatinib (see Benefit-Risk assessment section).

The approved indication is aligned with the population studied in the pivotal clinical trial.

8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Scemblix (asciminib) is included in the additional monitoring list since it contains a new active substance.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

Therapeutic context

9.1.1. Disease or condition, therapeutic indication

Philadephia chromosome positive CML is a rare disease with a prevalence 1:17000 in EU and an incidence 1.2 - 1.5:100000. With introduction of TKIs, the prognosis improved so much, that for responding disease, patients can expect near normal life expectancy.

T315I mutation occurs in 1-5% of CML patients, mostly while on treatment. Expected overall survival is substantially shorter in this subpopulation, 5-year OS-rate of 66% was reported for patients with CML the T315I mutation (Cortes, Kim et al. 2018). CML T315I is resistant to all approved TKI, with the exception of ponatinib. Asciminib is a potent inhibitor of ABL/BCR::ABL1 tyrosine kinase inhibiting the ABL1 kinase activity of the BCR::ABL1 fusion protein, by specifically targeting the ABL myristoyl pocket, while other TKI target the ATP pocket.

The new indication included in this procedure is:

Scemblix is indicated for the treatment of adult patients with Ph+ CML-CP with the T315I mutation who are resistant to, intolerant to or ineligible for ponatinib.

The applied dose regimen for the new indication is 200 mg b.i.d orally, which is 5x higher than the currently approved dose regimen of 40 mg b.i.d. orally.

9.1.2. Available therapies and unmet medical need

Since 2013, ponatinib is approved in the EU for CML with T315I mutation in chronic phase, accelerated phase and blast phase. Approval of ponatinib for CML with T315I mutation in chronic phase was based on a cohort of the PACE Trial, a single-arm, open-label, international, multicentre trial which enrolled 64 patients with CML with T315I mutation in chronic phase and reported an MMR of 58%. In 2018, 5-year OS rate of 66% was reported for patients with CML harbouring the T315I mutation (Cortes, Kim et al. 2018). Later, the OPTIC trial reported a 4-year OS rate for CML-T315I of 86% for ponatinib 45mg/qd group (Deininger, Apperley et al. 2024).

In case of suboptimal response allogeneic stem transplantation, which is the only treatment option with curative potential, should be considered.

In view of the treatment recommendation for and availability of ponatinib there are different subpopulations in CML-CP with T315I mutation in chronic phase with potentially different benefit-risk aspects which were included in the initially applied indication above:

For patients not in MMR (induction of remission) e.g.:

1. CML-CP with the T315I mutation and ponatinib-naïve
2. CML-CP with the T315I mutation and ponatinib-intolerant
3. CML-CP with the T315I mutation and relapsed after or refractory to ponatinib

For patients in MMR after pre-treatment with ponatinib and/or allogeneic stem cell transplant e.g.:

4. CML-CP with the T315I mutation and ponatinib-intolerant
5. CML-CP with the T315I mutation and have other reasons to switch

9.2. Main clinical studies

The application is based on clinical data from the single pivotal study X2101, being a non-randomised, uncontrolled, open-label, multi-cohort, first-in-human Phase 1/2 study with a dose escalation and a consecutive dose expansion phase exploring asciminib as monotherapy and combination therapy mostly in CML patients. Study X2101 was analysed and amended multiple times. The population of adult patients with Ph+ CML-CP with a T315I mutation (i.e. the targeted population of this application for extension of indication) is a post-hoc defined subpopulation of Arm 1 in this study. It includes 45 patients not in MMR at screening and treated with the intended dose of 200 mg bid. Recruitment of the whole study started in April 2014 (FPFV), study was completed in March 2023 (LPLV).

Study X2101 was already submitted as supportive evidence in the dossier of the initial MAA of Scemblix in April 2022. Subsequently, the final CSR was submitted for variation EMEA/H/C/005605/II/0017. The efficacy and safety results for the target population with T315I were already included but not the primary focus.

In addition, real-world data from the market access program (MAP), the chart review A2004, were submitted as supportive data.

