# Assessment report

## Scemblix

International non-proprietary name: asciminib

Procedure No. EMEA/H/C/005605/0000

## Note

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

# Administrative information

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| Name of the medicinal product: | Scemblix |
| Applicant: | Novartis Europharm Limited<br>Vista Building<br>Elm Park<br>Merrion Road<br>Dublin 4<br>IRELAND |
| Active substance: | Asciminib hydrochloride |
| International Non-proprietary Name/Common Name: | asciminib |
| Pharmaco-therapeutic group<br>(ATC Code): | protein kinase inhibitors, bcr-abl tyrosine kinase inhibitors<br>(L01EA) |
| Therapeutic indication(s): | Scemblix is indicated 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 (see section 5.1) |
| Pharmaceutical form(s): | Film-coated tablet |
| Strength(s): | 20 mg and 40 mg |
| Route(s) of administration: | Oral use |
| Packaging: | blister (PCTFE/PVC/alu) |
| Package size(s): | 20 tablets and 60 tablets |

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# List of abbreviations

| | |
|---|---|
| 2G | Second generation |
| 3G | Third generation |
| ABL1/ABL1 | Italicized: Abelson oncogene; non-italicized: Abelson protein |
| ABL2/ABL2 | Italicized: Abelson related oncogene; non-italicized: Abelson related protein |
| ADME | Absorption, distribution, metabolism, and excretion |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| aGFR | Adjusted glomerular filtration rate |
| ALL | Acute lymphoblastic leukemia |
| Allo-SCT | Allogeneic stem cell transplantation |
| ALT | Alanine aminotransferase |
| AOEs | Arterial occlusive events |
| AP | Accelerated phase |
| AST | Aspartate aminotransferase |
| AUC | Area under curve |
| AUCinf | AUC from time zero to infinity |
| AUClast | AUC from time zero to the time of the last quantifiable concentration |
| AUCtau | AUC from time zero to the end of the dosing interval tau |
| BC | Blast crisis |
| BCR | Breakpoint Cluster Region |
| *BCR-ABL1* | Chimeric BCR-ABL1 oncogene |
| BCR-ABL1 | BCR-ABL1 oncoprotein with dysregulated ABL1 kinase activity |
| BCRP | Breast Cancer Resistance Protein |
| BCS | Biopharmaceutics classification system |
| b.i.d. | bis in diem/twice a day |
| BLRM | Bayesian logistic regression model |
| BMA | Bone marrow aspirate |
| BP | Blastic phase |
| CCyR | Complete Cytogenetic Response |
| CHMP | Committee for Medicinal Products for Human Use |
| CHR | Complete hematological response |
| CI | Confidence Interval |
| CIF | Cumulative incidence function |
| Cmax | Observed maximum plasma (or serum or blood) concentration following drug administration |
| CMH | Cochran–Mantel–Haenszel |
| Cmin | Trough concentration |
| CL | Systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration |
| CL/F | Apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration |
| CLr | Renal clearance from plasma (or serum or blood) [volume / time] |
| CML | Chronic Myeloid Leukemia |
| CML-AP | Chronic myeloid leukemia in accelerated phase |
| CML-BP | Chronic myeloid leukemia in blast phase CML-CP |
| CML-CP | Chronic myeloid leukemia in chronic phase |
| COVID-19 | Coronavirus Disease of 2019 |
| CSF | Clinical service formulation |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| Ctrough/Cmin | Plasma concentration (measured concentration at the end of a dosing interval at steady state [taken directly before next administration]) |
| CV | Coefficient of variation |
| CYP | Cytochromes P450 |
| DDI | Drug-drug interaction |
| DMPK | Drug metabolism and pharmacokinetics |
| EAIR | Exposure-adjusted incidence rate EC50 Half maximal effective concentration ECOG Eastern Cooperative Oncology Group ELN  European Leukemia Net |
| EMA | European Medicines Agency |
| EOsT | End of study treatment |
| EOT | End of treatment |
| EQ VAS | EuroQol Visual Analogue Scale |
| EWOC | Escalation with overdose control |
| FAS | Full Analysis Set |
| FCT | Film-coated tablet |

| FDA | Food and Drug Administration |
|---|---|
| FIH | First in human |
| FMI | Final market image |
| GGT | Gamma-glutamyltransferase |
| GMR | Geometric-mean ratio |
| HCRE | Highest clinical relevant exposure |
| hERG | Human ether-à-go-go-related gene |
| HF | High-fat (breakfast) |
| IC50 | Half maximal inhibitory concentration |
| IC90 | 90% inhibitory concentration |
| ICH | International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use |
| IRT | Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System |
| IS | International standard |
| Ka | Absorption rate constant |
| KM | Kaplan-Meier |
| LPLV | Last patient last visit |
| MAP | Managed access program |
| MCyR | Major cytogenetic response |
| mCyR | Minor Cytogenetic Response |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMR | Major molecular response |
| MTD | Maximum tolerated dose |
| NCCN | National Comprehensive Cancer Network |
| NE | Not estimable |
| NMQ | Novartis MedDRA Query |
| OS | Overall survival |
| Ph+ CML | Philadelphia chromosome-positive chronic myelogenous leukemia |
| Papp | Apparent permeability coefficient |
| PBPK | Physiologically based pharmacokinetic |
| PCR | Polymerase Chain Reaction |
| PCyR | Partial Cytogenetic response PD  Pharmacodynamic(s) |
| PFS | Progression-free survival |
| P-gp | P-glycoprotein |
| Ph+ | Philadelphia chromosome positive |
| PK | Pharmacokinetics |
| PopPK | Population PK |
| PRO | Patient-reported outcomes |
| q.d. | Once daily |
| QTcF | QT interval corrected by Fridericia's formula |
| QTL | Quality tolerance limit |
| RDE | Recommended dose for expansion |
| RQ-PCR | Real time quantitative polymerase chain reaction |
| SAE | Serious adverse event |
| SBP | Summary of biopharmaceutics |
| SCP | Summary of clinical pharmacology |
| SD | Standard deviation |
| SOC | System organ class |
| SOP | Standard operating procedure |
| TEAE | Treatment-emergent adverse event |
| T1/2 | Terminal elimination half-life |
| TDD | Total daily dose |
| TKI | Tyrosine kinase inhibitors |
| Tmax | Time to reach the maximum concentration after drug administration |
| TTF | Time to treatment failure |
| UGT | Uridine 5-diphospho-glucuronosyltransferase |
| ULN | Upper limit of normal |
| V1 | Volume of central compartment, representing V1/F |
| V2 | Volume of peripheral compartment, representing V2/F |
| Vz | Volume of distribution during the terminal elimination phase |

# 1. Background information on the procedure

## 1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 22 June 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Scemblix, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 March 2020.

Scemblix, was designated as an orphan medicinal product EU/3/20/2261 on 24 March 2020 in the following condition: for the treatment of chronic myeloid leukaemia (CML).

The applicant applied for the following indication: "Treatment of patients with Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP), previously treated with two or more tyrosine kinase inhibitors (TKIs)".

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

## 1.2. Legal basis, dossier content

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

## 1.3. Information on Paediatric requirements

Pursuant to Article 7 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) and the granting of a (product-specific) waiver and on the granting of a class waiver. At the time of submission of the application, the PIP P/0052/2020 was not yet completed as some measures were deferred.

## 1.4. Information relating to orphan market exclusivity

### 1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

### 1.4.2. New active Substance status

The applicant requested the active substance asciminib *(as hydrochloride)* contained in the above

medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

## 1.5. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

| Date | Reference | SAWP co-ordinators |
|---|---|---|
| 15 December 2016 | EMEA/H/SA/3426/1/2016/III | Martin Mengel, Jan Sjöberg |
| 12 October 2017 | EMEA/H/SA/3426/2/2017/I | Sheila Killalea, Christian Gartner |
| 27 June 2019 | EMEA/H/SA/3426/1/FU/1/2019/PED/II | Flora Musuamba Tshinanu, Alexandre Moreau |
| 23 July 2020 | EMEA/H/SA/3426/1/FU/2/2020/PA/II | Karri Penttilä, Minne Casteels |

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

*Quality*

- Choice of starting material for commercial manufacture of the drug substance.

*Non-clinical*

- Adequacy of the non-clinical safety package in support of MA.

*Clinical*

- Acceptability of the clinical pharmacology studies performed in support of MA.

- Adequacy of general study design elements, including rationale for choice of the 40mg dose BID, definition of the patient population to support the claimed indication, choice of bosutinib as comparator, primary and secondary endpoints and associated sample size, alpha adjustment methods and proposed statistical analysis, for the pivotal study supporting MA (CABL001A2301).

- Sufficiency of the expected safety database in support of the proposed indication.

- Possibility of pursuing an extrapolation approach for the paediatric CML population, including sufficiency of literature and modelling/simulation data to support similarity of responses to TKIs in CML adult and paediatric populations and supportive exposure-response relationships.

- Acceptability of the design changes implemented to the pivotal study (CABL001A2301).

## 1.6. Steps taken for the assessment of the product

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

Rapporteur: Janet Koenig          Co-Rapporteur: Paula Boudewina van Hennik

The appointed CHMP co-rapporteur had no such prominent role in Protocol assistance relevant for the indication subject to the present application.

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| The application was received by the EMA on | 22 June 2021 |
| The procedure started on | 15 July 2021 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 11 October 2021 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 18 October 2021 |
| The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on | 20 October 2021 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 11 November 2021 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 16 February 2022 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on | 14 April 2022 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 07 April 2022 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on | 22 April 2022 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 19 May 2022 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 10 June 2022 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Scemblix on | 23 June 2022 |

# 2. Scientific discussion

## 2.1. Problem statement

### 2.1.1. Disease or condition

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of transformed, hematopoietic progenitor cells characterized by overproduction of immature myeloid cells and mature granulocytes in the spleen, bone marrow, and peripheral blood.

### 2.1.2. Epidemiology

CML mainly affects adult patients with an average age at diagnosis of 65 years. Approximately 8,450 new cases of CML could be diagnosed and about 1,130 people could die of the malignancy in the US during 2020 (Howlader et al 2020). In Europe, a similar incidence of CML has been reported with 10 to 15 cases/million/year, without any major geographic or ethnic differences (Hochhaus et al 2017).

### 2.1.3. Biologic features, Aetiology and pathogenesis

The hallmark of CML is the Philadelphia (Ph) chromosome found in up to 95% of patients. The Ph chromosome results from a reciprocal translocation t(9;22)(q34;q11) which fuses a portion of the Abelson (*ABL1*) gene on chromosome 9 with a portion of the breakpoint cluster region (*BCR*) gene on chromosome 22.

The resulting fusion gene encodes a chimeric protein (BCR-ABL1), resulting in a constitutively active tyrosine kinase domain. This oncoprotein promotes cell growth and replication through downstream signaling pathways such as RAS, RAF, JUN kinase, MYC, and STAT (Jabbour and Kantarjian 2018).

Treatment with TKIs, inhibiting theses consequences of the mutation and re-establishing a constitutively active tyrosine kinase domain has dramatically improved the prognosis in CML associated with a nearly normal life-expectance in affected patients.

### 2.1.4. Clinical presentation, diagnosis and stage/prognosis

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

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

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

### 2.1.5. Management

Since the approval of imatinib in 2001, the 10 year survival rates for patients with CML have improved from approximately 20% to around 80-90%, and targeted therapy with TKIs has become the gold standard of treatment (Jabbour and Kantarjian 2018). There are four TKIs approved for the treatment of newly diagnosed CML (imatinib, nilotinib, dasatinib, bosutinib), with imatinib being the most commonly

used in clinical practice in CML-CP patients (Apperley 2015, Banegas et al 2019, and Hochhaus et al 2020).

For patients with CML-CP who experience treatment failure (intolerance or resistance) to previous TKI therapy, the therapeutic options are limited. Treatment selection is further complicated by consideration of the patients' comorbidities, age, emergence of mutations, and the safety profile of each particular TKI (Hochhaus et al 2017, Hochhaus et al 2020, NCCN 2020).

After treatment failure on a 2G-TKI, ponatinib, a 3G-TKI, is an option. However, clinical guidelines do not recommend its use in patients with existing cardiovascular risk factors because cardiovascular toxicity can occur in about 30% of patients (Cortes et al 2018, Hochhaus et al 2020, NCCN 2020).

Despite available therapies for CML have greatly broadened treatment choices and improved patient outcomes, there remain challenges in the management of CML. The choice and sequencing of TKIs remains controversial with the complexity of safety and tolerability considerations in the context of a long-term therapy (Mauro et al 2013, Cortes and Kantarjian 2016). Especially patients treated in the third and further lines of therapy represent a population with a high unmet need requiring therapies with potent anti-leukemic activity to control the disease and with a well-tolerated safety profile.

The current European Treatment guidelines (Hochhaus et al, 2020) summarises the current situation and concludes for the treatment beyond the second line:

"The definition of an acceptable response to third, fourth or fifth line treatment cannot be formalised, but a *BCR-ABL1* transcript level >1% or a cytogenetic response less than complete (Ph+ >0%) are insufficient for optimal survival. There are no comparative studies and the choice of TKI should be guided by the sensitivity profile of specific *BCR-ABL1* KD-mutations if possible, and, in particular T315I where only ponatinib is efficacious. Suboptimal responses to two or more TKIs should lead to prompt consideration of an allogeneic stem cell transplantation (allo-SCT)."

Insofar, an efficacious inhibitor that targets the myristoyl pocket of BCR-ABL1, in contrast to the currently available TKIs that target the BCR-ABL1 ATP binding site and does not interact with the ATP-binding site may be beneficial. It offers the chance for activity against cells expressing clinically observed ATP-binding TKI resistant mutations. However, whether inhibition of the new binding site is also associated with an improved safety and tolerability when administered as monotherapy compared to TKIs binding to the ATP-binding site of BCR-ABL1 remains open, since inhibition of a new binding site may also lead to different toxicities in humans.

Asciminib in principle may thereby fulfil a medical need in the treatment of CML, particularly in the situation of post 2G-TKI treatment failure as currently applied.

Currently authorized TKIs for Ph+ CML patients with resistance or intolerance to prior therapy, with details on the magnitude of their treatment effect and most frequent adverse drug reactions are presented in Table 1 below.

**Table 1 Currently authorized (EU) TKIs for Ph+ CML-CP patients with resistance or intolerance to prior therapy**

| Drug (dosage) Relevant indication for CML | Study Number of prior TKIs-CP CML | Primary efficacy analysis results | Warnings and precautions | Most common ADRs of any grade at an incidence ≥ 20%* |
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| **Nilotinib** (400 mg b.i.d.) Adult patients with CP and AP Ph+ CML with resistance or intolerance to prior therapy including imatinib | Phase II, open-label, uncontrolled, multicenter trial (NCT00109707, EUDRACT:2004-001483-51) 1 prior TKI (100% imatinib) (imatinib-resistant or intolerant CML) | Unconfirmed MCyR (minimum follow-up of 6 months) (N=232): 40% (95% CI: 33, 46) | Myelosuppression, QT prolongation, sudden death, fluid retention and edema, cardiovascular events, Hepatitis B reactivation, special monitoring of adult Ph+ CML patients in chronic phase who have achieved a sustained deep molecular response (treatment discontinuation), laboratory tests and monitoring (blood lipids, blood glucose), interactions with other medicinal products, food effect, hepatic impairment, serum lipase, total gastrectomy, tumour lysis syndrome, lactose, paediatric population | 24-Month Analysis: Rash, pruritus, nausea, diarrhea, constipation, vomiting, headache, fatigue, pyrexia, arthralgia, pain in extremity, cough, nasopharyngitis |
| **Dasatinib** (100 mg q.d.) Adult patients with CP, AP, and BP CML with resistance or intolerance to prior therapy including imatinib | Phase III, randomized, open-label trial (NCT00123474, EUDRACT: 2005-001294-99) 1 prior TKI (100% imatinib) | MCyR at 6 Months 100 mg or 140 mg q.d. (N=247): 51.8% (95% CI: 45.4, 58.2) 50 mg or 70 mg b.i.d. (N=251): 49% (95% CI: 42.7, 55.4) | Clinically relevant interactions, special populations (patients with hepatic impairment), myelosuppression, bleeding, fluid retention, pulmonary arterial hypertension, QT-prolongation, cardiac adverse reaction, thrombotic microangiopathy, Hepatitis B reactivation, effects on growth and development in pediatric population, excipients | 84 months follow-up: Fluid retention, headache, diarrhea, fatigue, dyspnea, musculoskeletal pain |
| **Bosutinib** (500 mg q.d.) Adult patients with CP, AP, and BP Ph+ CML previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options | Phase 1/2, single-arm, open-label, multicenter trial (NCT00261846, EUDRACT: 2005-004230-40) 1 prior TKI (imatinib only) ≥2 TKIs (imatinib and at least 1 additional TKI) | MCyR at Week 24 (1 prior TKI; imatinib only; N=266): 33.8% (95% CI: 28.2, 39.9) MCyR by Week 24 (≥2 TKIs; N=108): 26.9% (95% CI: 18.8, 36.2) | Liver function abnormalities, diarrhea and vomiting, myelosuppression, fluid retention, serum lipase, infections, proarrhythmic potential, renal impairment, severe skin reactions, tumor lysis syndrome, hepatitis B reactivation, cytochrome P-450 (CYP)3A inhibitors (concomitant use), CYP3A inducers, food effect | 48 Months follow-up: Diarrhea, nausea, abdominal pain, rash, thrombocytopenia, vomiting, anemia, fatigue, pyrexia, cough, headache, ALT increased, edema |

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|---|---|---|---|---|
| **Ponatinib** (Starting dose is 45 mg q.d. orally, with a reduction to 15 mg q.d. upon achievement of ≤1% *BCR-ABL1* IS)<br><br>Chronic phase, accelerated phase, or blast phase CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation | PACE (NCT01207440, EUDRACT: 2010-020414-28): starting dose of 45 mg orally q.d.)<br><br>Phase 2, single-arm, open-label, international, multicenter trial<br><br>N=449<br>1 prior TKI (32; 7%)<br>2 prior TKIs (155; 35%)<br>≥3 prior TKIs (262; 58%)<br>OPTIC (NCT02467270, EUDRACT: 2014-001617-12): 45 mg q.d. with reduction to 15 mg (45 mg=94; 30 mg=94; 15 mg=94)<br>Starting dose 45 mg (N=94):<br>1 prior TKI (1; 1%)<br>2 prior TKIs (43; 46%)<br>≥3 prior TKIs (50; 53%) | MCyR (6 months minimum follow-up for all patients):<br><br><u>Overall Resistant or Intolerant CP-CML N=267):</u> 54% (95% CI: 48, 60)<br><u>Patients without T315I (N=203):</u> 49% (95% CI: 42, 56)<br><u>Patients with T315I N=64):</u> 70% (95% CI: 58, 81) ≤1% *BCR-ABL1* IS at 12 months: Overall: 42% (95% CI: 32, 53) | Myelosuppression, arterial occlusion, venous thromboembolism, hypertension, aneurysms and artery dissections, congestive heart failure, pancreatitis and serum lipase, hepatotoxicity, hemorrhage, hepatitis B reactivation, posterior reversible encephalopathy syndrome, QT prolongation, medicinal product interactions (moderate and strong CYP3A inhibitors/CYP3A inducers, anti-clotting agents), QT prolongation, special populations (hepatic impairment, renal impairment), lactose | ADRs in PACE (60 months of follow-up): Rash and related conditions, arthralgia, abdominal pain, fatigue, constipation, headache, dry skin, fluid retention and edema, hepatic dysfunction, hypertension, pyrexia, nausea, hemorrhage, pancreatitis/lipase elevation, Arterial occlusive events (AOEs), diarrhea, neuropathy and myalgia<br>ADRs in OPTIC (median duration of exposure 1 year): Rash and related conditions, |

## 2.2. About the product

Asciminib (ABL001), administered orally, is a potent inhibitor of ABL/BCR-ABL1 tyrosine kinase. BCR-ABL1 is a chimeric oncoprotein with the constitutively active ABL1 tyrosine kinase domain. Asciminib inhibits the ABL1 kinase activity of the BCR-ABL1 fusion protein, by specifically targeting the ABL myristoyl pocket.

**Figure 1: Structural formula:**
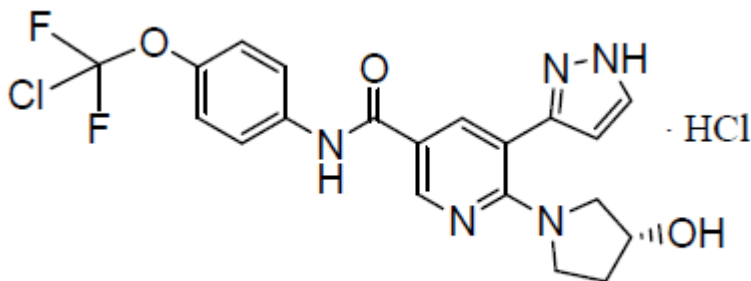


At the time of application, asciminib had not yet been approved anywhere in the world and applied for approval of the indication *"treatment of adult patients with Philadelphia-chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) previously treated with two or more tyrosine kinase inhibitors"*.

The recommended total daily dose of asciminib for adult patients with Ph+ CML-CP previously treated with 2 or more tyrosine kinase inhibitor (TKI) is 80 mg to be taken orally as 40 mg twice daily (b.i.d.).

Mode of action:

Asciminib (ABL001) is an inhibitor that targets the myristoyl pocket of BCR-ABL1, in contrast to the currently available TKIs that target the BCR-ABL1 ATP binding site. By virtue of asciminib not interacting with the ATP-binding site, asciminib maintains activity against cells expressing clinically observed ATP-binding TKI resistant mutations. Additionally, due to asciminib specifically targeting the ABL kinase family (ABL1, ABL2, BCR-ABL1), asciminib offers the potential for improved safety and tolerability when administered as monotherapy when compared to TKIs binding to the ATP-binding site of BCR-ABL1.

## 2.3. Type of Application and aspects on development

Asciminib as a single agent or in combination with other TKIs has been assessed in CML patients in third-line and beyond (3L+), in T315I mutation positive CML, in Ph+ ALL and as add-on to frontline imatinib treatment in patients not achieving deep molecular response.