9.3. Favourable effects

X2101

Efficacy results are available for 45 patients in CML-chronic phase harboring the T315I mutation who were not in MMR at screening and received the new dose regimen of 200 mg b.i.d.; 26 patients were pre-treated with ponatinib, and 19 patients were ponatinib-naïve.

MMR (MR3) by week 24 - was reported for 19/45 patients, i.e. 42.2% (95% CI 27.7-57.8%).

In **ponatinib-naïve patients**

- MMR (MR3) by week 24**: 11/19 patients, i.e. 57.9%** (90% CI 36.8-77%) and
- MR 4.5 by week 48: 8/19 patients

In **ponatinib-pre-treated patients**

- MMR (MR3) by week 24: **8/26 patients 30.8%** (90% CI 16.3-48.7),
  incl. 3/13 ponatinib resistant patients;
  incl. 4/7 ponatinib intolerant patients
- MR 4.5 by week 48: 4/26 patients;
  incl 1/13 ponatinib resistant patients
  incl. 3/7 ponatinib intolerant patients

Exposure of at least 144 weeks was reported for 27/45 patients (56.3%).

RWD chart review A2004

The supportive RWD chart review A2004 enrolled 31 patients from the MAP and analysed an observation period of one year.

19 patients were not in MMR at enrolment and were treated with the intended dose. 4/19 patients not in MMR (21.1%) achieved MMR by 6 months.

12 patients in MMR at enrolment and were treated with the intended dose.

9.3.1. Uncertainties and limitations about favourable effects

The efficacy claims are based on a single pivotal uncontrolled open-label phase I/II study.

The exploratory nature of the study, the implementation of major protocol amendments potentially based on study data and lack of hypothesis testing, are major sources of uncertainty in the interpretation of the results.

Due to the non-randomised, uncontrolled, open-label design, the risk of bias and more particularly the selection of patients, cannot be eliminated.

The indication applied for is based on a post-hoc defined subpopulation of the pivotal study with a limited number of patients.

Patients in MMR at baseline

The only source is the RWD chart review A2004.
Uncertainty due to the extremely limited strength of evidence remain: data source is retrospective secondary use with inherent potential selection bias, heterogeneity in data availability, potential

selection bias and immortal time bias, uncertainty about representativity of the MAP patients, number of missing observations for primary and secondary endpoints, observation period at maximum 1 year.

Uncertainty also remain on the clinical meaning of MMR in the absence of data on depth of response at baseline and during treatment which were not reported. In addition, evidence is limited to data of 12 patients, 3/12 following SCT, with no detailed information on depth of response at baseline and during treatment.

9.4. Unfavourable effects

All patients with CML-CP harbouring the T315I mutation (n=70), treated with any dose of asciminib single agent had at least one AE regardless of study treatment relationship. AEs ≥3 grade occurred in 60.4% of the 48 subjects. 37.5% had treatment related AEs ≥3 grade. SAEs were observed in 29.2% of the population, but only 4.2% were assessed as treatment related by the investigator. 10.4 % of the included subjects discontinued due to a safety event. 4 patients died (2 due to arterial occlusive events).

In the 200 mg b.i.d. cohort, **arterial occlusive events** were reported in 6/48 (12.5%) patients; majority of them were of CTCAE grade 1 or 2. Grade 3 events were reported in 2/48 (4.2%) patients, and grade 4 event was reported in 1 (2.1%) patient. The most frequent AEs reported (all grades, ⩾ 4% of all patients) by PT were Cerebrovascular accident (6.3%) and Peripheral arterial occlusive disease (4.2%). SAEs were reported in 4 (8.3%) patients. No patient required dose adjustment or temporary interruption. No patient had AOEs that led to treatment discontinuation. Concomitant medication or therapy was required in 4 (8.3%) patients. **Two patients had AOEs with fatal outcome: one event each for cerebrovascular accident and myocardial infarction. AOEs did not resolve in 5 (10.4%) patients at the time of data cut-off date. Although most of these patients had pre-treatment with ponatinib, it cannot be excluded that asciminib may contribute to AOEs.**

Pancreatic toxicity including acute pancreatitis and pancreatic enzyme elevations was reported in 15/48 (31.3%) patients., with grade 3/4 events reported in 11/48 (22.9%) patients (2 additional patients since the Primary Analysis data cut-off). Majority of these events (25.0% of patients) were suspected to be treatment related. Increased lipase (25.0%), increased GGT and increased amylase (12.5% each) were the most frequent grade 3/4 abnormality post-baseline noted in ⩾ 10% of patients. None of these events was serious or fatal. One patient discontinued treatment due to increased lipase. Most of these AEs resolved or were resolving at the time of Final Analysis data cut-off.

Myelosuppression related events were reported in 14/48 (29.2%) patients (3 additional patients since Primary Analysis data cut-off), with grade 3/4 events reported in 10/48 (20.8%) patients (1 additional patient since Primary Analysis data cut-off). The majority of these events (18.8% of patients) were suspected to be treatment related. None of these events was serious or fatal. One patient discontinued treatment due to neutrophil count decreased, platelet count decreased, and pancytopenia.

In the 200 mg b.i.d. cohort, haemorrhage events were reported in 10/48 (20.8%) patients (2 additional patients since Primary Analysis data cut-off); all except one of them were of CTCAE grade 1 or 2. One patient had grade 3 SAE of post procedural haemorrhage, which resolved at the cut-off date. No grade 4 events were reported. None of these events required dose adjustment/interruption, led to treatment discontinuation or were fatal. All these AEs were resolved at the time of data cut-off date for this report.

Hepatotoxicity events (including laboratory terms) were reported in 15/48 (31.3%) patients (3 additional patients since Primary Analysis data cut-off). **One patient had concurrent elevations of ALT or AST > 3 x ULN and total bilirubin > 2 x ULN and alkaline phosphatase < 2 x ULN**

meeting the Hy's law biochemical criteria. Grade 3 events were reported in 6/48 (12.5%) patients (1 additional patient since Primary Analysis data cut-off) and no grade 4 event was reported. Seven (14.6%) of 48 patients (1 additional patient since Primary Analysis data cut-off) were reported with events that were suspected to be treatment related. None of these events were serious, led to treatment discontinuation or were fatal. Most of these AEs resolved or were resolving at the time of Final Analysis data cut-off.

GI toxicity events were reported in 24/48 (50.0%) patients. Grade 3 events were reported in 5/48 (10.4%) patients, and no grade 4 event was reported. GI toxicity events suspected to be related to study treatment were reported in 14 (29.2%) patients. SAEs were reported in 3 (6.3%) patients. None of these events led to treatment discontinuation or were fatal. Most of these AEs resolved or were resolving at the time of data cut-off date.

Hypersensitivity events were reported in 16/48 (33.3%) patients (4 additional patients since the Primary Analysis data cut-off). The majority of the events were Grade 1-2 rash events. None of these events required dose adjustment/interruption, led to treatment discontinuation or were fatal. The majority of these AEs resolved at the time of Final Analysis data cut-off.

Oedema and fluid retention were reported in 9/48 (18.8%) patients (2 additional patients since Primary Analysis data cut-off); grade 3 events were reported in 3/48 (6.3%) patients, and no grade 4 event was reported. Individual PTs were infrequent with no AE reported in ≥ 10% of patients except for Oedema peripheral in 5 (10.4%) patients.

Musculoskeletal pain and back pain were reported in 29.2 % of the subjects, one of them had AEs ≥3 grade, drug relationship is uncertain.

9.4.1. Uncertainties and limitations about unfavourable effects

The safety database is very limited with 48/70 subjects with CML-CP harbouring the T315I mutation, of whom only 34 subjects had a treatment intensity of >90 % normally needed to establish efficacy and reflect the safety of the 200 mg b.i.d. dose. Differentiation between safety outcome in subjects who were pretreated with ponatinib and those who are ponatinib-naïve is not possible.