In this application, data from an ongoing Phase III study [Study ABL001A2301 Primary endpoint analysis] (hereafter referred to as Study A2301) and ongoing Phase I study [Study ABL001X2101 Primary analysis] (hereafter referred to as Study X2101) provide robust evidence to support the proposed indication in Ph+ CML-CP.

Study CABL001A2301 is a Phase III, multi-center, open label, randomized study of asciminib 40 mg b.i.d. versus bosutinib 500 mg q.d. in patients with CML-CP, previously treated with two or more TKIs. Study CABL001X2101 is a first in human (FIH) dose escalation Phase I, multi-center, open-label study of asciminib in patients with Ph+ CML or Ph+ ALL. Overview of these studies is provided Table 12.

The efficacy claims for asciminib in third line and beyond (3L+) for patients with Ph+ CML CP who are resistant and/or intolerant to treatment with at least 2 prior TKIs are based primarily on the results from the primary analysis of the registration Study A2301. Supportive evidence of efficacy of asciminib as a single-agent in 3L+ Ph+ CML-CP is provided by data from the subset of patients with CML-CP not harboring the T315I mutation from the Study X2101.

The safety profile of asciminib in patients with Ph+ CML-CP previously treated with two or more TKIs is primarily based upon the results of study A2301, with supportive evidence from Study X2101. It is further supported by analyses in safety pools comprising of data from Study A2301 and Study X2101 (all CML-CP/-AP patients treated with asciminib monotherapy regardless of T315I mutation).

Exposure to treatment with asciminib in Study A2301 is currently limited and the overall size of the exposed population seems limited to about 356 patients and about 48 weeks (median; additional data cut off: 6.01.2021). Updated data including longer follow-up data from week 96 (cut-off date of 06-Oct-2021), were submitted after the initial submission during the procedure.

The applicant has discussed the development plan of asciminib and proposed package to support the marketing authorisation application (MAA) with the EMA in a scientific advice meeting on 30-Nov-2016. In general, it seems that CHMP's guidance as given in previous scientific advice was adequately followed. In addition, a pre-submission meeting with the CHMP Rapporteur, the Co-Rapporteur on 04th of November 2020 (and with EMA on 04 of December 2020). These meetings were held to clarify the overall strategy for the planned MAA for asciminib in order to align on the overall content and format of the planned MAA in support of the proposed indication and procedural and regulatory aspects for the MAA for asciminib.

## 2.4. Quality aspects

### 2.4.1. Introduction

The finished product is presented as film-coated tablet containing 20 mg or 40 mg of asciminib (as hydrochloride salt) as active substance.

Other ingredients are:

- 20mg strength:
  Lactose monohydrate, Microcrystalline cellulose (E460i), Hydroxypropylcellulose (E463), Croscarmellose sodium (E468), Polyvinyl alcohol (E1203), Titanium dioxide (E171), Magnesium stearate, Talc (E553b), Colloidal silicon dioxide, Iron oxide (yellow and red) (E172), Lecithin (E322) and Xanthan gum (E415).

- 40mg strength:
  Lactose monohydrate, Microcrystalline cellulose (E460i), Hydroxypropylcellulose (E463), Croscarmellose sodium (E468), Polyvinyl alcohol (E1203), Titanium dioxide (E171), Magnesium stearate, Talc (E553b), Colloidal silicon dioxide, Iron oxide (black and red) (E172), Lecithin (E322) and Xanthan gum (E415).

The product is available in PCTFE/PVC/Alu blisters as described in section 6.5 of the SmPC.

### 2.4.2. Active Substance

#### 2.4.2.1. General Information

The chemical name of asciminib is *N*-[4-(chlorodifluoromethoxy)phenyl]-6-[(3*R*)-3-hydroxypyrrolidin-1-yl]-5-(1*H*-pyrazol-3-yl) pyridine-3-carboxamide hydrochloride corresponding to the molecular formula $C_{20}H_{18}ClF_2N_5O_3 \cdot HCl$. It has a relative molecular mass of 486.30 g/mol (salt form) and the following structure:

**Figure 2 *active substance structure:***
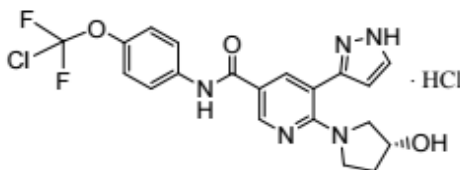


The active substance is a white to slightly yellow powder. It is slightly soluble in water, absolute ethanol and isopropanol, soluble in methanol, but practically insoluble in acetone.

The chemical structure of asciminib was confirmed by a combination of elemental analysis, HR-MS, UV-spectroscopy, IR-spectroscopy, ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR.

The active substance exhibits stereoisomerism (one stereocentre). The *R*-form is manufactured, the *S*-form is routinely controlled as an impurity.

The solid-state properties of the active substance were measured by XRPD and DSC. The active substance exhibits polymorphism. Two anhydrous crystalline modifications A and B have been identified. A third form, modification C, was observed as a physical mixture but could not be isolated as a pure

form. Modification A is routinely manufactured and is stable. Polymorphic identity is routinely controlled by means of XRPD testing (release and stability testing).

Active substance solubility is relevant for finished product performance (i.e. in-vitro drug release). The provided solubility data indicate poor solubility of the active substance in aqueous media, especially if the pH is above 3. However, the active substance is able to form super saturated solutions at pH 4.5 and 6.8.

Active substance particle size is relevant for finished product manufacturability and finished product performance. The active substance particle size is routinely controlled. The limits are justified based on developmental studies and particle size results used for the manufacture of clinical batches of finished product.

It has been established that the active substance is not hygroscopic as less than 0.05% water uptake was measured after 1 day exposure at 92% relative humidity at 25 °C.

### 2.4.2.2. Manufacture, process controls and characterisation

Asciminib hydrochloride is synthesized in a convergent synthesis, with three chemical transformations in the two side chains and four chemical transformations in the main chain, followed by hydrochloride salt formation and milling. The synthesis starts from well-defined starting materials with acceptable specifications.

A reaction scheme including all starting materials, reagents, catalysts, solvents, intermediates and the active substance is provided. A detailed narrative description is given for each step. Input quantities, yields, process parameters and IPCs are stated.

The selection of starting materials is based on general principles outlined in the ICH Q11. Each starting material has defined structure and chemical properties. The manufacturing process of each material and impurity profile is known. Carry-over of impurities is discussed. Scientific advice was given by CHMP regarding acceptability of starting materials (EMA/CHMP/SAWP/642260/2017) and the Applicant has followed the recommendations of the CHMP.

No reprocessing is proposed and only fresh solvents are used during the process. Critical process steps are indicated and their control is described. Control of intermediates is explained. Specifications are presented for each isolated intermediate.

The active substance is non-sterile. Accordingly, no process validation and/or evaluation data were submitted in the course of the MA application.

Information on manufacturing process development is provided including involved manufacturers, applied synthetic processes and scale up. Late phase toxicological and clinical batches (including primary stability batches) were manufactured according to an earlier synthetic process which is considered representative to the commercial process. Release data presented demonstrate similar quality between the respective batches and the commercial batches. Clinical batches and primary stability batches are thus representative of active substance generated by the commercial process at the commercial site.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

A comprehensive discussion on actual and potential impurities (including mutagenic impurities) of starting materials, isolated intermediates and final DS is provided (including, reagents, solvents, catalysts, by-products and degradations products). Mutagenicity assessment has been performed in line

with ICH M7 assuming a maximum daily dose of 0.5 g/d. Impurities (including mutagenic impurities) are either controlled as specified or unspecified impurities in starting materials, intermediates and final the final active substance or appropriate purge/control was shown by means of purge factor calculation, spike and purge studies, otherwise demonstrated process understanding (e.g. investigation of the likelihood of formation of impurities under worst-case conditions) or analytical data for 6 representative batches. The finished product is intended for an advanced cancer indication as defined in the scope of ICH S9 and therefore, mutagenic impurities can be controlled according to ICH Q3A.

The active substance is packaged in a PE bags, placed in quadruple laminated foil bags (PE, PET, AL, PET). Bags are sealed and may be stored in drums. The primary packaging material (PE bag) complies with relevant Ph. Eur. and foodstuff legislation requirements. Packaging materials are appropriately controlled.

### 2.4.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

The active substance specification includes tests for: appearance (visual), particle size (laser light diffraction), identity (IR, XRPD), enantiomer (HPLC), residual solvents (GC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), heavy metals (ICP-OES, ICP-MS), related substances (HPLC), assay (HPLC) and microbiological purity (Ph. Eur.).

Relevant parameters are included in line with ICH Q6A and Ph. Eur. 2034 ('Substances for pharmaceutical use') and the specified limits are appropriately justified.

Related substances (including enantiomer) are controlled in line with ICH Q3A and Ph. Eur. 2034 identification- (NMT 0.10% for unspecified impurities) and qualification (NMT 0.15% for specified impurities and enantiomer) thresholds.

Residual solvents, including benzene (potentially present as an impurity in other solvents), are controlled according to ICH Q3C option 1 limits.

Palladium, used as catalyst for active substance synthesis, is specified in line with the respective ICH Q3D option 1 limit (oral administration).

Skip testing of microbiological quality is proposed by the Applicant. This is acceptable as batch data from more than 20 batches is submitted and active substance is used in the manufacturing of a non-sterile solid dosage form.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch data is presented for early to late phase toxicological and clinical batches (including primary stability batches) as well as commercial batches. Reported batch data demonstrate the similar quality of late phase clinical batches (including primary stability batches) and commercial batches (irrespective of manufacturer or synthetic process). Overall, clinical batches and primary stability batches are representative for commercial active substance. Commercial batches comply with the active substance specification.

### 2.4.2.4. Stability

Stability data from three pilot scale batches of active substance, stored in a container closure system representative of that intended for the market, for up to 24 months under long term conditions (25°C / 60% RH) and intermediate conditions (30°C / 75% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH), according to the ICH guidelines, were provided.

All relevant parameters of the active substance specification were tested: appearance, identity by IR and XRPD, related substances by HPLC, enantiomer by HPLC, loss on drying, assay and microbial enumeration test. Residual solvents (including benzene), Pd content, assay of salt-forming agent and particle size have not been tested. This is acceptable as these parameters are not stability indicating.

Neither significant changes nor any trends were observed.

Batches manufactured by the commercial manufacturer have also been placed on stability. Results for commercial stability batches are presented for up to 6 months under accelerated conditions (40°C / 75% RH) and 9 months under long-term conditions (30°C / 75% RH). Neither significant changes nor any trends were observed. The active substance remains stable over the investigated period irrespective of the container closure system.

Stress studies (including photostability) demonstrate that active substance in solid state remains stable under any tested condition. Photostability has been tested in line with ICH Q1B.

Stress studies for active in solution indicate that specified impurities could potentially be formed, but would be detected by the related substances method (appropriate mass balance and peak purity is demonstrated). Stability indicating properties of the HPLC methods used for determination of assay and related substances are demonstrated by forced degradation studies. Asciminib hydrochloride was found to be stable in the solid state, but sensitive to acidic, alkaline and oxidative conditions and in solution.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

## 2.4.3. Finished Medicinal Product

### 2.4.3.1. Description of the product and pharmaceutical development

Asciminib 20 mg and 40 mg film-coated tablets are an immediate release dosage form for oral administration packaged in blisters. The two strengths (20 mg and 40 mg), which are dose proportional, are sufficiently differentiated by colour, size and debossing. The quantitative and qualitative composition is presented in the dossier.

Excipients used in the drug product formulation are: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide and different coating premixes for each strength. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report. The choice and amount of the excipients are based on compatibility studies as well as on pharmaceutical experience gained from the development of asciminib film-coated tablets and similar products. A discussion of each excipient and how it was chosen has been presented. Information on compatibility studies is provided. 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.

There are no overages, except for the non-functional film coating suspension due to equipment losses (which has been sufficiently justified). Physicochemical and biological properties are sufficiently discussed.

Asciminib hydrochloride is classified as a BCS class II compound with high permeability and strongly pH-dependent solubility. High saturated solubility is observed at acidic pH 1 and a decrease in solubility is observed with increasing pH (above pH 2). Asciminib hydrochloride is described as irregular particles and to ensure reproducibility during manufacturing, a milling step is performed by the active substance manufacturer to ensure a consistent particle size.

The active substance particle size limits have been set in the active substance specification.

Due to poor blend flow properties and low bulk and tapped density during the direct compression process, it was decided to develop a formulation and process using dry granulation via roller compaction. The material generated by roller compaction showed good processability and satisfactory in vitro dissolution results. Consistency of polymorphic form during manufacturing and shelf-life of drug product has been assessed using X–ray powder diffraction method. It can be concluded that no conversion of asciminib polymorphic form A occurs during finished product manufacture or shelf life.

A design of experiments (DoE) study was performed to optimize the formulation and select a final formulation for pivotal clinical trials. This study was done by altering the ratio of granules to extra-granular excipients in the formulation, selected excipient levels and drug substance particle size distribution (PSD). The final formulation was used throughout the pivotal clinical studies and in registration stability studies.

During development, the proposed dissolution method for the finished product has been optimized for the following parameters: choice of dissolution apparatus, medium volume and pH, temperature, and rotation speed. The dissolution temperature and volume selected are in line with Ph. Eur. recommendations and the EU bioequivalence guideline CPMP/EWP/QWP/1401/98, therefore no further justification is required. Selection of the rotation speed, dissolution medium and apparatus is justified by extensive development based on active substance and drug product characteristics and solubility data across solutions of different pH (1.2-pH 6.8). The selection of the dissolution medium for routine control is considered sufficiently justified by data presented.

The applicant explains that presence of asciminib free base is the most critical attribute impacting performance of the asciminib tablets. The dissolution method was developed to discriminate between batches containing a certain amount of free base of the active substance content. A correlation between the dissolution results and XRPD testing for formation of free base is described. The results justify the finished product acceptance criteria for routine dissolution testing - Q≥80% after 20 minutes according to Acceptance table 1 of harmonized EP, USP and JP (release: levels 1 and 2 only and shelf-life: levels 1, 2 and 3). This correlation is considered sufficient evidence for the discriminatory power of the dissolution method, while the method was found not to be discriminatory in terms of critical material attributes and critical manufacturing parameters within the ranges tested. The discriminatory power is considered adequately demonstrated. Information regarding bioavailability studies performed is sufficiently presented.

The process development consisted of a systematic approach based on scientific investigations and iterative risk management across production scales. Pivotal clinical batches and drug product registration stability batches were manufactured at pilot scale at Novartis Pharma AG, Basel, Switzerland. The manufacturing process was then transferred to Novartis Pharma Stein AG, which is the proposed commercial manufacturing site.

The primary packaging is PCTFE/PVC/Alu blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

### 2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of six main steps: pre-blending, dry granulation, screening, final blending, tableting and film-coating. The process is considered to be a standard manufacturing process.

A narrative process description and process-flow charts are provided for each step of the finished product manufacturing process. The manufacturing process involves preparation of the inner phase (granules) which are further blended with outer phase (extra-granular) excipients to form a final blend which is then compressed into tablets followed by film-coating.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

A hold time of 12 months for bulk film-coated tablets packed in low density polyethylene (LDPE) bag, closed and placed in a triple foil (PETP/Al/PE) bag with silica gel desiccant is accepted. The start of the shelf-life is calculated according to the requirements of the guideline CPMP/QWP/072/96: Note for Guidance on Start of Shelf-life of the Finished Product Dosage Form".

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Production scale batches of asciminib 20 mg (3 batches) and 40 mg (3 batches) film-coated tablets have been used for manufacturing process validation batches at the proposed commercial manufacturing site Novartis Pharma Stein AG, Switzerland. Validation batch data are presented for final blend, compression and film-coating steps and show that the manufacturing process, operated within the evaluated parameter ranges, can perform effectively and reproducibly produce a medicinal product compliant with specifications.

### 2.4.3.3. Product specification, analytical procedures, batch analysis

The finished product specifications include appropriate tests for this kind of dosage form; appearance (visual, size), mean mass, identity (NIRS, UV, HPLC), assay (NIRS, HPLC), degradation products (RTR / HPLC), water content (Ph. Eur.), dissolution (HPLC), uniformity of dosage units (NIRS / Ph. Eur.) and microbiological purity (Ph. Eur.).

Parameters included in specification comply with requirements of ICH Q6A and Ph. Eur. for this dosage form. Justification is provided for all tests that have been included in the specification. Potential degradation products have been discussed. Appropriate acceptance criteria have been defined.

The analytical methods used 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.

Real time release (RTRT) parameters are Identity, Assay, and uniformity of dosage units by content uniformity (all by NIRS). The NIRS method will be the primary test method for batch release dependent on a successful parallel testing phase. During the parallel testing phase, 15 batches per dosage strength will be tested both by NIRS and the alternative HPLC method. The NIR methods for identification, assay and content uniformity in general have been developed and validated in accordance with the Guideline on the use of near infrared spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations (EMEA/CHMP/CVMP/QWP/17760/2009) and are considered as acceptable. The switch from parallel testing to RTRT based on NIRS is documented in a post-approval

change management protocol (PACMP) which describes the studies to be performed and suitable acceptance criteria. The PACMP is considered acceptable and the changes can be made by type IA variation following successful implementation of RTRT by NIRS.

Stability indicating properties of the HPLC methods used for determination of assay and related substances are demonstrated by forced degradation studies. The microbial enumeration test method validation report is provided and is considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). 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.

Batch analysis data (3 batches each) for representative clinical, stability and production scale batches of Asciminib 20 mg and 40 mg film-coated tablets are presented. All results comply with the specifications.

### 2.4.3.4. Stability of the product

Stability data from three pilot scale batches of each strength of finished product stored for up to 24 months under long term conditions (25°C / 60% RH), 12 months under intermediate conditions (30°C / 75% RH) and for up to six months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

All stability data, except of 12 months stability data at 30 °C/75% RH and 6 months stability data at 40°C/75% RH comply to the specifications. After 6 months under accelerated conditions and 12 months under intermediate conditions, a degree of disproportionation of the salt form to free base was observed. Under accelerated conditions, water content also increased without an impact on other measured parameters. No significant change or trends were observed under long term conditions.

Additional stability studies, such as, freeze and thaw cycle test, photostability and open dish study have been performed. Photostability testing in line with ICH Q1B indicates that the finished product is not sensitive to light.

Based on available stability data, the proposed shelf-life of 24 months and storage conditions ("Do not store above 25°C" and "Store in the original package in order to protect from moisture") as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

### 2.4.3.5. Post approval change management protocol(s)

A post approval change management protocol (PACMP) to switch from parallel testing to RTRT based on NIRS is provided and is acceptable (see above under product specification).

### 2.4.3.6. Adventitious agents

Lactose monohydrate is the only excipient of animal origin. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

## 2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. There were no major objections raised on the submitted dossier and all other concerns raised have been satisfactorily resolved. 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.

## 2.4.5. Conclusions on the 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. Data has been presented to give reassurance on viral/TSE safety.

## 2.4.6. Recommendations for future quality development

Not applicable.

## 2.5. Non-clinical aspects

## 2.5.1. Introduction

The non-clinical program has been designed in accordance with the ICH S9, a guideline for non-clinical evaluation of anticancer pharmaceuticals. The pivotal toxicology and toxicokinetic studies submitted to support this application were conducted in rats, dogs and monkeys in compliance with GLP regulations. The dose-range finding studies do not claim GLP compliance. Asciminib salt was used for the GLP toxicology studies in rats (26-week) and monkeys and as solid dispersion in the 4-week rat and the dog study.

## 2.5.2. Pharmacology

### 2.5.2.1. Primary pharmacodynamic studies

A series of studies with ABL1 constructs featuring the myristoyl binding site of the ABL1 kinase domain revealed that asciminib binds to ABL1 with a $K_D$ of 0.5 nM. In biochemical assays, asciminib inhibited

ABL1 kinase activity with $IC_{50}$ values of 2.6 ± 0.8 nM (radiometric filter-binding assay) and 0.5 ± 0.1 nM (caliper assay).

In isothermal titration calorimetry experiments, the binding constant of asciminib to the *wild-type* ABL1[46-534] protein was 0.32 and 0.9 nM (two experiments) and therefore similar to that of the T315I mutant ($K_D$ values 0.5 and 0.8 nM). Inhibition of cell proliferation for engineered Ba/F3 cells dependent upon the T315I mutated BCR-ABL1 was characterised by the mean $IC_{50}$ value of 7.64 ± 3.22 nM. In contrast, the mean $IC_{50}$ value for Ba/F3 cells dependent on wild-type BCR-ABL1 was with 0.61 ± 0.21 nM much lower. The $IC_{50}$ values are mentioned in the SmPC.

Experiments on large tumour cell line panels revealed high selectivity of asciminib for BCR-ABL1 expressing cells (inhibition of cell proliferation at low nanomolar concentrations whereas $IC_{50}$ in other cell lines lay in micromolar range).

Asciminib inhibited the proliferation of Ba/F3 cells overexpressing wild-type BCR-ABL1 in the absence of IL3 with $IC_{50}$ of 0.25 nM. Also in Ba/F3 cells transfected with ABL1 constructs containing clinically relevant mutations (T315I, E255K, E255V, Y253H, F359V, Q252H, G250H and E459K), asciminib remained potent with $IC_{50}$ values ranging between 0.1 and 1 nM.

The Applicant submitted four in vivo studies shown in the Tabulated Summaries (Table below):

**Table 2        Pharmacology Tabulated Summaries**

| Type of study | Test system or protocol | Method of administration | Report number |
|---|---|---|---|
| The specificity of asciminib, a potential treatment for chronic myeloid leukemia, as a myristate-pocket binding ABL inhibitor and analysis of its interactions with mutant forms of BCR-ABL1 kinase | Effects on viability of cells dependent upon mutant form of BCR-ABL1 leading to resistance to ATP-competitive drugs used to treat CML or reduced sensitivity towards asciminib | | [Manley et al 2020] |
| **> In vivo pharmacology** | | | |
| In vivo efficacy of ABL001 in CML model with PKPD assessment | Pharmacokinetic, pharmacodynamic and efficacy studies in murine models of CML | Oral dosing of solutions or suspensions | [RD-2013-50145] |
| In vivo efficacy of ABL001 in T315I CML model | In vivo efficacy of ABL001 in T315I-mutant xenograft model | Oral dosing of solutions | [RD-2020-00314] |
| ABL001 and AMN107 combination efficacy in a CML xenograft model in mice | Comparison of effects of asciminib and nilotinib in murine model of CML | Oral dosing of solutions or suspensions | [RD-2013-50274] |
| In vivo efficacy of ABL001 in acute lymphoblastic leukemia (ALL) | Effects of asciminib in murine model of ALL | Oral dosing of solutions | [RD-2018-00292] |

Two primary metabolites of asciminib, the oxidation product and the pyrrolidine cleavage product, were found to be less potent in inhibition of ABL enzymatic activity (with ca. 10-fold higher $IC_{50}$ values in caliper assay) and in inhibition of cell proliferation in Ba/F3 cell line overexpressing BCR-ABL1 (with >6-fold higher $IC_{50}$ values). Taking into account the low levels of these metabolites in plasma of patients, their contribution to the pharmacological activity is expected to be minimal.

The in vivo efficacy of asciminib was evaluated in mice bearing KCL-22 xenografts, animal model of CML. Plasma exposure after single oral administration of asciminib increased dose-proportionally between 3 and 15 mg/kg, and appeared super-proportional at doses of 30 mg/kg and higher. Treatment with 3, 7.5, 15 and 30 mg/kg led to dose-proportional maximal inhibition of pSTAT5, a downstream signalling effector of BCR-ABL1, to 62%, 98%, 99% and 99%, respectively. At the 30 mg/kg dose level, greater than 80% inhibition of pSTAT5 was maintained for 16 hours after treatment.

In KCL-22 xenograft models, twice-daily administration of 7.5 mg/kg or higher doses induced significant tumour regression of more than 50%. The extent of regression increased with dose. The efficacy of once-daily treatment with 30 mg/kg asciminib resulted in 63% tumour regression and was thus comparable to that after twice-daily treatment with 15 mg/kg. Asciminib retained its efficacy in the nilotinib-resistant KCL-22R CML xenograft mouse model harbouring a T315I mutation, where twice-daily administration of 30 mg/kg led to 56% of tumour regression.

In disseminated Philadelphia chromosome-positive acute lymphoblastic leukaemia patient-derived xenografts, complete suppression of tumour burden was observed at 7.5 and 30 mg/kg BID.

Asciminib delayed the emergence of resistance compared to nilotinib. Animals receiving asciminib at 15 mg/kg BID or 30 mg/kg QD relapsed with a median time to endpoint of more than 40 days, whereas after nilotinib administration resistance development manifested earlier than 40 days post-treatment. At higher asciminib doses, emergence of resistance was further significantly delayed with median tumour relapse of more than 60 days.

Combination of asciminib with nilotinib appeared to be more effective than either drug alone. Asciminib at 30 mg/kg BID given together with nilotinib at 75 mg/kg BID induced 99% tumour regression, while lower extent of tumour growth inhibition was observed with either drug alone, although the difference was not statistically significant.

### 2.5.2.2. Secondary pharmacodynamic studies

In vitro kinase profiling over 335 protein and 14 lipid kinases showed no substantial activity on these targets at the concentration of 10 μM.

An off-target screening on a large panel of receptors, enzymes and transporters revealed a greater than 50% inhibition at 10 μM in the lipoxygenase 5-LO assay ($IC_{50}$ = 3.3 μM), the vesicular monoamine transporter VMAT2 functional assay ($IC_{50}$ = 3.5 μM), and for the serotonin 5HT2B receptor in antagonist mode ($IC_{50}$ = 5.1 μM). At higher concentration, activity was noted on the adenosine Ad3 receptor ($IC_{50}$ = 21 μM), 5HT2A as antagonism ($IC_{50}$ = 18 μM) and norepinephrine transporter NET ($IC_{50}$ = 22 μM). In patients receiving 40 mg BID, the geometric mean total plasma $C_{max}$ was 1.8 μM corresponding to the free plasma $C_{max}$ of 0.048 μM asciminib. In the case of 80 mg QD dosing schedule, mean free plasma $C_{max}$ was 0.1 μM. Even for the latter dosing, the safety margin is higher than 30, therefore, off-target related adverse reactions from interactions on lipoxygenase, vesicular monoamine transporter and the serotonin 5HT2B receptor are unlikely clinically relevant, especially given low brain penetration.

### 2.5.2.3. Safety pharmacology programme

Asciminib inhibited hERG potassium current with $IC_{50}$ value of 11.4 μM. Asciminib inhibited the Nav1.5 channel with a measured $IC_{50}$ of 29.7 μM and at the highest test concentration of 30 μM reduced the Cav1.2 current by 11% and the IKs current by 5.2%. This is far above the free maximal plasma concentration in patients.

Asciminib oral administration to male Beagle dogs up to 60 mg/kg did not affect diastolic arterial pressure. Treatment with 60 mg/kg asciminib resulted in increased heart rate (+44%) and decreased mean arterial pressure (-15%), which were reversible within 17 hours after dosing. On the contrary, a decrease in systolic pressure (-13%) and in arterial pulse pressure (-15%) were not reversible up to 24 hours after treatment with 60 mg/kg. A shortened QT interval at 60 mg/kg through 13 hours post-dose appears to be a consequence of concurrently increased heart rate.

In toxicology studies in rats, no effects of asciminib on central nervous and respiratory system were observed up to 600 mg/kg/day (see toxicology section).

### 2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed.

## 2.5.3. Pharmacokinetics

The absorption of asciminib was investigated after single-dose administration in Sprague-Dawley and Hanover Wistar rats, C57BL/6 mice, cynomolgus monkeys (intravenous and oral route), and in Beagle dogs (oral route).

For this purpose, the analytical LC-MS/MS methods for quantitative determination of asciminib in rat, mouse, dog, rabbit and monkey plasma as well as the method for measuring drug concentrations in rat plasma by means of HPLC with MS/MS detection were developed and in general successfully validated. Most validation criteria were met in all matrices. The carryover effect (asciminib response in the blank samples injected immediately after the ULOQ samples was more than 20% of the mean response at the LLOQ level) observed in all but rabbit plasma.

After intravenous administration of asciminib, plasma clearance was low to moderate as compared to hepatic blood flow and the half-life of the drug was short to moderate (1.1 – 3.7 h), in contrast to human (7 – 14 h). The volume of distribution was low to moderate across species, i.e. about 0.7- to 3-fold the body water. Following oral dosing, asciminib was moderately absorbed in most animals with exception of mice and dogs where the absorption was rapid. The oral bioavailability varied between species and was 21% in the mouse, 9% and 49% in the rat, 66% in the dog, and 37-76% in the monkey. In rats, the fraction absorbed was similar to absolute bioavailability indicating a minor first-pass metabolism effect. In monkeys, fraction absorbed was 1.4 times higher suggesting a moderate first-pass effect, which is consistent with the low plasma clearance. Gender differences were not investigated in the absorption studies.

The ability of asciminib to permeate across human gastrointestinal tract was assessed using a low efflux MDCK cell line where P-gp was knocked out. Incubation with the drug for 2 h at 10 µM in the apical compartment led to 88% recovery at the basolateral side pointing out high permeability of asciminib.

Dissolution of asciminib from film-coated tablets at 40 mg dose (two tablets containing 20 mg of a hydrochloride salt of asciminib each) was faster with increasing levels of bile acid, bile salt, and lecithin. The addition of cyclodextrin to the fasted intestinal media accelerated dissolution. Accordingly, the flux of asciminib decreased in the following order: flux aqueous buffer > fasted state intestinal media > fed state intestinal media. The flux in fasted intestinal media was slower when cyclodextrin was added.

The plasma protein binding was high and independent of concentration in all species tested (0.945 – 0.980, 0.973 in human). The human serum protein binding was similar to plasma protein binding suggesting that the anticoagulant heparin had no significant effect on the protein binding of asciminib. The blood-to-plasma ratio of asciminib was 0.80 in human and 0.88 – 1.02 in preclinical species, indicating that asciminib is distributed about 3- to 4-fold more in plasma than in red blood cells.

After oral administration of 30 mg/kg radiolabelled asciminib to rats, total radioactive components were eliminated relatively fast with $T_{last}$ being 48 hours or less. Only liver, skin and uveal tract had measurable radioactivity concentrations until 168 h. In male rats, the highest radioactivity concentration in most tissues occurred between 2 h and 4 h post dose. Tissues with highest radioactivity concentrations were kidney, liver, adrenal, pancreas, salivary gland, heart, fat (brown), spleen, lung, and gastrointestinal

tract. This is consistent with target organs of toxicity in animal models being pancreas, liver and adrenal gland. Melanin binding of asciminib was observed. The brain tissue/blood $C_{max}$ ratio of 0.0149 indicated little penetration of the blood-brain barrier. Moderate penetration into the reproductive system of male rats was found as the tissue/blood $AUC_{last}$ ratio in the testes was 0.510. In female rats, the overall distribution pattern was similar to that in male rats. The tissue radioactivity concentrations in female reproductive organs were similar to that in blood or muscle.

Asciminib was detected in foetal plasma of rats and rabbits in the embryo-foetal developmental studies indicating placental transfer. Transfer of asciminib to milk was not investigated.

Radiolabelled asciminib was used for the metabolism assessment. In vitro metabolism was characterised in mouse, rat, rabbit, dog, monkey and human hepatocytes. The time-course of asciminib consumption by hepatocytes was used to calculate intrinsic clearance values, which ranked as follows across species: rat > dog > monkey > human. Interestingly, clearance was markedly lower at higher drug concentration for all species studied, indicating possible involvement of transporters. Indeed, asciminib was found to be a substrate of P-gp and BCRP (see Clinical AR). Major in vitro biotransformation routes for different species were direct glucuronidation, amide hydrolysis, oxidation at the pyrrolidinol ring (ketone formation, hydroxylation, oxidative ring opening), and O-dealkylation. However, pronounced interspecies differences were observed: direct glucuronidation occurred most readily in human, to a lesser extent in the dog and monkey, and was noticeably absent in the rat, where the oxidative pathways were most prominent. For human, direct glucuronidation was the major biotransformation pathway, with the respective metabolites together accounting for ca. 18% of the radioactivity. The other major human metabolic reactions included oxidative ring opening and oxidation of alcohol to ketone, each contributing ca. 5% of the radioactivity. No unique human metabolites were detected.

Excretion and in vivo metabolism was evaluated in Hanover Wistar rats and cynomolgus monkeys. The species selection is justified as both rats and monkeys were used in the pivotal toxicology studies.

In general, asciminib metabolism was low in all species with 86% - 93% of total AUC as parent in plasma. No human major metabolites (AUC >10% total) were found.

In rats independently of the route of administration (i.v. and p.o.), the major metabolic route was oxidation of the pyrrolidine ring followed by ring opening forming a number of products. In rat plasma, asciminib was the major component (91% and 86% of drug-related material following i.v. and p.o. dosing, respectively). The most prominent metabolite in plasma was the product derived from the oxidation of alcohol to ketone (2.7% for i.v. and 4.1% for p.o.).

In the monkey, asciminib was metabolised mainly by oxidative pathways including hydroxylation, oxidation of alcohol to ketone, and oxidation of the pyrrolidine ring and subsequent ring opening. The major component in plasma was asciminib (91.1% and 88.4% of drug-related material after i.v. and p.o. administration, respectively) followed by the monohydroxylation product (3% - 4% of the dose). The direct O-glucuronide metabolites were found in urine but only to a negligible extent in faeces, probably due to their conversion back to the parent drug within the gastrointestinal tract.

In human plasma as found in the clinical study CABL001A2102, parent drug was the predominant drug-related component, with an average mean contribution to plasma radioactivity exposure of 92.7%. No metabolite with mean contribution to plasma radioactivity exposure ≥ 10% was detected. Therefore, further toxicological qualification of metabolites is not warranted. Circulating metabolites found were the direct O-glucuronide (4.93%), the ketone product of alcohol oxidation (1.88%), and the alcohol formed from oxidative opening of the pyrrolidinol ring (0.39%). The glucuronide metabolite was not found in the rat plasma due to the absence of glucuronidation pathway in rats but was observed in the monkey plasma. The other two above-mentioned metabolites were also detected in the rat and monkey plasma.

After intravenous or oral administration of radiolabelled asciminib to normal HanWistar rats, the majority of radioactivity (> 70%) was excreted into faeces. Following intravenous dosing to bile-duct cannulated rats, biliary excreted radioactivity accounted for 62.8% of asciminib dose indicating that majority of faecal excretion was from biliary elimination. 31.6% of radioactivity was recovered in faeces, with the majority being the parent drug (22.7% of the dose), suggesting gastrointestinal secretion. After oral asciminib administration to bile-duct cannulated rats, 47.8% of the dose was recovered in bile and 46.4% in faeces. Following both i.v. and oral administration of $^{14}$C-asciminib to cynomolgus monkeys, the radioactivity was predominantly excreted through faeces (>70% of the dose). In all pre-clinical species investigated irrespective of the administration route, renal excretion was minor and accounted for less than 10% of the dose.

## 2.5.4. Toxicology

Toxicology studies submitted included one single dose study and repeat-dose toxicity studies in rats, dogs and monkeys (up to 9 months duration), in vitro and in vivo genotoxicity studies, reproductive toxicity studies, phototoxic potential and a number of investigative studies. All pivotal studies were conducted in compliance with GLP regulations and used the intended clinical route of administration (oral).

### 2.5.4.1. Single dose toxicity

Asciminib was evaluated in one single dose toxicity study in male dogs with escalating doses up to 600 mg/kg. Within this study the potential toxicity, potential effects on electrocardiography and heart rate and the TK profile of asciminib was evaluated.

Single escalating doses of up to 60 mg/kg were tolerated by the animals whereas single escalating doses of 150 and 600 mg/kg resulted in severe vomiting. Hepatocellular injury was noted at 600 mg/kg due to alterations in ALT and AST activity. At this highest dose, one of the three animals exhibited an increase of heart rate; this effect correlated with the highest exposures of asciminib ($C_{max}$ and AUC).

### 2.5.4.2. Repeat dose toxicity

Non-pivotal 2 weeks repeat dose toxicity studies were conducted in rats, dogs and monkeys; in monkeys a one-week study was additionally conducted. The pivotal repeat-dose toxicity of asciminib was evaluated in rats (4- and 26-weeks), dogs (28-weeks), and monkeys (13- and 39-weeks); these studies were in compliance with GLP.

**Table 3 Non-pivotal Repeat dose toxicity studies**

| Species / strain | Number of animals & gender per group | Dose (mg/kg) | Noteworthy findings | Reference |
|---|---|---|---|---|
| Rat/ Wistar<br><br>Non-GLP | 5 male dogs | 0, 50, 200, 600 oral for 2 weeks | **200 mg/kg**<br>≥200 mg/kg/day minor effects on body weight/food consumption, vacuolation + single cell necrosis in harderian gland<br>**600 mg/kg**<br>Inflammation, RBC count↓, hemoglobin↓, hematocrit↓, bili↑, spleen weight↑, vacuolation + single cell necrosis in harderian gland | 1270173 |
| Dog / Beagle<br><br>Non-GLP | 2 males + 1 female<br>2 males + 2 female | 0, 15, 60 oral for 2 weeks<br>200 for 2 weeks | **60 mg/kg/day:**<br>emesis, excessive salivation, body weight↓, body weight gain↓, food consumption↓, amylase↑ (males), lipase↑ (males), alanine aminotransferase↑, red cell mass↓, reticulocytes↑, mean corpuscular volume↑, pancreatic acinar cell degeneration/necrosis (males)<br>**200 mg/kg/day:**<br>early euthanasia (1 female on day 9), emesis, excessive salivation, body weight↓, body weight gain↓, food consumption↓, amylase↑ (female), lipase↑ (female), alanine aminotransferase↑, red cell mass↓, reticulocytes↑, mean corpuscular volume↑, fibrinogen↑, potassium↓, pancreatic acinar cell degeneration/necrosis | 1270561 |
| Monkey/ Cynomolgus<br><br>Non-GLP | 3 males | 15, 60 oral for 1 week<br><br>150 for oral 2 weeks | **15 mg/kg**<br>mean red cell mass values (red blood cells, hemoglobin, and hematocrit)↓, total bili↑, mild to moderate prolongation in activated partial thromboplastin time in 1 animal, CK↑, ALT↑, AST↑, Globulin↑<br>**60 mg/kg**<br>total bili↑, Hb↓, Hk↓, Reti↑, Platelets↑, aPTT↑, CK↑, ALP↑, ALT↑, AST↑, Globulin↑<br>**150 mg/kg**<br>Emesis, 1 animal died, Amylase and lipase↑, emesis, Hb↓, Hk↓, Reti↑, ALP↑, ALT↑, AST↑, Globulin↑, Platelets↑, aPTT↑, lipase↑, amylase↑ | 1470175 |

In the non-pivotal studies, dogs exhibited the most adverse effects related to asciminib, especially pancreatic toxicity. At doses ≥60 mg/kg/day increased amylase and lipase activities correlated with degeneration/necrosis of pancreatic acinar cells observed microscopically. Pancreatic toxicity was also observed in the pivotal repeat-dose toxicity study in dogs. Microscopic effects on the pancreas together with increased amylase and lipase levels were also seen in **monkeys** at a dose of 150 mg/kg/day. However, since no control animals were integrated in the monkey study, the findings are difficult to interpret. Elevations in **liver** enzymes and/or bilirubin values were observed in **dogs** and **monkeys**. Microscopic observations included minimal infiltration in monkeys whereas in dogs no asciminib-related effects correlated with the elevated enzyme levels. Administration of asciminib resulted in reduction in **red blood** cell mass in **rat**, **dog** and **monkey** indicating hemolytic anemia.

The pivotal repeat-dose toxicity studies were performed in rats (4- and 26-weeks), dogs (28-weeks), and monkeys (13- and 39-weeks); these studies were in compliance with GLP.

**Table 4 Pivotal Repeat dose toxicity studies**

| Reference | Species/ Number of animals & gender per group | Dose (mg/kg) /Route | NOAEL mg/kg /day | Noteworthy findings |
|---|---|---|---|---|
| 1270619 | Rat/Wistar<br><br>10 or 16 animals /sex | 0, 50, 200, 600 ABL 001 daily oral for 29 days or control | ND | **50 mg/kg**<br>Spleen weight↑, adrenal weight↑, liver weight↑<br>**200 mg/kg**<br>Hepatocellular injury, inflammation (liver, spleen), F +M: RBC↓, M+F: degeneration of harderian gland, AST↑, F: ALT↑<br>**600 mg/kg**<br>Hepatocellular injury, inflammation (liver, spleen), F +M: RBC↓, M+F: degeneration of harderian gland, BW↓, body weight gain↓, food consumption↓, M: CYP2E↑, CYP4A↑, F: CYP3A↑, M+F: duodenum hypertrophy/hyperplasia, mucosa, M: ALT↑ |
| 1470225 | Rats/Wistar<br>20 animals/sex<br><br>16 animals/sex | 0, 15, 50, 200 oral daily for at least 26 weeks<br>0, 200 oral daily for at least 13 weeks followed by a 4-week recovery phase (6 animals/sex) | ND | **15 mg/kg**<br>Hepatocyte necrosis; RBC↓, Hb↓, Hk↓; liver alteration, pigment in the red pulp of spleen<br>**50 mg/kg**<br>2F found dead, at least one accidental, hepatocyte necrosis<br>**200 mg/kg**<br>2F found dead; transient hypoactivity, irregular respiration, pale or cold to touch body, thinning hair coat,<br>body weight↓, body weight gain↓, food consumption↓, inflammation, hepatocellular injury, F: AST↑, ALT↑, transaminase↑; M: abs. neutrophil↑; F: bili↑; liver weight↑, adrenal weight↑, spleen weight↑; adrenal cortex; hypercellularity in bone marrow |
| 1270620 | Dogs/beagle<br>3+15 mg/kg:<br>3 animals/sex<br>60 mg/kg: 5 animals/sex | 0, 3, 15, 60 oral daily for 28 days<br>2 animals given 60 mg/kg maintained for 28-day recovery | ND | **3 mg/kg**<br>large, thickened, discolored, firm pancreas<br>**15 mg/kg**<br>reticulocyte↑, large, thickened, discolored, firm pancreas; CYP1A↑<br>**60 mg/kg**<br>abnormal feces, emesis, excessive salivation; 1M: severe pancreas atrophy; body weight↓; food consumption↓; RBC↓; Hb↓; Hk↓;1F: ALT↑, AST↑, ALP↑; CYP1A↑ |
| 1470095 | Monkey/ cynomolgus<br>3 animals/sex + 2 animals for recovery in control + 100 mg/kg group | 0, 10, 30 100 oral daily for 13 weeks with 4-week recovery | 30 | **30 mg/kg**<br>F: body weight↓, RBC↓, Hb↓, Hk↓<br>**100 mg/kg**<br>Emesis; F: diarrhea, soft feces, M. BW↓, F+M: RBC↓, Hb↓, Hk↓, aPTT prolongation; bili↑, Kreat↑, cholesterol↑, globulin↑, liver weight↑, hepatocellular hypertrophy, kidney weight↑, tubular epithelial hypertrophy, decreased vacuolation in zona fasciculate in the adrenal gland |
| 1470799 | Monkey/cynomolgus<br><br>4 animals/sex | 0, 3, 15, 50 oral daily for 39 weeks | 50 | **3 mg/kg**<br>adrenal gland weight↑<br>**15 mg/kg**<br>Decreased vacuolation of adrenal cortex<br>**50 mg/kg**<br>Liver weight↑, Hepatocellular hypertrophy, pigment deposits in spleen+sternal bone marrow, excessive salivation, RBC↓, bili↑ adrenals↑ |

Target organs in the repeat-dose toxicity studies in rats were the hematopoietic system, liver, spleen, adrenal gland, harderian gland and the GI tract/duodenum. Most of the adverse effects resolved during the recovery phase. . Hepatic changes can be considered as the dominant effect in relation to the clinic. These changes were characterised by increased incidences of hepatocyte individual cell necrosis, centrilobular hepatocyte hypertrophy, increased periportal population of a mixed cellular infiltrate, increased incidence of mononuclear cells, pigmented hepatocytes and Kupffer cells, bile duct hyperplasia, and increased basophilic foci of cellular alteration hepatocellular necrosis. A NOAEL could not be established in the rat studies since hepatocellular necrosis occurred already at the lowest dose tested (≥15 mg/kg/day). This exposure was equivalent or even below the intended clinical dose of 80 mg QD.