From the reported data, it can reasonably be presumed that safety risks as reflected by most of the identified drug related adverse events of special interest are significantly higher:

- Pancreatic toxicity including acute pancreatitis and pancreatic enzyme elevations was increased and in the small population investigated grade 3/4 events were reported in a quarter of the exposed. Moreover, long term consequences of the high dose treatment (e.g. pancreatic destruction/diabetes mellitus etc.) are currently not known. Considering that not all events resolved, and treatment discontinuation occurred in a population with no treatment alternative beside HSCT, this uncertainty regarding pancreatic toxicity of the 200 mg dose is very important. Moreover, chronic pancreatitis may lead to the development of diabetes mellitus.
- Data with the 200 mg b.i.d. dose led to a significant increase of hepatotoxicity in terms of ALT/AST and bilirubin elevations. Thus, uncertainty exists whether the increased hepatotoxicity of the 200 mg b.i.d. dose is tolerable at the end in a larger population.
- The increase of arterial-occlusive events (AOEs) and the occurrence of cardiovascular deaths in the 200 mg b.i.d. cohort is concerning since such a dose dependent increase in risk is also well known for ponatinib. While asciminib inhibits the myristoyl pocket of BCR-ABL1 which is needed to achieve efficacy in T315I-CML, off-target interactions with other pathways may occur and a relevantly increased risk of potential fatal cardiovascular events as observed with ponatinib

cannot be excluded. On the other hand, 5 of the 6 subjects with AOEs were pre-treated with ponatinib and may have confounded the AOEs.

- Tyrosine Kinase Inhibitors (TKIs) as asciminib can have significant impacts on cardiac function, including potential cardiotoxicity. These impacts range from hypertension and arrhythmias to heart failure and reduced left ventricular ejection fraction (LVEF). The mechanisms behind these effects are complex, incompletely understood and involve both on-target and off-target effects of TKIs on cardiac cells. No systematically evaluation echocardiography is available at present. Whether the applied increase of dose will lead also to an increase of this type of events is uncertain but can be reasonable presumed.

9.5. Effects Table

Table 37 Effects Table for Scemblix for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) with the T315I mutation who are resistant to, intolerant to or ineligible for ponatinib" (data cut-off: 14-Mar-2023)

Effect (short description)	Measure	Treatment	Uncertainties/ Strength of evidence	Reference
Favourable Effects				
		Asciminib 200 mg b.i.d. ponatinib-pretreated pts (N=26)		
Major molecular response (MMR) rate by 24 weeks % (90% CI)	**MR3 - 0.1% of BCR-ABL (IS)**	**8/26** **30.8%** **(16.3-48.7)**	SoE: **objective measure** Unc: Uncontrolled, open-label Phase I data **depths of responses by ponatinib treatment unclear**	**Study X2101**
Major molecular response (MMR) rate by 96 weeks %	**MR3 - 0.1% of BCR-ABL (IS)**	**9/26** **34.6 %**	SoE: **objective measure** Unc: Uncontrolled, open-label Phase I data **depths of responses by ponatinib treatment unclear**	
Duration of MMR Cumul. number of pt with response Estimated rate (95% CI) at 96 weeks		**10** **79 (52.5, 100.0)**	SoE: **objective measure** Unc: Uncontrolled, open-label Phase I data	

Unfavourable Effects				
Safety event n (%)		*Asciminib 200 mg b.i.d. N=48*	Uncontrolled, open-label Phase I data Robustness and Reliability questionable	Reference
Adverse events		***48 (100)***		**Study X2101**
AEs with grade >=3		**29 (60.4)**		
SAEs		**14 (29.2)**		
Fatal SAEs		**3 (6.3)**		
AEs leading to dose adjustment/ interruption		**21 (43.8)**		
AEs requiring additional therapy		**39 (81.3)**		
Safety topic				
Pancreatic enzyme elevations (including acute pancreatitis)		**15 (31.3)**		
Hepatotoxicity (including laboratory terms)		**15 (31.3)**		
GI toxicity		**24 (50.0)**		
Arterial-occlusive events (AOEs)**		**6 (12.5)**		
Ischemic heart disease		**5 (10.4)**		
Ischemic CNS vascular conditions		**4 (8.3)**		
Hypersensitivity		**16 (33.3)**		

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; <sBA: serum bile acids>; <PELD: paediatric end-stage liver disease>; <MELD: model for end-stage liver disease score>; <SBD: surgical biliary diversion>; <OLT: orthotopic liver transplantation>; <PE: primary endpoint>; <SE: secondary endpoint>; <OR: odds ratio>.