Target organs in the repeat-dose toxicity study in dogs were the hematopoietic system, pancreas and liver. Pancreatic toxicity was the limited factor in this study. The pancreas as a target organ was already found in the single dose toxicity study. Although asciminib was tolerated up to the highest dose tested (60 mg/kg), a NOAEL could not be established due to the pancreatic toxicity which was observed at ≥3 mg/kg/day (corresponding to exposure multiples below the intended human dose of 40 mg BID or 80 mg QD). The reason of this toxicity was evaluated in additional studies but could not be established during these studies. Since pancreatic enzyme increase and pancreatitis events were reported in the clinical development program, effects on the pancreas should be carefully monitored in patients.

Target organs identified in the repeat-dose toxicity studies in monkeys were the liver, kidney, adrenal gland, hematopoietic system. Histopathologically, hepatic changes were characterised by reversible diffuse hepatocellular hypertrophy in monkeys and occurred at AUC exposures, which was 18-fold higher than the one achieved in patients at the 40 mg BID dose. The monkey studies were the only studies in which a NOAEL could be established: 30 mg/kg in the 13 week and 50 mg/kg in the 39-week study. Anatomic changes were not present at the end of the recovery period. However, changes in haematology could be an indicator of organ toxicity; thus, the appropriate values should be carefully monitored in the clinical setting.

Moderate CV effects (increased heart rate, decreased systolic pressure, decreased mean arterial pressure, and decreased arterial pulse pressure) were observed with asciminib in jacket telemetered male dogs at single dose of 600 mg/kg or in the invasive telemetry CV safety study at 60 mg/kg. There was no QTc prolongation. Based on the exposure achieved in the 4-week dog toxicity study, the anticipated $C_{max}$ at 600 mg/kg in dogs was estimated to be ≈ 142000 ng/mL, which would correspond to a free $C_{max}$ of 6.3 µM (Free fraction in dog: 0.02); a value 100-fold and 60-fold higher than the one achieved in patients at 40 mg BID and 80 mg QD respectively.

### 2.5.4.3. Genotoxicity

A standard battery of *in vitro* and *in vivo* genotoxicity tests was performed with asciminib. Main study details and results are summarised in the table below:

**Table 5 Genotoxicity tests**

| Type of test/study ID/GLP | Test system | Concentrations / Concentration range/ Metabolising system | Results Positive/negative/equivocal |
|---|---|---|---|
| Gene mutations in bacteria / 1213038 / No | Salmonella strains TA98/TA100 | +/- S9 (all strains): <br><br> 0, 5, 15, 50, 1150, 500 µg/plate <br><br> Plate incorporation method, 37°C for 3 days | **Negative** for relevant increase in reverse mutations <br><br> Cytotoxicity: ≥ 150 µg/plate in TA100 +/- S9. |

| Gene mutations in bacteria / 1270618 / Yes | Salmonella strains TA97a/TA98/TA100/TA1535/TA102 | +/- S9 (all strains):<br><br>0, 5, 15,81, 50, 158.1, 500, 1581, 5000 µg/plate<br><br>Plate incorporation and preincubation method, 37°C for 3 days | **Negative** for relevant increase in reverse mutations<br><br>Cytotoxicity: ≥158.1 and or µg/plate all strains +/- S9.<br>Precipitation: 5000 µg/plate |
|---|---|---|---|
| In vitro micronucleus assay in TK6 cells / 1214013 / No | TK6 cells | +/- S9 3 h incubation and 24 h recovery: 0 - 119.9 µg/mL<br><br> - S9 20 h incubation, 48 h recovery: 0 – 64.6 µg/mL | **No induction of micronuclei** +/- S9<br><br>Dose-related decreases in cell growth +/-S9, complete cell death at 64.6 µg/mL –S9 |
| In vitro micronucleus assay in human lymphocytes / 1670377 / Yes | Primary human peripheral blood lymphocytes | +/- S9 3 h incubation and 21 h recovery: 0 – 75 µg/mL<br>- S9 24 h incubation and 24 h recovery: 0 - 50 µg/mL | **No induction of micronuclei** +/- S9<br><br>Dose-related decreases in cell growth +/-S9 |
| In vivo micronucleus test / 1270619-01 / Yes | Han rats (6/sex/group)<br><br>micronuclei in bone marrow | 0, 50, 1000, 2000 mg/kg/day for 4 weeks<br><br>Vehicle: 7.5% (w/v) hydroxypropyl methylcellulose and 7.5% (w/v) Kollidon® VA 64 prepared in 1x phosphate buffered saline (Dulbecco's phosphate buffered saline)<br><br>Sampling time: at week 1 and after 4 weeks of treatment<br><br>No. of cells analysed/culture: approx. 20000 reticulocytes (RET) per animal | Week 1: no effect on the MN-RET frequencies<br><br>Week 4: statistical significant, dose-dependent increase in the percentages of MN-RET not exceeding the laboratory's historical control upper limit.<br>Statistically significant, dose dependent increases in RET frequencies, as indication of effects on bone marrow proliferation.<br><br>TK: |

|  |  | Males | | Females | |
|---|---|---|---|---|---|
| Dose (mg/kg) | Study day | AUC(0-24h) | Cmax | AUC(0-24h) | Cmax |
| 50 | 1 | 47700 | 4860 | 36300 | 5360 |
|  | 29 | 50200 | 5450 | 59600 | 5200 |
| 200 | 1 | 221000 | 15700 | 177000 | 12300 |
|  | 29 | 177000 | 16500 | 212000 | 16400 |
| 600 | 1 | 296000 | 13800 | 271000 | 16800 |
|  | 29 | 337000 | 21900 | 457000 | 31100 |

Cmax (ng/mL); AUC(0-24h) (ng h/mL)

Asciminib showed no evidence for a genotoxic potential.

### 2.5.4.4. Carcinogenicity

As this application is for the use of asciminib 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 no carcinogenicity studies were submitted, which was considered acceptable.

## 2.5.4.5.  Reproductive and developmental toxicity

**Table 6 Summary table of reproductive and developmental toxicity studies**

| Study Type | Species | TK collected | GLP |
|---|---|---|---|
| **Fertility and early embryonic development** | Han Wistar rat | No | Yes |
| **Embryo-foetal development** | Han Wistar rat | Yes | Yes |
| **DRF-Embryo-foetal development** | New Zealand White rabbit | No | No |
| **Embryo-foetal development** | New Zealand White rabbit | Yes | yes |
| **Pre-/postnatal development** | not conducted | | |

The potential for reproductive and/or developmental toxicity of asciminib was investigated in a study on fertility and early embryonic development in the rat and studies on embryo-foetal development in rats and rabbits. Asciminib was orally applied. Toxicokinetic data on maternal and foetal exposures were concomitantly obtained with the studies on embryo-foetal development. All pivotal studies were carried out in accordance with the relevant ICH guidelines and in compliance with GLP regulations. A study on pre-postnatal development was not performed.

In the study on fertility and early embryonic development, effects were observed on sperm motility and/or sperm counts and the number of live embryos at the highest dose of 200 mg/kg/day which equal AUC exposures 19-fold or 13-fold higher than those achieved in patients at the 40 mg twice-daily and 80 mg once-daily doses, respectively. Therefore, the NOEL for reproductive effects and early embryonic development was considered to be 50 mg/kg/day equalling clinical exposures approximately 5- or 3-fold higher than human therapeutic exposures at 40 mg twice daily, respectively 80 mg QD. Otherwise no maternal or paternal toxicity was noticed at 200 mg/kg/day.

In the study on embryo-foetal development in the rat, the high dose group of 600 mg/kg/day had to be terminated because of severe clinical signs and mortality. A slightly increased incidence of foetuses and litters with malformations (cleft palate, anasarca) and visceral variations observed in the mid dose group of 150 mg/kg/day was attributed to asciminib treatment. There was a dose-related increase in foetal weights from the low dose on (25 mg/kg/day). Foetal variations, primarily at 150 mg/kg/day, in the urinary tract and skeleton (skull, vertebral column and ribs) were suggestive of changes in the rate of development. Foetal exposure to asciminib was shown with foetal plasma levels showing approximately 1/10 of maternal levels. The maternal NOAEL was considered to be at 150 mg/kg/day. The embryo-foetal NOAEL was established at 25 mg/kg/day resulting in exposures which equal human therapeutic exposures.

In the embryo-foetal development study in rabbits, the high dose group of 300 mg/kg/day had to be terminated due to distinct signs of toxicity. An increased number of resorptions, a lower number of live foetuses and accordingly an increased post-implantation loss was noticed in the mid dose group of 50 mg/kg/day. Additionally, a low incidence of foetuses with cardiac malformations was observed in this dose group. Since similar abnormalities concerning the heart and major vessels were also noted in the dose-range finding study in the rabbit, a relationship to asciminib treatment cannot be discounted. Foetal exposure to asciminib was shown by obtaining toxicokinetic data from foetal and maternal plasma. The maternal NOAEL was considered to be 50 mg/kg/day. Based on the increased post-implantation loss and cardiac malformations observed, the embryo-foetal NOAEL was established at 15 mg/kg/day. Exposures at this dose equal human therapeutic exposures.

Since asciminib showed teratogenicity in rats and rabbits at human therapeutic exposures, a pre-/postnatal development study was not performed

### 2.5.4.6. Toxicokinetic data

The recommended daily dose of asciminib in patients is 40 mg/day BID or 80 mg QD. Because of the relatively high sensitivities of the animal species to the toxic effects of asciminib, a margin of safety either could not be established or was low with respect to the repeat dose toxicity studies relative to the exposure levels obtained in humans at the human oral dose of 40 or 80 mg/day. One exception were the repeat-dose toxicity studies in monkeys.

**Table 7 Asciminib exposure multiples in toxicity studies at NOAEL when compared to the exposure in patients at 40 mg QD**

| Species / Study number | NOAEL[b] (mg/kg) | Sex | AUC0-24h[c] (ng/mL•h) | Cmax[c] (ng/mL) | Exposure multiple[a] | |
|---|---|---|---|---|---|---|
| | | | | | Based on mean AUC0-24h in humans[a] | Based on mean Cmax in humans[a] |
| 4-week rat 1270619 | 50[d] | Male | 50200 | 5450 | 4.77 | 6.87 |
| | 50[d] | Female | 59600 | 5200 | 5.66 | 6.56 |
| 26-week rat 1470225 | 15[d] | Male | 15600 | 2140 | 1.48 | 2.70 |
| | 15[d] | Female | 14500 | 1490 | 1.38 | 1.88 |
| 4-week dog 1270620 | 3[d] | Male | 6050 | 871 | 0.57 | 1.10 |
| | 3[d] | Female | 7070 | 1070 | 0.67 | 1.35 |
| 13-week monkey 1470095 | 30 | Male | 155000 | 12600 | 14.73 | 15.89 |
| | 30 | Female | 181000 | 13300 | 17.20 | 16.77 |
| 39-week monkey 1470799 | 50 | Male | 190000 | 13400 | 18.05 | 16.90 |
| | 50 | Female | 222000 | 14400 | 21.09 | 18.16 |

[a]Based on 40 mg BID steady-state data (Phase 3 study dose level) [Study ABL001X2101] (data cut-off: 02-Apr-2020), Mean Cmax at steady-state = 793 ng/mL, AUC0-24h = 10525 ng·h/mL; [b]NOAEL: No Observed Adverse Effect Level; [c]Values at the end of the stated treatment-period; [d]Since no NOAEL could be defined in the study the lowest administered dose is taken for calculation

Source: [Table 2.6.7.7A-Study 1270619], [Table 2.6.7.7B-Study 1470225], [Table 2.6.7.7C-Study 1270620], [Table 2.6.7.7D- Study 1470095], [Table 2.6.7.7E-Study 1470799]

**Table 8. Asciminib exposure multiples in toxicity studies at NOAEL when compared to the exposure in patients at 80 mg QD**

| Species / Study number | NOAEL[b] (mg/kg) | Sex | AUC0-24h[c] (ng/mL•h) | Cmax[c] (ng/mL) | Exposure multiple[a] | |
|---|---|---|---|---|---|---|
| | | | | | Based on mean AUC0-24h in humans[a] | Based on mean Cmax in humans[a] |
| 4-week rat 1270619 | 50[d] | Male | 50200 | 5450 | 3.32 | 3.06 |
| | 50[d] | Female | 59600 | 5200 | 3.94 | 2.92 |
| 26-week rat 1470225 | 15[d] | Male | 15600 | 2140 | 1.03 | 1.20 |
| | 15[d] | Female | 14500 | 1490 | 0.96 | 0.84 |
| 4-week dog 1270620 | 3[d] | Male | 6050 | 871 | 0.40 | 0.49 |
| | 3[d] | Female | 7070 | 1070 | 0.47 | 0.60 |
| 13-week monkey 1470095 | 30 | Male | 155000 | 12600 | 10.26 | 7.07 |
| | 30 | Female | 181000 | 13300 | 11.98 | 7.47 |
| 39-week monkey 1470799 | 50 | Male | 190000 | 13400 | 12.57 | 7.52 |
| | 50 | Female | 222000 | 14400 | 14.69 | 8.09 |

[a]Based on 80 mg QD steady-state data [Study ABL001X2101] (data cut-off: 02-Apr-2020), Mean Cmax at steady-state = 1781 ng/mL, AUC0-24h = 15112 ng·h/mL; [b]NOAEL: No Observed Adverse Effect Level; [c]Values at the end of the stated treatment-period; [d]Since no NOAEL could be defined in the study the lowest administered dose is taken for calculation

Source: [Table 2.6.7.7A-Study 1270619], [Table 2.6.7.7B-Study 1470225], [Table 2.6.7.7C-Study 1270620], [Table 2.6.7.7D- Study 1470095], [Table 2.6.7.7E-Study 1470799]

#### 2.5.4.7. Local Tolerance

The local tolerance of asciminib has been evaluated using the murine local lymph node assay (LLNA TIER I). The result of this study demonstrated that asciminib appeared to be a strong sensitiser, since the cell count index exceeded the threshold of 1.3 at the lowest concentration of 0.25% (1.65). Moderate irritating potential was ascribed to asciminib and should adequately labelled in the SmPC.

#### 2.5.4.8. Other toxicity studies

*Studies on impurities*

In silico testing of potential mutagenic impurities was performed with Derek Nexus, Lhasa Ltd. Case Ultra, MCASE Inc. and Sarah Nexus, Lhasa Ltd. systems. According to the Applicant predictions were performed in years 2015, 2016, 2019 and 2020 and different version numbers of the programs have been used.

In silico positive impurities were tested with follow up Ames tests. Theses assays were not performed under GLP conditions but according to the study protocols, general rules of OECD and UK MHRA were followed.

The impurities thionyl chloride (CAS 7719-09-7), Glycerol (CAS 56-81-5), p-nitrophenol (CAS 100-02-7), p-aminophenol (CAS 123-30-8), N,N-Diisopropyl ethylamine (DIPEA, CAS 7087-68-5), Methanesulfonic acid (CAS 75-75-2), 4-(trifluoro methoxy)aniline (CAS 461-82-5), and (cyclohex-2-en-1-one, CAS 930-68-7) were assessed for their mutagenic potential using literature data. Based on this review, only thionyl chloride (CAS 7719-09-7) was considered to be mutagenic impurity.

*Phototoxicity*

The in vivo mouse oral photo-local lymph node assay demonstrated a phototoxic potential at dose ≥ 200 mg/kg/day. At the no-observed-adverse-effect level (NOAEL) of 60 mg/kg/day, the $C_{max}$ was 12000

ng/mL, exposure 15- or 6-fold than the $C_{max}$ exposure in patients at the dose of 40 mg BID or 80 mg QD, respectively.

*Mechanistic studies*

The toxicological effects of asciminib was established when administered as a single dose followed by 3 days of observation (sighting phase) and as a daily dose (repeat phase) for 2 weeks to male dogs. The study was also designed to assess the time-course toxicity effects and the toxicokinetic profile of asciminib. 60 mg/kg asciminib administered as single dose to male beagle dogs was generally tolerated. Further, the same dose was not tolerated after repeated dosing for up to 2 weeks with toxicity findings similar to previously known findings of asciminib in beagle dogs (Study 1270620).

One further study was performed in order to investigate/characterise the early onset pancreatic toxicity in male dogs, when administered at 60 mg/kg/day for 3 to 7 days.

In a 4-week dog toxicity study (study no. 1270620), administration of asciminib resulted in atrophy of the pancreas at 60 mg/kg. The pancreas was replaced by adipocytes with bands of fibrous tissue on the mesenteric surface with bands of fibrous tissue extending through the adipocytes. Degeneration/necrosis of acinar cells with fibrosis was present in males and females given ≥15 mg/kg/day. The effects were not reversible. Increased amylase and lipase activities correlated with pancreatic acinar cell degeneration/necrosis.

In this mechanistic study similar findings were present in the animals: There was an increase in lipase and amylase activity which correlated with pancreatic findings including acinar and duct cell degeneration and fibroplasia. Oedema and inflammatory cell infiltration was limited to animals most severely affected by acinar and duct cell degeneration. The mechanism of this toxicity could not be attributed to a specific cell signature. As a result, the reason for the pancreatic toxicity which was present only in the dog could not be elucidated. However, changes if lipase and amylase values should be carefully monitored in the clinical setting.

In addition, evaluation of the pancreatic toxicity included assessment of circulating microRNAs in dog plasma as markers of pancreatic injury. MicroRNAs are known to play an important role in pancreatic physiology and each islet cell type has a specific pattern of microRNA expression (Klein et al. 2013). The treatment with a drug inducing pancreas injury or the progression of pancreas injury during disease shows an increase of plasma levels of microRNAs (Erener et al. 2013, Chakraborty et al. 2011). Measurement of mRNA signature was done at several time points within a two week investigative study in male dogs.

One out of three dogs had a slight increase of pancreatic exocrine, endocrine alpha- and beta-cells microRNA signatures. This result is difficult to interpret. It may be concluded that these changes of pancreatic microRNA signatures were concomitant to the mild increases of lipase and amylase activities and correlated with the presence of pancreas injury.

Because there is a very high overall protein sequence conservation of ABL1 and ABL2 kinase domains across human and toxicology relevant species (mouse, rat, rabbit, dog, minipig, cynomolgus and rhesus monkeys), the potential of on-target side effects occurring across these domains was evaluated. Further, the potential impact of any amino acid variant on asciminib (ABL001) binding affinity using 3D structural data was evaluated.

Based on protein sequence homology and structural modelling, from a sequence analysis, asciminib is likely to bind similarly to rat, rabbit, dog, cynomolgus monkey and human ABL1/ABL2.

## 2.5.5. Ecotoxicity/environmental risk assessment

A Phase I ERA has been provided for the active substance asciminib hydrochloride in accordance with the current guideline (EMEA/CHMP/SWP/4447/00).

The PEC surfacewater value is below the action limit of 0.01 μg/L and the ERA can stop in Phase I. Asciminib hydrochloride is not a potential PBT substance as log Kow is below the trigger value of 4.5.

Based on the data provided it can be expected that asciminib hydrochloride will not pose a risk to the environment when used in accordance with the SmPC.

## 2.5.6. Discussion on non-clinical aspects

**Pharmacodynamic effects**: *In vitro*, asciminib inhibits the tyrosine kinase activity of ABL1 at mean $IC_{50}$ values below 3 nanomolar. In patient-derived cancer cells, asciminib specifically inhibits the proliferation of cells harbouring BCR::ABL1 with $IC_{50}$ values between 1 and 25 nanomolar. In cells engineered to express either the wild-type or the T315I mutant form of BCR::ABL1, asciminib inhibits cell growth with mean $IC_{50}$ values of 0.61 ± 0.21 and 7.64 ± 3.22 nanomolar, respectively. In mouse xenograft models of CML, asciminib dose-dependently inhibited the growth of tumours harbouring either the wild-type or the T315I mutant form of BCR::ABL1, with tumour regression being observed at doses above 7.5 mg/kg or 30 mg/kg twice daily, respectively. The $IC_{50}$ values are mentioned in the SmPC.

Experiments on large tumour cell line panels revealed high selectivity of asciminib for BCR-ABL1 expressing cells. Two primary metabolites of asciminib, the oxidation product and the pyrrolidine cleavage product, were found to be less potent in inhibition of ABL enzymatic activity and due to their low levels of these metabolites in plasma of patients, their contribution to the pharmacological activity is expected to be minimal.

Combination of asciminib with nilotinib appeared to be more effective than either drug alone. Based on the pharmacokinetic data, the applicant claimed that asciminib exposure was similar in single-agent use and in the combination, so that the synergistic interaction cannot be attributed to pharmacokinetic drug interactions. This conclusion was not agreed. As is clear from plasma concentration vs. time profile in study RD-2013-50274, AUC of asciminib is higher when combined with nilotinib. Similar moderate increase in exposure in the combination setting was observed in the clinical study X2101 and was related to the ability of nilotinib to inhibit UGTs and moderately CYP3A4. The SmPC of the product was updated accordingly.

No substantial off-target kinase activity was detected. A greater than 50% inhibition was found for lipoxygenase, for the vesicular monoamine transporter and for the serotonin 5HT2B receptor with $IC_{50}$ in low micromolar range, however the safety margin for the 80 mg QD dose is higher than 30, therefore, off-target related adverse reactions from interactions on the above-mentioned targets are unlikely clinically relevant, especially given low brain penetration.

Asciminib had no marked effects on hERG and some other cardiac channels (Nav1.5, IKs, L-type Cav1.2) and on cardiovascular parameters in dogs.

In order to study pharmacokinetics of asciminib in pre-clinical models, the analytical LC-MS/MS methods for quantitative determination of the drug in rat, mouse, dog, rabbit and monkey plasma were developed and in general successfully validated. The general problem in the validation was the carryover effect observed in all but rabbit plasma. The applicant examined bioanalytical raw data from the respective toxicokinetic studies for the possible impact due to the observed carryover. The observed greatest difference (high to low) between sequential incurred samples was 31.5 - 155 times (depending on the study), instead of 1000 times in the method validation. Based on the most significant carryover in each

matrix (42.2% - 72.5% of the response at the LLOQ level depending on the matrix) observed in the validation runs, the estimated maximum contribution from the high concentration sample to the immediate next sample was calculated as 0.9% - 5.5% depending on the matrix and the respective toxicokinetic study. It was concluded that the observed carryover in the method validation has no impact on study sample analysis.

After intravenous administration of asciminib, plasma clearance was low to moderate and the half-life of the drug was short to moderate. Following oral dosing, asciminib was moderately absorbed in most animals with exception of mice and dogs where the absorption was rapid. The studies were performed only with male animals. The applicant justified the use of only male animals by the fact that in the asciminib toxicity studies, no apparent AUC and Cmax difference were seen between male and female animals (see Toxicology section). Since in the toxicity studies, performed in rat, dog and monkey, the male to female ratios of AUC and Cmax over the different dose ranges or time of dosing were generally acceptable (usually less than 2-fold different, the use of male animals only was not considered to have an impact on understanding the pharmacokinetics of asciminib in the preclinical species. Some studies were conducted with free base and some with the chloride salt of asciminib, the latter being the clinically used formulation. This is acceptable since the intended clinical administration route is oral, and the free base is expected to be protonated in the stomach.

The plasma protein binding was high and independent of concentration in all species tested (0.945 – 0.980). After oral administration of radiolabelled asciminib to rats, tissues with highest radioactivity concentrations were kidney, liver, adrenal, pancreas, salivary gland, heart, fat (brown), spleen, lung, and gastrointestinal tract. This is consistent with target organs of toxicity in animal models being pancreas, liver and adrenal gland. Melanin binding of asciminib was observed. Little penetration of the blood-brain barrier was detected. Asciminib was detected in foetal plasma of rats and rabbits in the embryo-foetal developmental studies indicating placental transfer.

Major in vitro biotransformation routes of asciminib for different species were direct glucuronidation, amide hydrolysis, oxidation at the pyrrolidinol ring (ketone formation, hydroxylation, oxidative ring opening), and O-dealkylation. For human, direct glucuronidation was the major biotransformation pathway. The other major human metabolic reactions included oxidative ring opening and oxidation of alcohol to ketone. No unique human metabolites were detected.

In rats, the major metabolic route was oxidation of the pyrrolidine ring followed by ring opening forming a number of products. In rat plasma, asciminib was the major component. In the monkey, asciminib was metabolised mainly by oxidative pathways. The major component in plasma was asciminib. The direct O-glucuronide metabolites were found in urine but only to a negligible extent in faeces, probably due to their conversion back to the parent drug within the gastrointestinal tract. In human plasma, parent drug was the predominant drug-related component. No metabolite with mean contribution to plasma radioactivity exposure ≥ 10% was detected. Therefore, further toxicological qualification of metabolites is not warranted.

In rats and monkeys, asciminib was mainly excreted into faeces. The majority of faecal excretion was apparently from biliary elimination. In all pre-clinical species investigated irrespective of the administration route, renal excretion was minor and accounted for less than 10% of the dose.

Target organs besides the pancreas were liver, hematopoietic system, adrenal gland and the gastro-intestinal tract. Most of the findings reversed during a 4-week recovery phase.

Elevations in liver enzymes and/or bilirubin values were observed in rats, dogs and monkeys and were characterised by centrilubolur hepatocyte hypertrophy slight bile duct hyperplasia and increased individual hepatocyte necrosis in rats and reversible diffuse hepatocellular hypertrophy in monkeys. These changes were fully reversible.

A minimal to mild, regenerative reduction in red blood cells mass in rat, dog and monkey has been observed and was consistent with a regenerative, extravascular, haemolytic anaemia.

Minimal mucosal hypertrophy/hyperplasia (increase in thickness of the mucosa with frequent elongation of villi) was present in the duodenum of rats treated at high doses of asciminib (600 mg/kg/day). These changes were fully reversible.

In rats and monkeys, minimal or slight hypertrophy of the adrenal gland and mild or moderate decreased vacuolation in the zona fasiculata occurred. These changes were fully reversible.

Dose-limiting toxicity in dogs only was mortality as a consequence of pancreatic toxicity. This pancreatic acinar atrophy was observed at AUC exposures below to those achieved in patients at the 40 mg BID or 80 mg QD dose. There was a correlation between the presence of increased serum amylase and lipase activities and the presence of pancreatic acinar cell damage at necropsy. The reason for this toxicity was evaluated in several repeat-dose toxicity studies including different dose and time frames and an assessment of circulating microRNAs. However, the cause for this mortality could not be clearly attributed to a specific cell signature. Pancreatic enzyme increase should be carefully monitored in the clinical setting (see section 4.4 of the SmPC).

Administration of asciminib resulted in moderate CV effects (increased heart rate, decreased systolic pressure, decreased mean arterial pressure, and decreased arterial pulse pressure) were observed in jacket telemetered male dogs at single dose of 600 mg/kg or in the invasive telemetry CV safety study at 60 mg/kg. There was no QTc prolongation indicating no effect on QT prolongation. Only few events of electrocardiogram QT prolonged were reported in the clinical studies. However, an effect of asciminib on QT prolongation cannot be completely ruled out (see section 4.4 of the SmPC).

Reproductive toxicity of asciminib was evaluated in a study of fertility and early embryonic development in the rat and embryo-toxicity studies in rats and rabbits. A study on pre-postnatal development was not performed which was agreed beforehand in a Scientific Advice by EMA.

It is unknown whether or not asciminib is present in human milk. Since there is the potential for serious adverse reactions in nursing infants the following advice on use during breast-feeding: "Because of the potential of serious adverse reactions in the breast fed newborn/infant, breast-feeding should be discontinued during treatment and for at least 3 days after stopping treatment with asciminib." is given under SmPC section 4.6. This is in line with the EMA "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling" (EMEA/CHMP/203927/2005), and with other products of this class and thus agreed. However, the wording of the SmPC concerning breast-feeding should also be reflected in the wording of the PIL. Therefore, the wording of the PIL has been updated to reflect the wording of the SmPC.

Asciminib showed no evidence for a genotoxic potential in a standard genotoxicity battery. Carcinogenicity studies have not been conducted in accordance with ICH S9.

Asciminib was found to be phototoxic in vitro and in vivo.

In silico positive impurities were tested with follow up Ames tests. Theses assays were not performed under GLP conditions however according to the study protocols, general rules of OECD and UK MHRA were followed and lack of full GLP compliance is acceptable.

Asciminib PEC $_{surfacewater}$ value is below the action limit of 0.01 μg/L. and is not a PBT substance as log $K_{ow}$ does not exceed 4.5. Asciminib hydrochloride will not pose a risk to the environment when used in accordance with the SmPC.

## 2.5.7. Conclusion on the non-clinical aspects

The pharmacology, pharmacokinetics and toxicology of asciminib have been adequately characterised.

## 2.6. Clinical aspects

### 2.6.1. Introduction

#### GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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

An overview of 9 clinical pharmacology studies (PK data from 310 subjects including 24 subjects with impaired hepatic function and 8 subjects with impaired renal function) and 2 patient studies (PK data from 353 patients with CML) is presented in the PK/PD part of the Clinical Assessment Report.

**Table 9          Tabular overview of clinical studies**

| Protocol No., Countries & Study Dates | Study Design, Purpose & Population Studied | Primary Objective, Primary Endpoint | Total No., Age Range (mean), Group No. | Treatment, Route, Regimen, Duration of Therapy, Dosage | Study Status & Reports of Study Results |
|---|---|---|---|---|---|
| **Pivotal phase III trial** | | | | | |
| **Protocol: CABL001A2301** Countries: Argentina, Australia, Brazil, Bulgaria, Canada, Czech Republic, France, Germany, Hungary, Israel, Italy, Japan, Lebanon, Mexico, Netherlands, Republic of Korea, Russian Federation, Romania, Serbia, Saudi Arabia, Spain, Switzerland, Turkey, United Kingdom, United States Start: 26-Oct-2017 End: ongoing | Design, purpose & population: A phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with chronic myelogenous leukemia in chronic phase (CMLCP), previously treated with 2 or more tyrosine kinase inhibitors Randomisation: 2:1 ratio to asciminib 40 mg BID or bosutinib 500 mg QDR Stratification: Randomization was stratified by major cytogenetic response (MCyR) at screening | The primary objective was to compare the major molecular response (MMR) rate at Week 24 in patients on asciminib vs. patients on bosutinib. The primary clinical question of interest was: Whether the efficacy of asciminib (40 mg BID) was superior to bosutinib (500 mg QD) in patients with CML-CP, previously treated with 2 or more TKIs, with regards to achieving MMR at 24 weeks while on study treatment and without meeting any treatment failure criteria prior to 24 weeks, regardless of dose modification, dose interruption, or deviation in any intake of concomitant medications. of concomitant medications. | Total: 233 Age: 19-83 (51.0) years Groups: 2 ABL001 - 157 bosutinib – 76 | Orally Form(s): ABL001 20 and 40 mg tablets, bosutinib 100 and 500 mg tablets Duration: 96 weeks plus 5 year follow-up Doses: ABL001 40 mg b.i.d. oral bosutinib 500 mg q.d. oral | Study Status: ongoing Report no. [CABL001A2301] 24 week primary analysis Report date: 19-Apr-2021 Other reports: [DMPK-RCABL001A2301-int-02] [CABL001A2301 UGT report] |
| **Supportive Data from Phase I trial** | | | | | |
| **CABL001X2101** Countries: Australia, France, Germany, Italy, Japan, Singapore, South Korea, Spain, The Netherlands, United States Start: 14-Apr-2014 End: ongoing | A phase I, multicenter, open-label study of oral ABL001 in patients with chronic myelogenous leukemia or Philadelphia Chromosome-positive | Primary Objectives: To determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of: | Total: 200 Age: 22-88 (54.5) years Groups: 5 Arm 1: asciminib as single agent in | Form(s): ABL001 hard non-gelatin capsule 5, 20 or 50 mg ABL001 film coated tablets 20, 40 and 50 mg (introduced in amendment #5) | Study Status: ongoing Report no. [CABL001X2101] Primary analysis for RDE/MTD determination and efficacy |

| Protocol No., Countries & Study Dates | Study Design, Purpose & Population Studied | Primary Objective, Primary Endpoint | Total No., Age Range (mean), Group No. | Treatment, Route, Regimen, Duration of Therapy, Dosage | Study Status & Reports of Study Results |
|---|---|---|---|---|---|
| | acute lymphoblastic leukemia | □ asciminib as single agent in patients with CML-CP/-AP<br>□ asciminib in combination with nilotinib in patients with CML-CP/-AP<br>□ asciminib in combination with imatinib in patients with CML-CP/-AP<br>□ asciminib in combination with dasatinib in patients with CML-CP/-AP<br>□ asciminib as single agent in patients with CML-BP and Ph+ ALL<br><br>Primary Endpoint:<br>Incidence of dose limiting toxicities (DLTs) during the first cycle of study treatment<br><br>**Secondary objectives:** • To characterize the safety and tolerability of asciminib as single agent and in combination with either nilotinib or imatinib or dasatinib<br>• To assess preliminary anti-CML activity associated with asciminib as single agent and in combination with either nilotinib or imatinib or dasatinib and anti Ph+ ALL activity associated with asciminib as single agent<br>• To assess the PK profiles of all study drugs in single agent and combination arms in plasma<br>• To characterize the safety, tolerability and efficacy of asciminib as single agent in patients with CML-CP/-AP with T315I mutation | patients with CML-CP/-AP<br>Arm 2: asciminib in combination with nilotinib in patients with CML-CP/-AP (amendment 4)<br>Arm 3: asciminib in combination with imatinib in patients with CML-CP/-AP (amendment 6)<br>Arm 4: asciminib in combination with dasatinib in patients with CML-CP/-AP (amendment 6)<br>Arm 5: asciminib as single agent in patients with CML-BP and Ph+ ALL | Duration:<br>There was no fixed duration of treatment for patients in this study (dose escalation and dose expansion parts). Treatment can continue until patient experiences unacceptable toxicity that precludes any further treatment, disease progression, or treatment was discontinued at the discretion of the Investigator or by the patient decision.<br>Doses:<br>10 mg, 20 mg, 40 mg, 80 mg, 150 mg, 160 mg, 200 mg B.I.D.<br>80 mg, 120 mg, 200 mg Q.D. orally under fasted conditions<br>20 mg or 40 mg B.I.D. + nilotinib 300 mg B.I.D. orally under fasted conditions | Report date: 15-Apr-2021 |

## 2.6.2. Clinical pharmacology

### 2.6.2.1. Pharmacokinetics

The clinical pharmacology related information and PK profile of asciminib has been evaluated in healthy volunteers (single and multiple doses of 40 mg, single 80 mg dose in hADME study) and patients with CML-CP without and with the T315I mutation at a dose range between 10 to 200 mg BID and 80 to 200 mg QD. PK and PD data were also evaluated in several models, including IVIVC, popPK, PBPK and ER.

Asciminib was analysed in human plasma using a validated LC-MS/MS method with the LLOQ of 1.00 ng/mL (expressed in free base) and a dynamic range of 1.00 to 5000 ng/mL for the analyte using 25 or 50 μL of human plasma.

*Absorption*

Asciminib HCl is very slightly soluble, although above pH 3 the drug substance solution is able to form of a supersaturated solution which precipitates over time as the free base form (see quality part). The two forms of asciminib drug substance (free base and HCl salt form) demonstrated a strong pH dependent solubility profile in aqueous solution. Asciminib HCl film-coated tablet 40 mg formed a supersaturated solution in pH 4.5 and 6.8, the amount of the asciminib in solution was therefore greater than the one expected by the equilibrium solubility values across the neutral pH.

Different formulations have been used in the clinical studies: asciminib free base as solid dispersion in capsule (strengths of 5, 20, and 50 mg) and FCT formulation (strength of 20 mg) and asciminib HCl in FCT formulation (strengths of 20 mg and 40 mg). All PK-relevant studies, such as DDI, special populations, have utilised the FMI tablet (Final Market Image) that was bioequivalent to the early capsule.

Two stage biorelevant dissolution studies with fasted state simulated gastric (FaSSGF) and intestinal (FaSSIF) fluids were performed using the 40 mg FCT. The results showed that the asciminib tablet was rapidly dissolved in FaSSGF (pH 1.6) and remained in solution in FaSSIF (pH 6.5) while one would have expected precipitation based on the equilibrium solubility values. With increasing levels of bile acid, bile salt and lecithin, the flux of asciminib through a membrane decreased (aqueous buffer > FaSSIF > FeSSIF). These results suggest that asciminib may be prone to sequester when high levels of bile acids are present in the gastrointestinal tract.

The absolute bioavailability of asciminib was not evaluated in clinical studies. The estimated absolute bioavailability was 73% in the PBPK model. The bioavailability of asciminib decreased with food and was more pronounced with a high-fat meal with 62.3% decrease in AUCinf compared to 30% decrease with a low-fat meal. Tmax was observed at mean 2 hours, and was delayed by 1 and 2 hours when administered with a low-fat and high-fat meal, respectively (Figure 3 below).
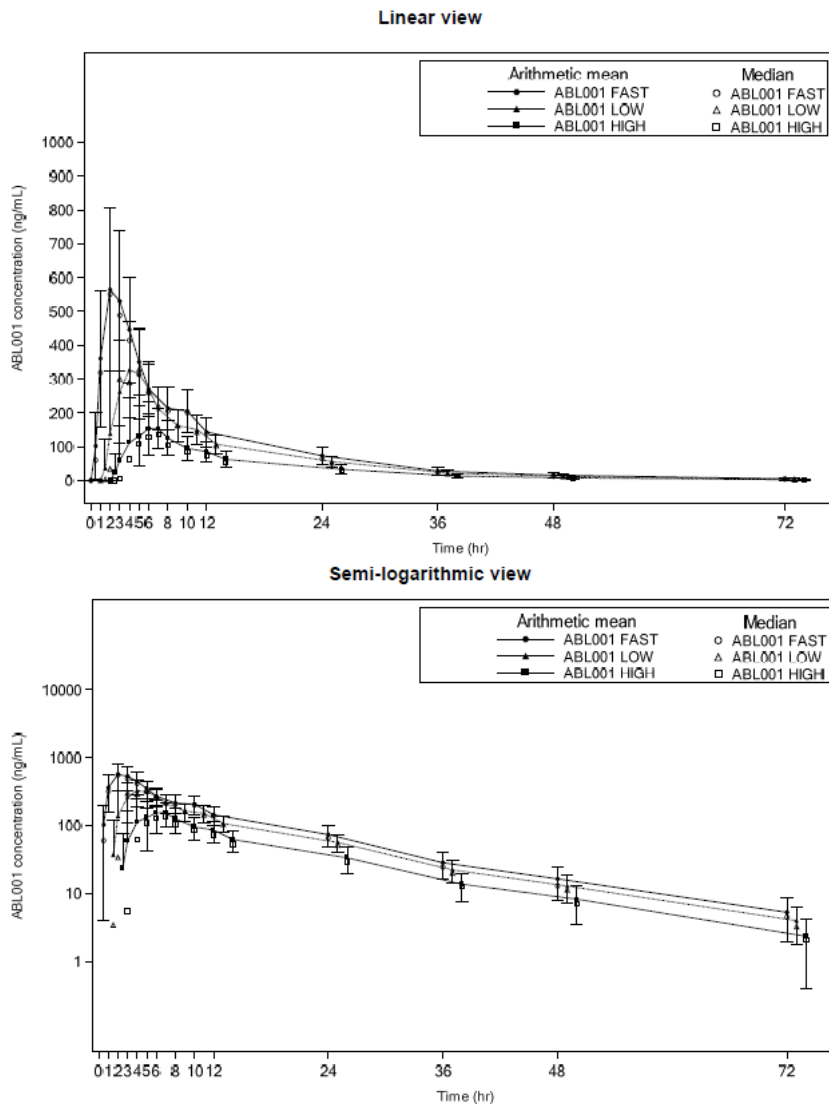
Source: CSR Figure 11-5

**Figure 3  Median and arithmetic mean (SD) concentration-time profiles – study E2101**

*Distribution*

The fraction of asciminib binding to plasma proteins was 97.3% in human, i.e. unbound fraction in plasma (fu) was 2.7%. In the mass balance study, the mean (SD) blood / plasma ratio for total radioactivity averaged over 0.5 to 48 hours, was 0.581 (0.04).

The geo-mean (geoCV%) apparent volume of distribution (Vz/F) was 89.0 L (6.1%) based on the mass balance study and the PopPK analysis. For a typical individual (70 kg male) the combined apparent volumes of central and peripheral compartments were approximately 111 L (V1 46.5 L, V2 64.5 L), suggesting distribution into tissues.

Based on animal data, no or little CNS exposure to asciminib is expected in human.

*Elimination*

The apparent terminal elimination half-life ($T_{1/2}$) was observed in HV with 10.5 - 14 hours.

The apparent clearance (CL/F) of asciminib was 4.34 L/hr in <u>HV</u> (geomean; 80 mg single dose in mass balance study), thus, for human PK a low first-pass metabolism effect is expected. Based on PopPK in <u>patients</u> the apparent clearance was 6.31 L/hr for a total daily dose of 80 mg.
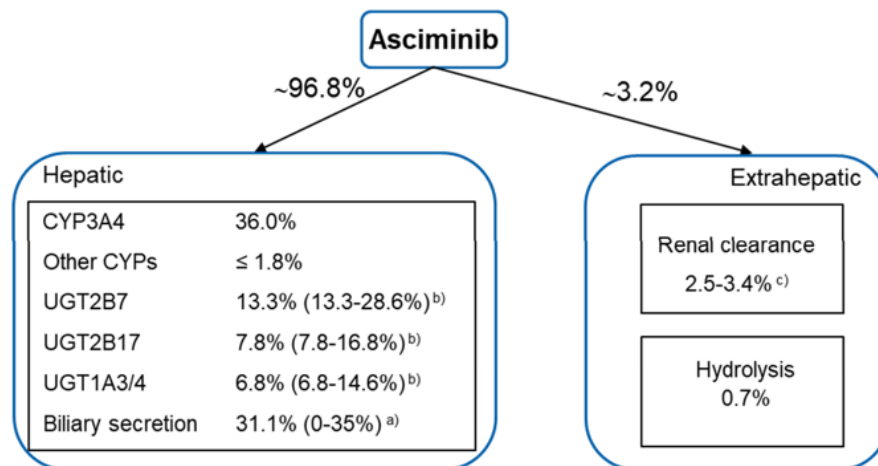


All reported values are approximations.
[a] To simplify, the sum of intestinal and biliary secretion was reported under biliary secretion as estimated value (range)
[b] estimated value (range based on different fractional contributions of biliary secretion and glucuronidation),
[c] renal clearance range based on bioavailabilities of 73% and 100%.
Source: [DMPK-R2000208-Figure 7-1]

**Figure 4 Proposed main elimination pathways**

In the mass balance study A2102 mean recovery of radioactivity in urine and faeces was 91.0±2.25% of dose with 80.0±1.58% for faeces and 11.0±1.46% for urine.

Parent asciminib was the main drug-related component in <u>plasma</u> at all time points analysed, with mean 92.7% of the total radioactivity $AUC_{0-24}$ hours. Metabolite M30.5 (direct O-glucuronide) accounted for 4.93% of total AUC. Minor metabolite M44 accounted for 1.88% of total AUC. Trace amount of M29.5 (0.39%) was also detected. 10 radiolabelled metabolites were characterized and quantified in the excreta.

In <u>urine</u>, unchanged asciminib ranged from 1.8 to 3.1% of the administered radioactive dose, with an average value of 2.5%. The estimated mean CLr of asciminib (0.108 L/hour) was minimal with only 1.4% of the glomerular filtration rate (7.5 L/hour), suggesting minimal renal transporters involvement.

In the cumulative <u>faeces</u> asciminib accounted for 53.7% to 58.5% of the administered radioactive dose, with an average value of 56.7%. The O-glucuronide metabolite M30.5 that was detected in urine as the dominant component was absent in faeces because it was presumably converted back to parent in the gastro-intestinal lumen. The amount of unchanged asciminib in faeces may therefore be overestimated as it also included the undetermined amount of M30.5.