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

Efficacy

In general, the level of evidence of pivotal data discussed in this extension of indication procedure is low. This is due to the fact that efficacy claims are based on single pivotal study (study X2101), being a non-randomised, uncontrolled, open-label, multi-cohort, first-in-human Phase 1/2 study. Study X2101 was analysed and fundamentally amended multiple times. All patient populations discussed in this procedure are post-hoc defined subpopulations of this study. No scientific advice on the clinical

development in the sought indication was requested.

The initially requested new indication was independent of treatment-line, pre-treatment with ponatinib and MMR status at treatment initiation ("treatment of adult patients with Ph+ CML-CP harbouring the T315I mutation"). Thus, for the evaluation of efficacy different subgroups needed to be addressed to reflect the clinical decisions in view of different prognosis and alternative treatment options. For patients with CML-CP with the T315I mutation **not in MMR** the subgroups **ponatinib-naïve**, **ponatinib pretreated** (including ponatinib-intolerant and ponatinib-resistant) represent different clinical entities. **Pre-treated patients in MMR** at treatment initiation are a distinct patient group.

Ponatinib naïve patients not in MMR

As ponatinib was an approved efficacious treatment in CML-CP patients with the T315I mutation at the time of starting enrolment of the T315I cohort and recommended e.g. by ESMO, it would have been appropriate to consider a randomised controlled study design comparing asciminib to ponatinib or to focus on patients pre-treated with ponatinib. The severity, rarity of the condition, the safety issues which were addressed in the post-marketing studies for ponatinib, the well-organised study landscape in CML and the availability of scientific advice in the context of an orphan development would have enabled evidence generation pre-approval. Instead, the assessment of the efficacy in **ponatinib-naïve** patients (MMR (MR3) by week 24: 11/19 patients, i.e. 57.9%) was severely hampered by the absence of comparative data.

Indirect comparisons to PACE and OPTIC were presented but were not sufficiently robust for B/R assessment. For asciminib the cohort with 200 mg b.i.d. was selected, for ponatinib the 45 mg cohort is relevant. A recent publication of a matching-adjusted indirect comparison reported superiority of ponatinib (Garcia-Gutierrez, Huang et al. 2024). According to the MAH, the authors used premature data of X2101. Indeed, this may have resulted in an underestimation of the treatment effect of asciminib. The MAH presented a comparison of the crude MMR rates and an analysis using the publicly available "pre-MAIC and MAIC data from PACE and OPTIC". This is, however, also not appropriate for B/R assessment. Valid indirect comparison relies on the documented similarity of design and patient populations of the treatment options to be compared. In the absence of baseline characteristics for the OPTIC trial, this could not be verified. As comparative data to ponatinib are lacking and numbers are small, it could not be assessed from the submitted data whether the size of MMR rate, the depth of responses and the duration of responses is comparable or inferior to ponatinib treatment in ponatinib-naïve patients. The benefit in the subpopulation ponatinib-naïve remains uncertain.

Due to these fundamental limitations, the indication was restricted to patients resistant to, intolerant to or ineligible for ponatinib.

Ponatinib pre-treated patients not in MMR

Ponatinib pre-treated patients not in MMR with CML-CP harbouring the T315I mutation include subgroups of ponatinib-intolerant and ponatinib-resistant. Currently, for these patients the only efficacious treatment option is stem cell transplantation. As these patients were not in MMR at baseline, MMR by 6 months can be considered as an appropriate main endpoint. Although the numbers are small and the evidence generated in a single arm setting, an MMR rate of 30.8 % (8/26 patients) is considered to be relevant and may be of benefit, in particular for those achieving a deep and or durable MMR.

Ponatinib pre-treated patients in MMR at treatment initiation

For this clinical setting after pre-treatment with ponatinib and/or allogeneic stem cell transplant, the meaning of the endpoint MMR by 24 weeks is not obvious. For a robust assessment, detailed information on the depth of response at baseline and during treatment would be needed. In this application, the only data source was the RWD chart review A2004 with extremely limited strength of

evidence: the data source is retrospective secondary use with inherent potential selection bias, with heterogeneity in data availability, potential selection bias and immortal time bias, uncertainty about representativity of the MAP patients, number of missing observations for primary and secondary endpoints, and an observation period of a maximum of 1 year. Evidence was limited to data from 12 patients, including 3/12 following SCT. These data can neither be considered as sufficient nor robust for benefit-risk evaluation. Due to these fundamental limitations, the indication was restricted to patients resistant to, intolerant to or ineligible for ponatinib.

Safety

In general, asciminib's safety profile was adequately characterised during the initial approval procedure for the **40 mg b.i.d dose** and was assessed as tolerable and potentially favourable regarding safety compared with bosutinib in the third line CML indication.

Known safety risks are mainly due to gastrointestinal toxicity, particularly pancreatic and hepatic toxicity (one Hy's law case reported), myelotoxicity and significantly more arterio-occlusive / cardiovascular events.

For the treatment of the newly applied target population with CML-CP harbouring the T315I mutation a five-fold higher dose of **200 mg b.i.d.** is needed. According to general rules of safety pharmacology, a significantly higher degree of toxicity for this posology is expected and a trend in an increase in event rates and a higher degree of severity particularly for the adverse events of special interest is apparent from the limited data available.

Since the safety assessment for this dose is restricted to 48 subjects investigated in trial X2101 of whom only 34 subjects had an adequate treatment intensity of >90 %, it remains challenging to characterise reliably a potential increase of risk for the target population with this higher dose.

Safety data from the retrospective real-world study A2004 in patients with CML-CP harbouring the T315I mutation is less informative and not reliable for an adequate safety assessment.

Thus, risk evaluation of high-dose asciminib (200 mg bid) was based on a very small population. This hampered significantly the level of evidence of the risk assessment and uncertainties remain regarding potential increased toxicity for the 200 mg b.i.d. compared with the 40 mg dose.

From the limited database available, it appears that particularly the pancreatic and hepatic toxicity is significantly increased and tolerability may be challenged. Moreover, the increase of risk for arterial occlusive events (AOE) in general and the occurrence of cardiovascular and cerebrovascular cases of death is uncertain and generally seen as critical. However, since AOE data appears to be confounded by the pre-treatment with ponatinib, bias for such events is possible.

The absence of evidence for other safety signals in the few patients treated with the high dose regimen requires additional vigilance during treatment. Further risk assessment is warranted in line with the proposed routine pharmacovigilance included in the RMP together with the need for an intensified monitoring regarding potential adverse events during treatment.

Additionally, neither clinical nor pharmacokinetic data are available for the 200 mg b.i.d.dose in subjects with severe renal or hepatic organ impairment. Since PBPK modelling was not suitable for extrapolation to this 5-fold higher dose, no appropriately data-based dose recommendations could be made for these special populations with severe impairment.

In consequence, the uncertainties about the risks associated with the five-fold higher dose of 200 mg b.i.d. have been appropriately included in the product information to promote the physician's vigilance for these issues.

In light of the number of patients concerned in the EU (at least 2000-4000), it would be welcomed if randomised controlled data in ponatinib-naïve patients and patients in MMR were to be generated to support a future B/R assessment and potential extension of indication.

9.6.2. Balance of benefits and risks

The benefit risk balance in the restricted indication for adult patients with Ph+ CML-CP with the T315I mutation who are resistant to, intolerant to or ineligible for ponatinib is positive.

9.7. Benefit-risk conclusions

The benefit-risk is positive for the restricted indication:

"*Scemblix is indicated for the treatment of adult patients with Ph+ CML-CP with the T315I mutation who are resistant to, intolerant to or ineligible for ponatinib (see section 5.1)*"