The main biotransformation pathways of asciminib are oxidation at the pyrrolidinol ring and direct glucuronidation. Negligible biotransformation pathway included oxidation of alcohol to ketone, O-dealkylation and amide hydrolysis. Various combinations of the above biotransformation reactions were also observed.

Asciminib has one chiral centre and the therapeutic isomer has R-configuration, with no observed inter-conversion.

Considering the low human plasma exposure of M29.5 (0.39%) and M44 (1.88% of total AUC) after a single asciminib dose of 80 mg, the contribution of both metabolites to total pharmacological activity in human is negligible (0.22% and 0.80% for M29.5 and M44, respectively).

The different UGT2B7 phenotypes and allele-combination genotypes did not result in statistically significant difference in $C_{trough}$ levels.

### *Dose proportionality and time dependencies*

Exposure, both AUC and Cmax, increased in an over-proportional manner for BID regimens between 10-200 mg, and increased nearly dose proportional for QD regimens between 80-200 mg.

Accumulation of asciminib exposure was observed at steady state with the geo-mean ratio of 1.65-2.29 for the BID dosing. No time-dependent PK was observed.

The intra-individual variability in healthy volunteers was low with approximately 6-29%, the inter-subject variability was low to moderate with 14-52% for AUC and Cmax.

In CML patients, the inter-subject variability at 40 mg BID was moderate with 47-50% for AUClast and Cmax, respectively.

### *Pharmacokinetics in target population*

In the ongoing multicentre, open-label, 5-arm, dose escalation first-in-human Phase I study X2101 in patients with CML or Ph+ ALL the MTD/RDE (recommended extension dose) the PK profile and preliminary evidence of efficacy in a dose range of 10-280 mg was evaluated. Full PK sampling was performed on C1D1, C1D15, C2D1. Pre-dose samples were also taken up to cycle 6. See Table below for a PK summary.

Geo-mean CL decreased from 8.40 to 3.81 L/hr (for 10 mg BID to 280 mg BID, resp.), with 7.6 L/hr for 40 mg BID. Clearances for 80-200 mg QD doses were between 5.29-5.76 L/hr.

In the pivotal Phase III, multi-centre, open-label, active-controlled randomized study A2301 Ph+ CML-CP patients received 40mg BID. Full PK sampling was obtained for 14 patients, all patients provided samples for sparse PK.

Geo-mean (geo-CV%) $C_{trough}$ from the full-sampling group at C2D1 was 297 ng/ml (47.2%). $C_{trough}$ levels in the total population (full and sparse PK) remained similar over the 24 week study time.

# Table 10 Summary of asciminib PK parameters across studies in patients with CML

| Dose/Study | Cmax (ng/mL) | Tmax (hr)[1] | AUC0-12hr (ng*hr/mL) | AUClast (ng*hr/mL) | CL/F (L/hr) | Racc |
|---|---|---|---|---|---|---|
| [Study A2301-PE] | n = 14 | n = 14 | n = 13 | n = 14 | n = 13 | |
| 40 mg tablets b.i.d. Week 2 Day 1 | 931 (46.7) | 1.97 (0.983; 3.33) | 5760 (34.0) | 5120 (47.8) | 6.94 (34.0) | |
| [Study X2101-PA] CML-CP/-AP Cycle 1 Day 1 | Cmax (ng/mL) | Tmax (hr)[1] | AUCinf (ng*hr/mL) | AUClast (ng*hr/mL) | CL/F (L/hr) | Racc |
| 40 mg b.i.d. | n = 30 536.85 (74.29) | n = 30 2.10 (1.95, 5.62) | - | n = 30 2246.76 (69.25) | - | |
| 80 mg q.d. | n = 18 1157.54 (46.46) | n = 18 2.06 (1.13; 6.00) | n = 14 12886.7 (42.46) | n = 18 10752.4 (42.90) | n = 14 6.21 (42.46) | |
| Cycle 2 Day 1 | | | AUCtau (ng*hr/mL) | | | |
| 40 mg b.i.d. | n = 30 793.26 (48.92) | n = 30 2.01 (1.00; 6.00) | n = 23 5262.32 (48.49) | n = 30 3967.03 (49.64) | n = 23 7.60 (48.49) | n = 15 1.65 (56.82) |
| 80 mg q.d. | n = 17 1780.98 (23.34) | n = 17 2.00 (0.95; 4.10) | n = 17 15112.4 (27.85) | n = 17 15001.3 (28.27) | n = 17 5.29 (27.85) | n = 16 1.30 (20.29) |
| Patients with CML-CP and with confirmed T315I mutation | | | | | | |
| Cycle 1 Day 1 40 mg b.i.d. | n = 1 728.00 | n = 1 3.00 | - | n = 1 2973.18 | - | - |
| 80 mg q.d. | n = 1 445.00 | n = 1 6.00 | - | n = 1 5443.57 | - | |
| Cycle 2 Day 1 40 mg b.i.d. | n = 1 865 | n = 1 5.98 | - | n = 1 5179.93 | - | - |
| 80 mg q.d. | n = 1 1300.00 | n = 13.00 | n = 1 14439.8 | n = 1 14354.8 | n = 1 5.54 | |

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).
Source: [Study A2301 Primary endpoint analysis-Table 11-10], [Study X2101 Primary analysis-Table 14.2-11.1.1], [Study X2101 Primary analysis-Table 14.2-11.1.2]

- **Study X2101 non-compartmental PK comparison of 40 mg BID vs. 80 mg QD**

Non-compartmental analysis from study X2101 showed that at steady state (C2D1), $AUC_{0-24hr}$ (= total daily exposure, i.e., 2x $AUC_{tau}$ for 40 mg BID) and $C_{max}$ were 40% and 130% higher, respectively, and $C_{trough}$ ($C_{min}$) was 23% lower at 80 mg QD compared to 40 mg BID.

**Table 11 Statistical analysis of PK parameters of asciminib in Study X2101**

| PK parameter (unit) | Visit | Treatment group | n* | Adjusted geo-mean | Comparison(s) | Geo-mean ratio | 90% CI Lower | 90% CI Upper |
|---|---|---|---|---|---|---|---|---|
| AUC0-24hr (ng*hr/mL) | Cycle 1 Day 15 | 40 mg b.i.d. | 10 | 8093 | | | | |
| | | 80 mg q.d. | 16 | 14051 | 80 mg q.d. / 40 mg b.i.d. | 1.74 | 1.36 | 2.22 |
| | Cycle 2 Day 1 | 40 mg b.i.d. | 23 | 10886 | | | | |
| | | 80 mg q.d. | 17 | 15112 | 80 mg q.d. / 40 mg b.i.d. | 1.39 | 1.11 | 1.74 |
| Cmax (ng/mL) | Cycle 1 Day 15 | 40 mg b.i.d. | 12 | 646 | | | | |
| | | 80 mg q.d. | 16 | 1505 | 80 mg q.d. / 40 mg b.i.d. | 2.33 | 1.81 | 3.00 |
| | Cycle 2 Day 1 | 40 mg b.i.d. | 30 | 785 | | | | |
| | | 80 mg q.d. | 17 | 1781 | 80 mg q.d. / 40 mg b.i.d. | 2.27 | 1.83 | 2.81 |
| Ctrough (ng/mL) | Cycle 1 Day 15 | 40 mg b.i.d. | 29 | 250 | | | | |
| | | 80 mg q.d. | 17 | 208 | 80 mg q.d. / 40 mg b.i.d. | 0.83 | 0.62 | 1.12 |
| | Cycle 2 Day 1 | 40 mg b.i.d. | 30 | 258 | | | | |
| | | 80 mg q.d. | 16 | 198 | 80 mg q.d. / 40 mg b.i.d. | 0.77 | 0.57 | 1.03 |

AUC0-24hr is equal to AUCtau in the 80 mg q.d. group and AUCtau multiplied by 2 in the 40 mg b.i.d. group.
Model is a linear mixed model of the log-transformed PK parameters.
Included in the model were treatment group, visit and their interaction as fixed effects and random subject effects.
Results were back transformed to get adjusted geometric mean, geometric mean ratio and 90% CI.
n* = number of observations used for analysis.
Source: Appendix 5.2



AUC0-24 is equal to AUCtau in the 80 mg QD group and AUCtau multiplied by 2 in the 40 mg BID group.
Diamond represents the mean and circle represents values outside of 1.5*IQR.
Lower and upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3, respectively.

Source: SCP Post-text Figure 1
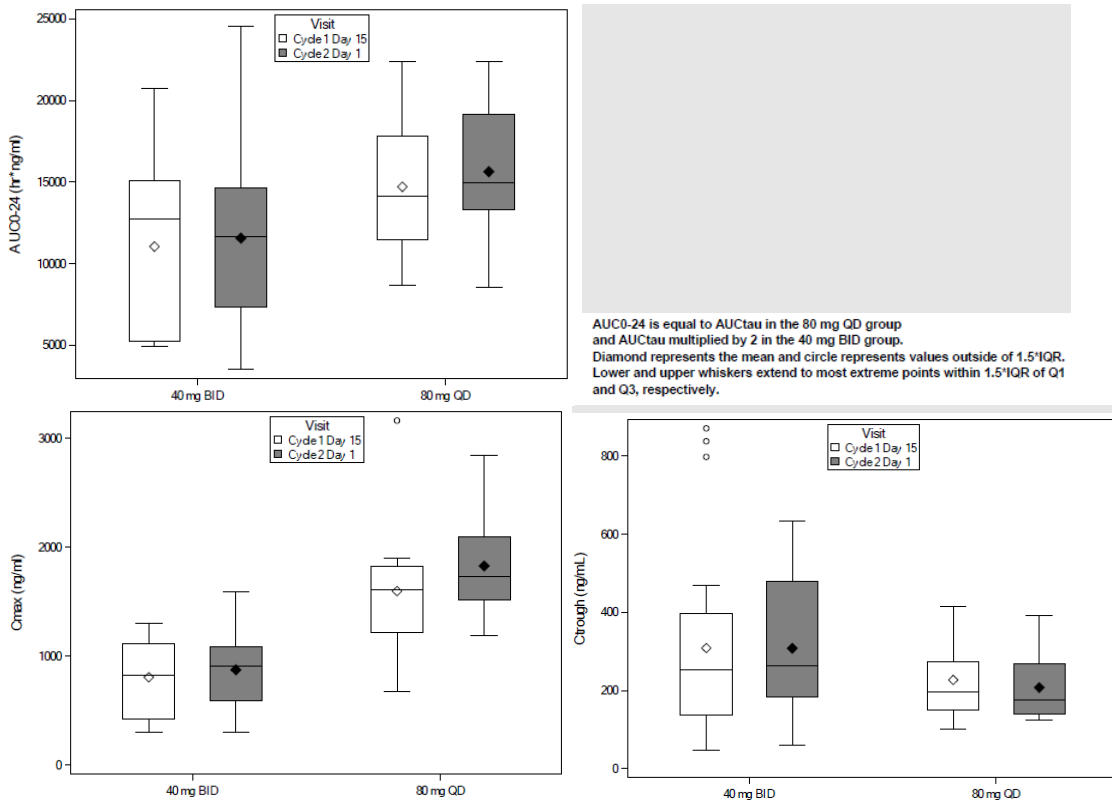
**Figure 5 Boxplots of PK parameters of asciminib - study X2101**

The final PopPK model based on studies A2301 (n=154) and X2101 (n=199; 34x40 mg BID and 12x80 mg QD) was used to evaluate the PK profiles of the two regimens by simulating 500 subjects

each. Based on the simulation, the average $AUC_{0-24h}$ values were comparable between the two regimens 40 mg BID and 80 mg QD. $C_{max}$ and $C_{min}$ were approximately 70% higher and 27% lower, respectively, for 80 mg QD compared to that of 40 mg BID, respectively.

**Table 12   Summary of simulated PK metrics of 40 mg BID and 80 mg QD**

| Regimen | Cmin (ng/mL) | Cmax (ng/mL) | AUC0-24hr (ng*hr/mL) |
|---|---|---|---|
| 40 mg b.i.d. | 302 (60%) | 908 (40%) | 12638 (43%) |
| 80 mg q.d. | 215 (77%) | 1463 (40%) | 12646 (43%) |

Arithmetic mean and %CV are presented
Source: [PopPK Report-Table 7-10]

***Population PK modelling***

PK modelling was used for further analysis of the pharmacokinetics of asciminib.

A two-compartment PopPK model for asciminib with a delayed first-order absorption and was used to characterize PK of asciminib. An over-proportional increase of exposure with dose was described through the PopPK model using dose as a covariate on CL already in the base model. Using dose as a covariate on bioavailability, was not sufficient to describe the PK of asciminib. Also allometric scaling with fixed exponents at 0.75 and 1 for CL and V1 was already incorporated in the base model.

Modelling revealed nominal total daily dose, baseline body weight and baseline aGFR were to be statistically significant covariates on CL. Formulation was found to be a statistically significant covariate of ka. Modelling results for the final PopPK covariate model parameter estimates are shown in the following table.

Using total daily dose as a covariate results in no differentiation between the 40 mg BID and the 80 mg QD regimen. Results for the evaluation of the dose regimen as a covariate were submitted and showed a better fit for the 40 mg BID regimen compared to the 80 mg QD regimen.

## Table 13: Final PopPK covariate model parameter estimates

| Parameter (unit) | Estimate | SE | RSE (%) |
|---|---|---|---|
| **Fixed Effects** | | | |
| Tlag (h) | 0.375 | 0.00127 | 0.34 |
| Ka (1/h) | 1.96 | 0.175 | 8.96 |
| $\theta^{\ddagger}$ (Formulation on Ka) | -1.02 | 0.12 | 11.8 |
| CL( L/h) | 6.31 | 0.171 | 2.72 |
| $\theta^{\ddagger}$ (aGFR on CL) | 0.308 | 0.0763 | 24.8 |
| $\theta^{\ddagger}$ (Dose on CL) | -0.344 | 0.0296 | 8.6 |
| $\theta^{\ddagger}$ (BW on CL) | 0.75 | FIXED | FIXED |
| V1(L) | 46.5 | 1.71 | 3.68 |
| $\theta^{\ddagger}$ (BW on V1) | 1 | FIXED | FIXED |
| Q (L/h) | 6.51 | 0.335 | 5.15 |
| V2(L) | 64.5 | 7.92 | 12.3 |
| **Standard deviation of the Random Effect** | | | |
| $sd_{Ka}$ | 0.785 | 0.0485 | 6.18 |
| $sd_{CL}$ | 0.416 | 0.0175 | 4.2 |
| $sd_{V1}$ | 0.416 | 0.0265 | 6.36 |
| $sd_{V2}$ | 1.57 | 0.106 | 6.73 |
| **Correlations** | | | |
| Correlation V1~ CL | 0.57 | 0.0623 | 10.9 |
| **Error Model Parameters** | | | |
| Residual Error (additive) | 44.6 | 1.58 | 3.54 |
| Residual Error (proportional) | 0.283 | 0.00396 | 1.4 |

Source:
vob/CABL001X/mas/mas_2/model/pgm_001/Final/PopPK/Runs/FinalModel/FinalModel/summary.txt

### *Special populations*

In the dedicated renal impairment study A2105 6 subjects in the normal cohort, and 8 subjects in severe renal impairment cohort were enrolled and received a single 40 mg asciminib dose.

Severe renal impairment resulted in an increase of +56% in AUCinf and +49% in AUClast with comparable Cmax (+8%). CL/F was reduced by -36%. $T_{1/2}$ was prolonged to 17.1 hours. Results for the unbound fraction were comparable.

### Table 14 Summary of PK parameters – Study A2105

| Study Dose | | Cmax (ng/mL) | Tmax (hr)[1] | AUCinf (ng*hr/mL) | AUClast (ng*hr/mL) | T1/2 (hr) | CL/F (L/hr) |
|---|---|---|---|---|---|---|---|
| [Study A2105] 40 mg, SD | Normal renal function | n = 6 564 (30.0) | n = 6 2.03 (1.02; 2.05) | n = 6 5550 (28.7) | n = 6 5480 (28.5) | n = 6 12.5 (21.9) | n = 6 7.21 (28.7) |
| | Severe renal impairment | n = 8 607 (52.1) | n = 8 2.00 (2.00; 8.00) | n = 8 8630 (50.7) | n = 8 8180 (50.0) | n = 8 17.1 (35.4) | n = 8 4.64 (50.7) |

Source: derived from SCP Table 2-1
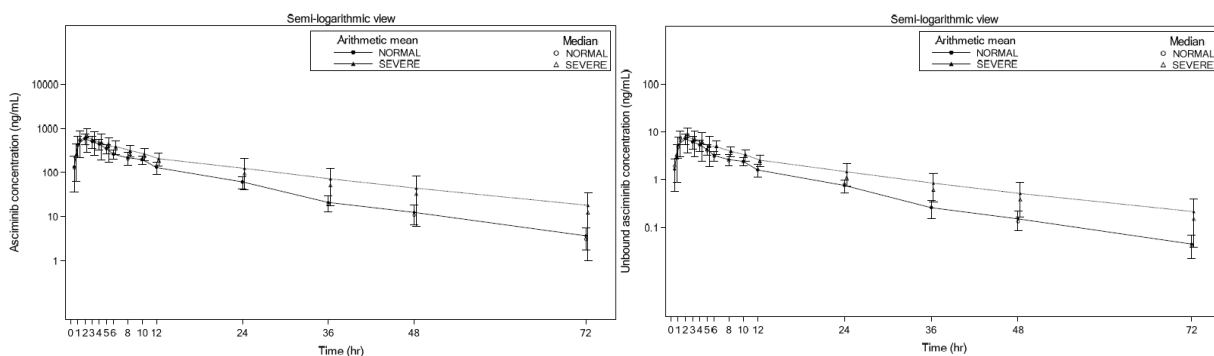
Source: Figures 11-1 and 11-3 CSR

**Figure 6 Concentration profiles of asciminib and unbound fraction in RI - study A2105**

In the popPK analysis, renal function was found to be a statistically significant covariate on clearance. The applicant states that this effect is clinically not relevant and no dose adjustment for subjects with renal impairment is needed.

The dedicated hepatic impairment study A2103 assessed the PK of 40 mg asciminib in 32 non-cancer subjects with impaired hepatic function based on Child-Pugh (CP) classification and healthy subjects with normal hepatic function (8 subjects per group).

Compared to normal, CP-A showed 22% higher AUCinf, 21% higher AUClast, 26% higher Cmax; CP-B had similar exposure (3% higher AUCinf and AUClast, 1.7% lower Cmax); CP-C had 66% higher AUCinf, 55% higher AUClast, and 29% higher Cmax. CL/F of asciminib was comparable among normal, mild and moderate HI groups but lower for the severe group. $T_{1/2}$ of in the severe group was prolonged. Results for unbound fractions were comparable.

**Table 15 Summary of PK parameters – study A2103**

| StudyDose | | Cmax (ng/mL) | Tmax (hr)[1] | AUCinf (ng*hr/mL) | AUClast (ng*hr/mL) | T1/2 (hr) | CL/F (L/hr) |
|---|---|---|---|---|---|---|---|
| [Study A2103] 40 mg, SD | Normal hepatic function | n = 8 | n = 8 | n = 8 | n = 8 | n = 8 | n = 8 |
| | | 578 (15.1) | 2.00 (1.00; 4.00) | 4910 (21.1) | 4840 (21.0) | 14.1 (13.6) | 8.15 (21.1) |
| | Mild hepatic impairment | n = 8 | n = 8 | n = 8 | n = 8 | n = 8 | n = 8 |
| | | 731 (19.0) | 2.00 (1.75; 3.00) | 5980 (34.2) | 5860 (33.3) | 15.6 (12.2) | 6.69 (34.2) |
| | Moderate hepatic impairment | n = 8 | n = 8 | n = 8 | n = 8 | n = 8 | n = 8 |
| | | 568 (14.0) | 2.00 (1.00; 4.00) | 5050 (23.8) | 4960 (23.3) | 13.0 (26.3) | 7.93 (23.8) |
| | Severe hepatic impairment | n = 8 | n = 8 | n = 7 | n = 8 | n = 7 | n = 7 |
| | | 746 (33.2) | 1.50 (1.00; 4.00) | 8160 (32.0) | 7470 (32.4) | 17.5 (19.9) | 4.90 (32.0) |

Source: derived from SCP Table 2-1
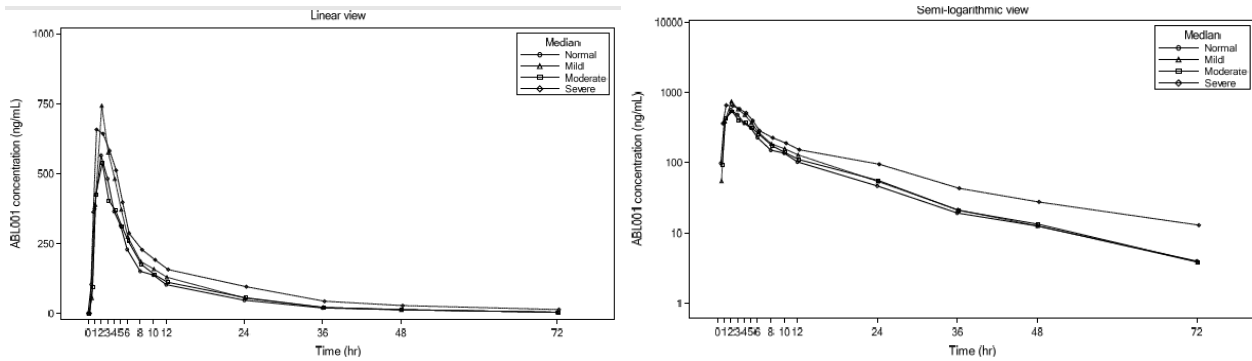
Source: Figure 11-1 CSR

**Figure 7 Concentration curves of asciminib in HI - study A2103**

In the popPK model, while not statistically significant, a trend to lower clearance was observed in the severe hepatic impaired group. The clearance for a typical patient following a total daily dose of 60 mg and 80 mg is 6.97 L/h and 6.31 L/h, respectively. The PopPK derived steady-state AUC0-24h for subjects with severe hepatic impairment (based on the individual estimates (EBE) of the subjects from the hepatic impairment study A2103) was 13018 ng*h/mL and hence marginally higher than the AUC0-24h in patients with CML with normal hepatic function (i.e., AUC0-24h: 12638 ng*h/mL for 40 mg b.i.d.).

Based on the popPK results there was no apparent difference in the PK of asciminib in female (43% of all patients) compared to male patients. Both race (non-Asian, Asian) and ethnicity (non-Japanese, Japanese) were found not to be statistically significant covariates on clearance and the impact of body weight on AUC was minimal. Age, studied over the range of 22 to 88 years in Study X2101 and of 24 to 83 years (asciminib treatment arm) in Study A2301, was not found to be a statistically significant covariate on clearance. In clinical PK studies only 8 patients between 65-74 years of age were evaluated for PK. However, the pivotal study included CML patients of up to 83 years, so that exposure data have been obtained at least from sparse sampling.

**Table 16 Age Distribution of patients across studies**

|  | Age 65-74 (Older subjects number/total number) | Age 75-84 (Older subjects number/total number) | Age 85+ (Older subjects number/total number) |
|---|---|---|---|
| CABL001A1101 | 0/23 | 0/23 | 0/23 |
| CABL001A2101 | 0/45 | 0/45 | 0/45 |
| CABL001A2102 | 0/4 | 0/4 | 0/4 |
| CABL001A2103 | 5/32 | 0/32 | 0/32 |
| CABL001A2104 | 0/20 | 0/20 | 0/20 |
| CABL001A2105 | 3/14 | 0/14 | 0/14 |
| CABL001A2106 | 0/47 | 0/47 | 0/47 |
| CABL001A2107 | 0/79 | 0/79 | 0/79 |
| CABL001E2101 | 0/47 | 0/47 | 0/47 |

No clinical study with asciminib has been conducted in children, hence the PK of asciminib in children is unknown.

***PBPK modelling***

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 for the doses of 80 and 200 mg. Furthermore, it was used to predict the effect of food, hepatic and renal impairment under these conditions.

The PBPK model was developed for 40 mg BID, only study CABL001X2101 included also a dosing regimen of 80 mg QD. Data from this study was then split into training PK dataset and a verification PK dataset. For a single dose of 40 mg in healthy subjects, the model predicted PK parameters within 26% of the observed values. For multiple dosing in a wider dose range (20-200 mg) including 80 mg QD the PBPK model predicted parameters within 45% of the observed values.

A stepwise "middle out" PBPK modelling workflow was implemented using Simcyp simulator 19.1 as outlined in the following figure:



*Dashed gray and solid green lines represent internal and external validation, respectively.*
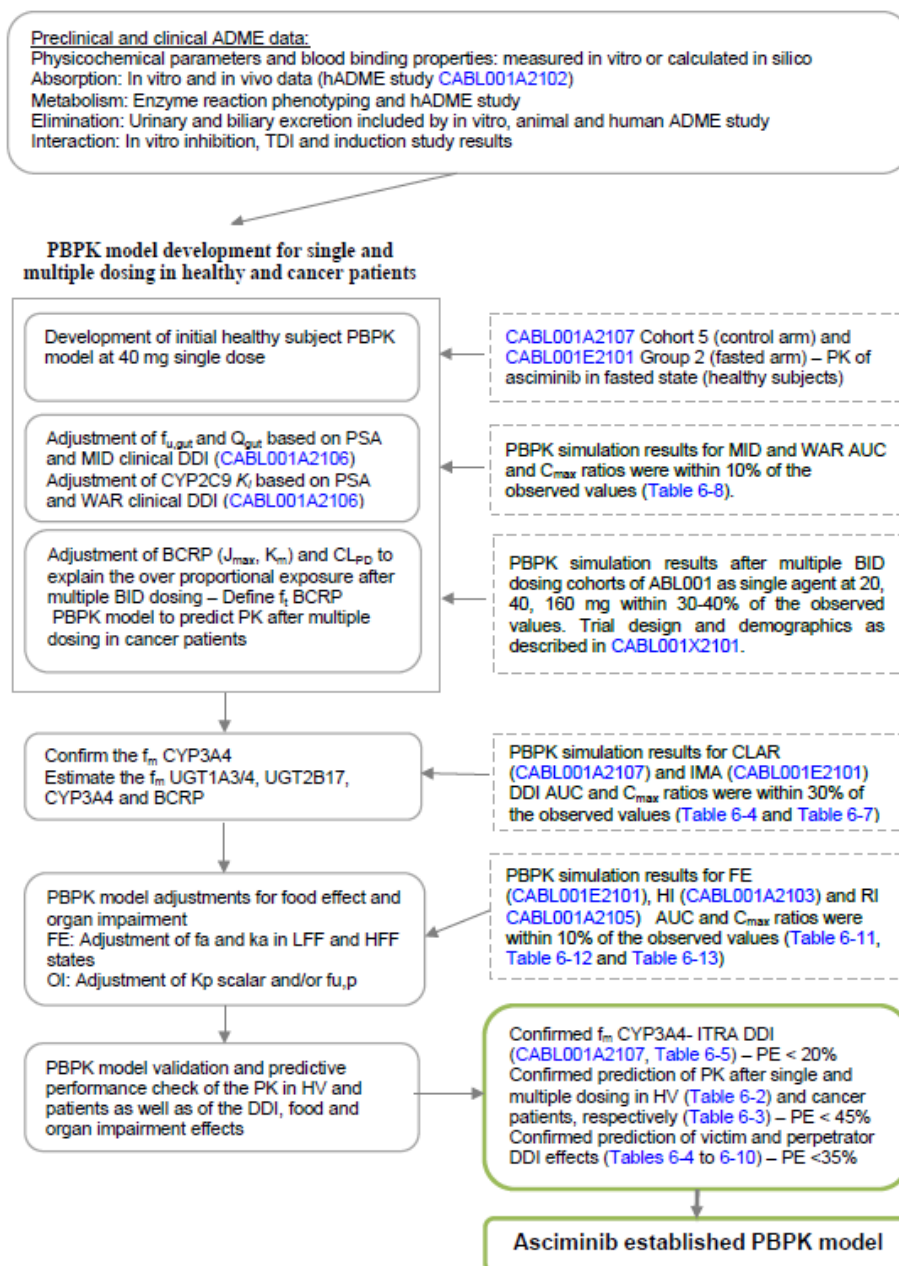
**Figure 8: Development strategy of the asciminib PBPK model**

*Pharmacokinetic interaction studies*

In combination with acid reducing agents (20 mg rabeprazole) in study A1101 the GMRs (AUC 0.99, Cmax 0.91) and 90% CIs of asciminib PK parameters were within 0.80 to 1.25, showing that bioavailability of asciminib was not affected by the co-administration of rabeprazole.

In study A2107 the strong CYP3A4 inhibitor itraconazole as oral solution unexpectedly decreased AUCinf and Cmax by -40% and -50%. In contrast, when itraconazole was given as a capsule, exposure (AUCinf: +4%) and Cmax (+4%) tended to be slightly increased and CL/F and Vz/F slightly decreased compared to asciminib alone.

With the strong CYP3A4 inhibitor clarithromycin AUCinf was increased by 36% and Cmax by 19%.

With the P-gp inhibitor quinidine, AUCinf and Cmax were slightly lower by -13% and -11%, resp., confirming that asciminib absorption and elimination is independent of P-gp.

With the strong CYP3A4 inducer rifampicin, AUCinf was slightly lower by -15% and -11%, and Cmax slightly higher +9%.

Study E2101 investigated the effect of multiple doses of 400 mg imatinib, an inhibitor of CYP3A4 (reversible and time-dependent), P-gp, UGT1A3/4, UGT2B17 and BCRP on single-dose 40 mg asciminib. Both, imatinib and asciminib were administered 30 minutes after start of a low-fat meal. Asciminib exposure was about doubled (+108%) in combination with imatinib under low-fat conditions and Cmax +59% increased, clearance was reduced to ~48% in combination.

In patient study X2101 in combination with nilotinib and imatinib AUCtau and Cmax of asciminib moderately increased by up to 2.1-fold, and no difference was observed in combination with dasatinib.

After multiple doses of asciminib, CYP3A4 and CYP2C9 were mildly inhibited, with exposure of substrate CYP3A4 midazolam increased for AUCinf +28% and Cmax +11%, and S-warfarin AUCinf +41 and Cmax +8%. The exposure of CYP2C8 substrate repaglinide was nearly unaffected by asciminib.

The inhibitory effect of asciminib on dasatinib, nilotinib and imatinib was also mild with AUC increases up to +52%.


*Pharmacokinetics using human biomaterials*

The objective of *study DMPK R1400553* was to evaluate the contributions of individual CYP and UGT enzymes to asciminib metabolism in human liver microsomes. In the kinetic analysis of individual CYP activity followed by scaling the individual contributions to asciminib hepatic intrinsic oxidative clearance, CYP3A4 was determined as a major contributor to the oxidative metabolism in human liver (~96.0%), followed by CYP2J2, CYP2C8, and CYP2D6. CYP4F12 contribution was assumed negligible due to its very low intrinsic clearance. Chemical inhibition of specific UGT enzymes showed that UGT2B7 is likely to contribute the most to the asciminib direct glucuronidation in human liver microsomes (~57%), with UGT1A3, UGT1A4, and UGT2B17 as minor contributors.

Based on the relative contribution of the oxidative pathway from *human ADME study CABL001A2102* and relative involvement of individual CYP enzymes from *study DMPK R1400553*, CYP3A4 was estimated to contribute 35.1% to the total clearance of asciminib in humans (*study DMPK R1709012*). Other CYP enzymes were estimated to contribute to a minor extent (CYP2C8: 0.5%, CYP2D6: 0.2%, CYP2J2: 0.76%). Using intrinsic clearance via each UGT enzyme involved calculated based on the data from *study DMPK R1300172* and the relative contribution of glucuronidation to the biotransformation from *study CABL001A2102*, contribution of UGT2B7 was determined as 27.9%. The contribution of UGT2B17 and

UGT1A3/UGT1A4 to asciminib total clearance was 16.3 and 14.1%, respectively (*study DMPK R1709012*).

In vitro studies of asciminib potential to inhibit metabolic enzymes revealed $K_i$ values in low micromolar range for CYP3A4/5, CYP2B6, CYP2C8, CYP2C9 and UGT1A1 (reversible inhibition in all cases as no time-dependent inhibition was observed).

In in vitro studies, asciminib was found to be substrate of P-gp and BCRP, but not of MATE1, OCT1, OCT2, OATP1B1, OATP1B3 and OATP2B1. It was not investigated whether asciminib is a substrate of MATE2-K, OAT1 and OAT3 but this is acceptable given a low contribution of renal excretion to elimination of asciminib.

In vitro studies revealed asciminib's potential to induce CYP3A4/5.


### *2.6.2.2. Pharmacodynamics*

### *Mechanism of action*

In contrast to ABL1 kinase inhibitors such as imatinib, nilotinib or dasatinib that bind to the catalytic ATP-binding site, asciminib targets the autoregulatory allosteric myristoyl pocket present in ABL catalytic SH1 domain, which is specific for this family of kinases (ABL1 and ABL2). Asciminib can thus also bind in addition to an ATP-competitive TKI. Asciminib binds with high affinity of $K_D$ 0.5 nM and induces the formation of an inactive kinase formation.

In a mouse xenograft model, a single asciminib dose of 7.5 mg/kg showed an $IC_{90}$ for pSTAT-5 inhibition of 121 ng/mL (i.e. 7.3 nM for unbound concentration). At the T315I mutation asciminib showed an $IC_{50}$ of 7.64 nM for inhibition of proliferation of T315I-expressing cells compared to wt cells 0.61 nM.

No studies were performed to assess PD or PK/PD of asciminib in healthy subjects. The PD of asciminib is evaluated based on a PD model of *BCR-ABL1* %IS levels.


### *Primary and Secondary pharmacology*

Triplicate 12-lead ECG readings were obtained from all patients with independent review. The data from Study X2101 were considered adequate to characterize the concentration-ECG relationship across doses ranging from 10 to 280 mg BID or 80 to 200 mg QD.

The concentration-effect analysis demonstrated that the therapeutic dose 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 BID These findings indicate a low proarrhythmic risk with asciminib as a single agent at 40 mg BID in CML patients without T315I mutation.

AEs related to QT prolongation reported in both CML studies were mostly confounded by other factors including concurrent medical conditions, and concomitant medications but the additive role of asciminib cannot be fully excluded. As some asymptomatic QTc prolongations and AEs related to QTc prolongation were observed, caution should be exercised when administering asciminib at 40 mg BID with drugs known to cause Torsade de Pointes.

### Exposure-response analyses

The analysis included 303 patients with CML-CP from Study A2301 and Study X2101. 267 patients received BID, 36 patients received QD dosing, including 67 subjects with T315I mutation. At baseline, majority of the subjects had >10% *BCR-ABL1* IS >1% levels.

The observed-data time-courses showed decreases in $\log_{10}$-transformed BCL-ABL for all dose regimens without an apparent dose-dependency. There was no gender-related difference in overall pattern in *BCR-ABL1* time course.

Computed median predicted MMR rate suggested a slightly positive exposure-efficacy relationship, though not a meaningful difference with 34%, 35%, and 39% for 40 mg BID, 80 mg QD and 200 mg BID at 48 weeks, respectively. For 40 mg BID, MMR rates at the evaluated time-points were comparable for patients who had 2 and ≥3 prior TKI treatments, but MMR rates were lower compared to 1 prior TKI.

**Table 17 MMR rate at 24- and 48-week for 40 mg BID**

| Variable | Category | 24-wk MMR rate (%) | 48-wk MMR rate (%) |
|---|---|---|---|
| Baseline BCR-ABL (log10-transformed) by percentiles (5, 25, 50,75, 95)‡ | 0.25% (-0.6) | 57.0 ±4.5 | 58.8 ±4.7 |
| | 0.5% (-0.3) | 48.6 ±5.2 | 52.4 ± 5.3 |
| | 1% (0) | 41.5 ±4.8 | 46.3 ± 5.3 |
| | 16% (1.2) | 19.1 ± 3.9 | 25.7 ± 3.8 |
| | 40% (1.6) | 13.5 ±3.4 | 19.6 ± 3.7 |
| | 79% (1.9) | 9.5 ±2.7 | 15.2 ± 3.5 |
| Baseline BCR-ABL by range | >0.1 – 1% | ± 49.9 ± 5.1 | 53.3 ± 4.7 |
| | >1% - 10% | 28.4 ± 4.2 | 34.7 ± 5.1 |
| | >10% - 100% | 12.5 ± 2.9 | 18.5 ±3.9 |
| Number of prior TKI treatment | 1 | 33.3 ± 4.7 | 37.6 ± 5.0 |
| | 2 | 26.1 ± 4.7 | 31.8 ± 4.9 |
| | ≥3 | 27.0 ± 4.0 | 32.1 ± 4.2 |

Data reported as mean ± standard deviation.
Source: ER report Table 4-8

As regards the mutT315I subgroup, at doses <200 mg BID, most of these patients did not experience a decrease in *BCR-ABL1* below -1 $\log_{10}$, or equivalently, 0.1% except those who had only one prior TKI treatment. MMR rates with 200 mg BID were 20.7% for 24 weeks and 23.7 % for 48 weeks.

At baseline, mutations (other than T315I and V299L) were identified in 17 of 157 patients randomized to asciminib and newly emerging mutations were seen in 12 patients in the asciminib arm. Due to the limited number of patients with each of the detected mutations, and the variability in the level of response observed, a conclusive statement on the possible contribution of mutations to a lower efficacy cannot be made at time of week 96 analysis.

The exposure-safety relationship was explored using various safety endpoints such as laboratory, vital signs abnormalities, fatigue/asthenia, TEAEs of grade 3 or higher, TEAE leading to dose reduction or dose interruption, changes in serum creatinine and QTcF change from baseline. For all safety endpoints analysed, there was a lack of clinical relevant difference in probability for a safety event with increase in the asciminib PK metrics within the investigated dose range.

## 2.6.3. Discussion on clinical pharmacology

**Pharmacokinetics**

The clinical pharmacology profile has been evaluated in healthy volunteers (single and multiple doses of 40 mg, single 80 mg in mass balance) and patients with CML-CP without and with the T315I mutation between 10 to 200 mg BID and 80 to 200 mg QD as well as several models including IVIVC, popPK, PBPK and ER.

The analytical methods were adequately described and validated and are considered suitable to analyse asciminib in human plasma. Also drug interference for the DDI studies was evaluated and acceptable.

The PBPK model applied (Study 2001088) was based mainly on 40 mg single dose data and a small number of patients for 80 mg QD. was used to build the model. For a single dose of 40 mg in healthy subjects, the model predicted PK parameters within 26% of the observed values, which is considered appropriate. The PBPK model was also applied (Study 2001088) to predict DDI scenarios which has not been tested clinically for the doses of 80 and 200 mg. Furthermore, it was used to predict the effect of food, hepatic and renal impairment under these conditions. For multiple dosing in a wider dose range (20-200 mg) including 80 mg QD the PBPK model predicted parameters within 45% of the observed values. The small number of patients for 80 mg QD is considered problematic and in addition to that over-proportional exposure with dose leads to further uncertainties in prediction. The Applicant concluded that the developed PBPK model can be used to predict DDI scenarios for doses and regimens which have not been tested clinically and for predictions regarding food effect and renal or hepatic impairment. However this was not considered acceptable.

Absorption: When a 40 mg FCT dose was tested, asciminib HCl formed a supersaturated solution in simulated gastric fluids. Still, for a supersaturated solution it might be expectable that precipitation could occur after drug intake if the dose, i.e. concentration, was increased. The applicant discussed that the excipient hydroxypropyl cellulose acts as precipitation inhibitor. In response to LOQ, additional dissolution data were obtained and used to update the IVIVC model and these data supported that asciminib precipitation at higher doses was minimal and absorption could be considered comparable at all doses. Asciminib is classified as BCS II with low solubility and moderate to high permeability, which can be agreed as the fraction absorbed is obviously above 85%, based on the mass balance study. In vitro, permeability in simulated gastric/intestinal fluids was reduced the higher the bile acid/bile salt/lipid content was. This was discussed by the applicant as resultant from sequestration of asciminib with bile acids. This is in accordance with reduced bioavailability in fed state, comparably with all formulations and independently of drug base or HCl salt. The food effect was more pronounced with high-fat with a reduction of exposure of about 65% compared to the low-fat state with ~30% decrease compared to fasted. Tmax was also delayed by 2 and 1 hours, respectively. Based on this, in both CML-patient studies the study drug was administered in fasted state, with at least 2 hours before and 1 hour after intake. In these studies patients received 40 mg BID, 12 hours apart. Considering these food requirements, BID dosing may become difficult for compliance. This was one reason for the applicant for applying also for a not approvable 80 mg QD regimen in addition to 40 mg BID as investigated in phase III. The information in the PI regarding intake with food is acceptable.

Distribution: Asciminib shows a high PPB of 97.3% (unbound fraction 2.7%) and mostly binds to serum albumin, followed by HDL and VLDL, with lesser contributions from alpha1-glycoprotein and LDL. The blood-plasma ratio was about 0.58 for total radioactivity in the mass balance study. Vz was calculated with 46.5 L and 64.5 L for the central and peripheral compartments, reflecting moderate distribution to peripheral tissues. Distribution into CNS is not expected.

Elimination: Mean total recovery of radioactivity in the mass balance study was >91%, which is sufficient for determination of the main elimination pathways in accordance with the requirements of the EMA DDI

GL. As AUC and Cmax are nearly dose-proportional, mass-balance data can be extrapolated from 80 mg to 40 mg dose. Main elimination route is hepatic after metabolism and about 31.1% of parent are excreted biliary/intestinal via BCRP. Renal excretion of unchanged asciminib is only ~ 2.5%. Asciminib can be considered a low-extraction drug as the apparent clearance is lower than 20% the hepatic blood flow. With a half-life of 10.5-14 hours in HV asciminib BID dosing will result in higher accumulation as in QD dosing. Main biotransformation pathways are via glucuronidation and oxidation. The 2 non-glucuronide metabolites of asciminib M29.5 and M44 have an about 2-2.5-fold lower activity than asciminib and their plasma concentrations are <2% of total AUC. Therefore, their contribution to a pharmacological effect can be considered negligible and their PK has not been further evaluated, which is acceptable. M30.5 is a direct glucuronide via UGT2B7 that is excreted biliary and was also the most abundant metabolite in urine (7.0%). Glucuronides excreted in bile are usually cleaved in GI tract, as was discussed by the applicant for M30.5. Based on non-clinical findings a potential for an enterohepatic circuit was questioned. Both the aspect of sequestration by bile acids and the large intestine environment which leads to low solubility of asciminib were discussed by the applicant and it can be agreed that a clinically relevant enterohepatic re-absorption is not expectable. UGT2B7 polymorphisms did not result in clinically relevant exposure difference. Inter-conversion via biotransformation processes of the therapeutic R-enantiomer to the S form has not been observed.

PK in patients: PK for AUC and Cmax was over-proportional after twice daily dosing and nearly dose-proportional after once daily dosing in CML patients. Trough concentrations increased with increasing dose and remained constant over the 24-week treating period. Steady-state had been reached at day 15 of treatment, with an accumulation ratio of 1.65 for 40 mg BID, which could be expected based on T1/2 of >10 hours. No time-dependency was observed. Asciminib showed a moderate inter-subject variability with ~43-50% for AUC and Cmax at both proposed BID and QD dosing regimens. The intra-individual variability in HV was low with approximately 6-29% for AUC and Cmax. PK data for smallest patient groups, especially 280mg BID were only presented as listing. Upon request the applicant tabulated primary and secondary PK parameters for all doses investigated in dose-finding study X2101. PK was slightly over-proportional at the dose range tested from 10mg BID to 120mg BID. CL/F in steady-state at the proposed dose regimens was (geo-mean) 7.6 L/hr at 40mg BID. MTD was not achieved in Study X2101, suggesting a large therapeutic window of asciminib. Based on the available safety, efficacy and PK data the applicant decided for the asciminib dose of 40 mg BID as the recommended Phase III dose.

Special populations

In the renal impairment study with a single 40 mg dose, subjects with severe renal impairment compared to normal renal function subjects had 56% higher AUCinf and 49% higher AUClast and a 36% lower CL/F. In the popPK analysis, renal function was found to be a statistically significant covariate on clearance. The applicant argues that this effect is clinically not relevant and no dose adjustment for subjects with renal impairment is needed. However, safety data suggest a worse safety profile for patients with moderate renal impairment compared to patients with normal renal function or mild renal impairment.

As the effect of renal impairment could be underestimated for the 40 mg BID posology, the PopPK model was further used to evaluate whether renal impairment was impacting asciminib PK behaviour by external validation and testing renal function as a categorical covariate (i.e., normal vs severe) on CL and V1. It was concluded that the current PopPK model is suitable for application in patients with severe renal impairment. No further significant co-variate effect was found than the aGFR. The median predicted AUC0-24 and Cmax for severely impaired patients are 40% higher than that of a typical individual with normal renal function, for a dose of 40 mg b.i.d. Given the relatively flat exposure-safety relationship over a 5-fold difference in exposure it could therefore be agreed that no dose adjustment is needed for subjects with renal impairment, including severe renal impairment.

For subjects with mild liver impairment (Child-Pugh A) AUC and Cmax were approximately 21-26% increased, whereas moderate cirrhosis (CP-B) had only minor effects (1.7-3% increase). In both categories elimination T1/2 and clearance were unchanged compared to normal. In the severe cirrhosis group (CP-C), after a single dose of asciminib AUCinf was 66% and Cmax 29% higher with reduced clearance and prolonged T1/2 (17.5 hours, max >23 h) showing that especially the elimination phase is impaired by CP-C liver disease. The PopPK derived steady-state AUC0-24h for subjects with severe hepatic impairment for 40 mg b.i.d. were only slightly higher than in patients with CML with normal hepatic function.

Similar to the discussion for RI in view of the much higher doses which did not result in major toxicities and no MTD, there might be a sufficiently broad therapeutic window in general, to accept that a dose reduction is not warranted for any grade of HI.

To address the concern of over- and underprediction of the PBPK model new sensitivity analysis on the percentage of re-absorption and additional exploratory PBPK simulations were performed. A model assuming no re-absorption via enterohepatic circulation described the observed data with least deviation.

As regards to other special population groups, no apparent difference in PK was observed for gender, race and ethnicity or weight. As asciminib is a low-extraction drug, no impact on total clearance due to reduced blood flow in elderly is immediately expected. No dose adjustment is necessary in these groups based on current knowledge. The PI is adequate in this respect.

Drug interactions – *in vitro*

CYP3A4 appeared to be the major contributor to Phase I metabolism and responsible for 35.1% of total metabolic clearance of asciminib in humans (as calculated based on in vitro and human ADME data). The relative contribution of UGT2B7, UGT2B17 and UGT1A3/4 was estimated as 27.9%, 16.3% and 14.1% of the total metabolism, respectively.

In vitro studies of asciminib potential to inhibit metabolic enzymes revealed Ki values in low micromolar range for CYP3A4/5, CYP2B6, CYP2C8, CYP2C9 and UGT1A1 (reversible inhibition in all cases as no time-dependent inhibition was observed).

According to the basic model, in vivo studies to assess the impact of inhibition of the aforementioned enzymes by asciminib on metabolism of the relevant substrates would be warranted. The applicant has provided a DDI risk assessment using the mechanistic static model. According to the latter, only in vivo studies with CYP3A4, CYP2B6, CYP2C8, CYP2C9 and UGT1A1 were deemed necessary for 80 mg QD, which was taken as "the-worst-case scenario". This is acceptable. In vivo effects were investigated for all these enzymes except UGT1A1. The applicant found no apparent increase in blood concentration of bilirubin, an endogenous substrate of UGT1A, in the clinical studies A2301 and X2101 and concluded that there was no relevant UGT1A1 inhibition by asciminib at doses of 40 mg BID and 200 mg BID (X2101 only). This was further supported by PopPK analysis that showed a lack of correlation between the probability of grade ≥2 increase in total bilirubin and any PK metrics analysed (daily AUC, Cmax, Cmin). It is agreed that the absence of an in vivo study with UGT1A1 is justified.

In in vitro studies, asciminib was found to be substrate of P-gp and BCRP, but not of MATE1, OCT1, OCT2, OATP1B1, OATP1B3 and OATP2B1. It was not investigated whether asciminib is a substrate of MATE2-K, OAT1 and OAT3 but this is acceptable given a low contribution of renal excretion to elimination of asciminib.

Asciminib was found to inhibit BCRP, P-gp, MATE2-K, OAT3, OATP1B1, OATP1B3, and OCT1 in vitro to an extent warranting in vivo studies. The ratio of unbound portal vein concentration for asciminib 40 mg b.i.d. to Ki,u value for OCT1 was 0.035. The respective values for OATP1B1 and OATP1B3 are 0.10 and 0.13 (80 mg q.d.). No exposure increase was observed for the OATP substrate repaglinide in study A2106

(geometric mean AUCinf ratio: 1.08), therefore, the OATP inhibition is considered unlikely. This is agreed. The ratio of unbound plasma concentration for asciminib 80 mg q.d. to Ki,u values for OAT3 and MATE2-K are 0.11 and 0.05, respectively. As these transporters are renal transporters and the contribution of the renal route to asciminib elimination is low, in vivo studies on DDI due to interference with MATE2-K and OAT3 can be waived.

In vitro studies revealed asciminib's potential to induce CYP3A4/5. As CYP3A4/5 induction is mediated by the pregnane X receptor (PXR), P-gp and OATP1B1 may also be induced. In line with the EMA Guideline on the investigation of drug interactions, in vitro induction studies of PgP and/or OATP1B1 in hepatocytes should be performed and the applicant committed to perform such in vitro studies as a post-authorisation measure (PAM).

*In vivo* – as victim

The PPI study suggested minor effect on rate and extent of asciminib absorption with increased pH by rabeprazole. Therefore, compared with the normal fasting gastric conditions, drug dissolution at higher gastric pH conditions should not be the rate limiting step for drug absorption. The SmPC does not state anything about pH affecting substances which is appropriate based on the minor effects.

For the controversial itraconazole results in A2107 the applicant provided the following discussions in the SCP: "*Further investigations of this unexpected result suggested that the most plausible explanation was a pre-systemic effect, potentially a complex formation with hydroxypropyl-beta-cyclodextrin, an excipient in the itraconazole solution used (hydroxypropyl-beta-cyclodextrin concentration was 40 times the concentration of itraconazole in the oral solution [8 g cyclodextrin per 200 mg itraconazole dose]). It has been hypothesized that hydroxypropyl-beta-cyclodextrin could have sequestered asciminib and therefore decreased the free asciminib concentration available for absorption in the gut.*"

SmPC section 5.2 provides information about the itraconazole oral solution, i.e. cyclodextrin DDI. Several other drugs and especially food contain cyclodextrin e.g. as emulsifying excipient. This DDI could thus also occur with other drugs or food and drinks containing cyclodextrin or other sequestering/trapping substances. The applicant is currently performing further in vitro tests with different cyclodextrins and committed to submit results as a PAM.

Asciminib exposure was only mildly affected by concomitantly administered drugs that are strong CYP3A inducers (rifampicin) or strong CYP3A4 inhibitors (itraconazole, clarithromycin). Although CYP3A4 is the main metabolising enzyme, this pathway was considered to only contribute to overall 36% to hepatic elimination – in addition to UGT-mediated glucuronidation and biliary secretion.

Smoking (UGT induction) did not relevantly affect asciminib PK based on the patient studies.

In the dedicated DDI study E2101 in HV, asciminib AUC was calculated as about doubled under co-administration with imatinib (inhibitor of CYP3A4, P-gp, UGT1A3/4, UGT2B17 and BCRP) with a low-fat meal, Tmax was delayed and clearance was 5.19 L/h. In this DDI arm, clearance for asciminib alone was 11.1 L/h, as compared to values in other HV single-dose studies of ~4.1-7 L/h. Taking into consideration that the same study (arm 2) evaluated the food effect of a single-dose of 40 mg asciminib and a low-fat meal was found to reduce exposure by 30%, delay Tmax by about 1 hour and increase clearance by 40% (from 6.86 L/hr to 9.7 L/hr), the SD asciminib PK parameters with imatinib under low-fat conditions were quite similar to the low-fat conditions only.

The applicant clarified the magnitude of sole imatinib-mediated DDI effect, i.e. excluding the food-effect, as perpetrator and victim by PBPK simulations which did not reveal any clinically relevant differences to the observed study results. This is reassuring.

With nilotinib (moderate inhibitor of CYP3A4, UGT2B17 and UGT1A3/4, BCRP) in fasted state accumulation increased up to about 2-fold as without perpetrator. PBPK modelling estimated a roughly

comparable distribution of pathway involvement in asciminib hepatic clearance, so it could be supported that each inhibition was only mild. Dasatinib (CYP3A4 inhibitor) effects in fasted state were minor only.

Regarding rifampicin, which is also an UGT1A inducer, the combined induction effect only led to a 15% decrease in exposure, with shorter half-life and a higher clearance, supporting that either pathway, CYP- and UGT-mediated, is only mildly affected.

Asciminib absorption and elimination was only minimally affected by P-gp inhibitor quinidine. Accordingly, P-gp inhibitors can be co-administered at all recommended doses without restrictions. The SmPC does not state anything about P-gp DDI which is appropriate based on the minor effects.

BCRP was considered by the applicant to be saturated at intestinal concentrations, so that a contribution to efflux was deemed irrelevant; regarding liver efflux, the applicant discussed that in the PBPK model inclusion of BCRP improved prediction and explained that due to the lowest Km (intracellular 0.14µM) it would be saturated first, with a fractional contribution of ~31%. Based on this, no clinical DDI study was performed. This can be accepted.

_In vivo_ – as perpetrator

In the clinical perpetrator DDI study asciminib was a mild inhibitor (i.e. AUC increase 1.25-2-fold or clearance $\leq$ 50% decrease) of CYP3A4 (midazolam) and CYP2C9 (warfarin). It had no clinically relevant effect on CYP2C8 (repaglinide; also a substrate of OATP1B1/3) at 3 days of 40mg BID. According to the static model it was the 80 mg single dose that would have an effect on CYP2C8, but not the 40mg dose. The applicant satisfactorily justified that 40 mg BID for 3 days was sufficient to study the DDI.

In CML patients, dasatinib, imatinib (3A4 substrates) and nilotinib (3A4 and 2C8 substrate) were only mildly affected by co-administration of various doses of asciminib; however, a conclusive assessment of those DDI data is hampered by the very small patient numbers.

Transporter inhibition for UGT1A1 was not evaluated in a dedicated DDI study. In the SmCP it was discussed: "_In the clinical studies A2301 and X2101, no apparent increase of bilirubin blood concentration, an endogenous substrate of UGT1A1, has been observed, indicating that there was no relevant UGT1A1 inhibition by asciminib at doses of 40 mg BID and 200 mg BID (X2101 only). This was further supported by PopPK analysis that showed a lack of correlation between the probability of grade $\geq$2 increase in total bilirubin and any PK metrics analysed (daily AUC, Cmax, Cmin)._" This is acceptable.

For OATP1B1/3, repaglinide was only mildly affected. For BCRP and OATPs a risk assessment with rosuvastatin was performed by M&S and estimated only low DDI potential also with 80 mg.

Based on the results of RIS assessment, the CYP3A4 induction effect can be considered negligible. At both doses, the resulting net effect is a weak CYP3A4 inhibition.

Overall, none of the clinically investigated or modelled DDI, both for asciminib as victim or perpetrator, at the proposed doses 40 mg BID and 80 mg QD revealed a strong effect. Only for some simulation a moderate effect was observed.

**Pharmacodynamics**

Asciminib is an allosteric high-affinity inhibitor of BCR-ABL1 kinase. It does not bind to the catalytic ATP-binding pocket where also the resistance-promoting acquired T315I mutation is located.

A Proof-of-concept study was not performed. Final RP3D selection of 40 mg BID was obviously not based on clear clinical PD effects, but based on ER assumptions considering preclinical experiments and popPK simulations from the phase I study X2101 in CML-patients.

ER analyses for efficacy were utilised to retrospectively evaluate a potential relationship of reduction of _BCR-ABL1_ IS with dose from the CML study data, both for non-T315I-mutated BCR-ABL1 and T315I-

mutated). No significant dose-/exposure-response effect was observed between 10 mg BID and 200 mg BID asciminib. However, some differences for number of TKI-pretreatment lines and *BCR-ABL1* baseline levels were seen: the less prior lines and the lower the baseline level the higher the MMR rate at 24 weeks and 48 weeks.

Considering the allosteric inhibition mechanism and the unbound Cmin above IC90 for pSTAT-5 inhibition for dose regimens at least above 80 mg QD, potential reasons for an absent (observed and simulated) clinically relevant ER effect were justified by the applicant with a near efficacy plateau that might have already been reached at the lowest dose tested.

The applicant was asked to clarify whether (secondary) mutations under treatment have been detected and investigated in accordance with the objectives of study A2301 and whether they led to reduced efficacy. From the data at the week 96 analysis no specific pattern of reduced or lack of efficacy could be derived, not only because of small patient numbers but also due to contrasting responses for the same mutation (e.g. for M244V or Y253H mutations).

The safety ER analyses revealed a lack of clinically relevant differences in exposure-response for various safety parameters between doses of 40 mg BID, 80 mg QD and 200 mg BID. The various tabulations from the linear mixed effects models or logistic regressions were impossible to summarise. Considering the proportion of patients having observed AEs with the different doses up to 200mg BID, as discussed during the presubmission meeting for thrombocytopenia, there seems a low exposure-response relationship for safety.

Overall, based on the data from study X2101, the risk for QTcF prolongation above the clinically relevant threshold of 10msec is low at both proposed dose regimens. The SmPC and PL contain, though, a warning that caution should be exercised when concomitant drugs known to cause Torsade de Pointes are given.

Exposure-response was also evaluated for in T315I-mutated BCL-ABL. In general, asciminib showed a PD effect also in this group, though at much higher doses and still a lower effect than in non-mutated CML-CP patients. For comparison, the in vitro IC50 for T315I was ~10-fold higher than for wild-type and the obtained Cmin with 200 mg BID was comparably so (2799 ng/ml vs. ~200ng/ml for 80mg QD). Data can still be considered supportive in so far that an ATP-binding pocket T315I-resistance might obviously be partially overcome by an inhibition of the allosteric binding site as with asciminib.

Despite the genotyping for PK from A2301, biomarker data that were collected for exploratory endpoints will be evaluated after end of study. For this, a post-approval commitment is expected (PAM-REC). The applicant also explained that exploratory biomarker analyses for asciminib in combination with other TKIs, with exception of BCR::ABL mutation analysis was removed from the protocol of study X2101 due to technical infeasibility.

Clinical data regarding genetic impact on PD response is limited to the T315I mutation, these data are discussed in the efficacy section.

## 2.6.4. Conclusions on clinical pharmacology

It is concluded that asciminib pharmacokinetics are overall well investigated.

For special populations with severe renal or hepatic impairment based on the current data it is concluded that no dose adjustment is needed. The DDI potential is overall only mild in magnitude. Similarly, PD is mostly satisfactorily evaluated. A few open aspects will be addressed by the applicant as PAMs.

In the Phase III Study A2301, asciminib 40 mg twice daily (b.i.d.) posology was further evaluated based on based on preclinical evidence, the results of the PopPK-exposure analysis and the pharmacokinetic, efficacy and safety data available from the first in-human study phase 1 trial X2101. The applicant

proposed in the SmPC a recommended total daily dose of asciminib for adult patients with Ph+ CML-CP previously treated with 2 or more tyrosine kinase inhibitor (TKI) of 80 mg to be taken orally either as 80 mg once daily (q.d.) or as 40 mg twice daily (b.i.d.). In view of CHMP, the 80 mg once daily (q.d.) posology was to be removed throughout the SmPC because:

- Non-compartmental analysis at steady-state showed that the main PK parameters were not comparable: Cycle 1 d15: 80mg QD vs. 40mg BID $AUC_{0-24hr}$ 1.74 (90% CI 1.36-2.22), $C_{max}$ 2.33 (90% CI 1.81-3.00), $C_{min}$ 0.83 (90% CI 0.62-1.12);

- The 80 mg once daily (q.d.) posology was investigated in a limited number of patients only (n=17) and the exposure-response modelling is not sufficiently robust for decision-making;

- The risks for the 80 mg once daily (q.d.) posology are not sufficiently characterized, in particular for special populations or DDI, mostly investigated with 40 mg twice daily (b.i.d.) posology.

More data will be provided post-approval from the ongoing trial A2302, which compares the outcome of both posologies.

## 2.6.5. Clinical efficacy

Asciminib (ABL001) is an inhibitor that targets the myristoyl pocket of BCR-ABL1, in contrast to the currently available TKIs that target the BCR-ABL1 ATP binding site. By virtue of asciminib not interacting with the ATP-binding site, asciminib maintains activity against cells expressing clinically observed ATP-binding TKI resistant mutations. Therefore, approval in adult patients for the treatment of Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors is applied.

**Efficacy claim** for the applied indication "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" is based on the results of the primary analysis of the **pivotal Phase III study [CABL001A2301]** (ASCEMBL, hereafter referred to as **Study A2301**) (corresponding to a data cut-off date of 25-May-2020, current efficacy cut off-date: 96 weeks -06-Oct 2021).

**Supportive evidence** from the **first phase 1 trial in patients [CABL001X2101]** (hereafter referred to as **Study X2101**; corresponding to a data cut-off date of 02-Apr-2020) is available. However, since the primary endpoint of trial X2101 was the incidence of dose limiting toxicities (DLTs) during the first cycle of study treatment, the main focus of this data is clearly safety (evaluation of MTD and safety and tolerability of asciminib) and information regarding efficacy remains secondary**.**

**No combined efficacy analyses could be performed for studies A2301 and X2101 as intra-patient dose escalation was allowed in Study X2101.**

The design of Study A2301 including the comparator arm was discussed with EMA before study initiation.

The applicant confirmed that both studies, trial A2301 and X2101, were conducted in full compliance with Good Clinical Practice and were closely monitored by the sponsor for compliance with the protocol and its procedures described therein.

### 2.6.5.1. Dose response study(ies)

Selection of the asciminib 40 mg BID dosing schedule was based on preclinical evidence, the results of the PopPK-exposure Analysis [RD-2019-00440], [RD-2013-50145], [PopPK Report] and the

pharmacokinetic, efficacy and safety data available from the first in-human study phase 1 trial X2101. In this study patients with CML-CP who had prior treatment with at least 2 prior TKIs, received treatment with increasing doses of oral asciminib monotherapy between 10 mg to 200 mg on a continuous BID schedule). The maximum tolerated dose (MTD) for asciminib monotherapy in patients with CML-CP was not achieved; based on the totality of available data the 40 mg BID dose was selected as recommended Phase II dose (RP2D).

Nevertheless, increased toxicity was observed at doses ≥ 80 mg BID (pancreatitis) as well as a trend for higher rates of discontinuation due to AE, dose limiting toxicity (DLT), and grade 3/4 AE with increasing doses above this limit.

Simulations performed using asciminib population PK-PD model predicted that the probability of achieving *BCR-ABL1* mRNA $\geq$ 1 log reduction at 6 and 12 months was higher with 40 mg BID compared to 20 mg BID. Moreover, estimates from Study X2101 were found to be above the threshold trough concentration required for 90% inhibition of pSTAT5 derived from a preclinical PK-PD KCL-22 mouse xenograft model (free IC90: 30 to121 ng/mL, after correction for protein binding) and in vitro gIC50 assessed in the KCL-22 cell line (1 ng/mL = 2.1 nM after correction for protein binding).

The applicant thus, decided to select the asciminib 40 mg BID posology for further evaluation in the Phase III Study A2301. From the results of Study A2301 this dose is now applied for the target population.

### 2.6.5.2. Main study(ies)

**Title of study**

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

<u>EudraCT number</u> 2016-002461-66

<u>Study initiation date</u>: 26-Oct-2017 (first patient first visit)

<u>Data cut-off date</u>: 25-May-2020 (**primary endpoint completion date**, study is **ongoing)**

Updated data including longer follow-up data from week 96 cut-off date of 06-Oct-2021, were submitted after the initial submission during the procedure and reflect the current outcome for this report.

### *Methods*

- **Study Participants**

Male or female $\geq$ 18 years of age with a diagnosis of CMLCP, who had received prior treatment with 2 or more ATP binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib), and were treatment failure (as per guidelines adapted from the 2013 ELN recommendations) or intolerant to the most recent TKI. As bosutinib has no activity against BCRABL1 T315I and V299L mutations, patients who had T315I or V299L mutations documented in their medical records were not eligible for this study.

For patients intolerant to the most recent TKI therapy, the threshold for *BCR-ABL1* ratio was reduced from $\geqslant 1$ to >0.1% by Amendment 3 to the protocol, in order to ensure that the CML third line patient population is adequately represented. No more than 66 patients (approximately 30% of the overall study population) that were intolerant to their most recent TKI therapy with *BCR-ABL1* <1% were to be recruited to ensure that the CML third line patient population is adequately represented.

Exclusion criteria were adequately defined in order to ensure homogeneity of the included population and to avoid imbalance of intrinsic or extrinsic risks between both arms. Exclusion of subjects with well-known specific treatment risks (T315I or V299L mutation, second chronic phase of CML after previous progression to AP/BC or previous/planned hematopoietic stem-cell transplantation) is deemed acceptable for this trial.

No issue of concern was identified regarding the selected study population from the inclusion and exclusion criteria.

- **Treatments**

Asciminib and bosutinib were administered as tablets to be taken orally in accordance with a 40 mg BID and 500 mg QD dosing regimen, respectively. Asciminib was to be taken in fasted state; food was to be avoided for at least 2 hours before the dose and for at least 1 hour after the dose (water was permitted); whereas bosutinib was to be taken in fed state.

Dose escalation beyond the standard doses of 40 mg BID for asciminib was not permitted. For bosutinib, dose escalation to 600 mg QD was permitted according the approved posology. Similarly, the approach for dose reduction/interruption is adequately defined in the study protocol. For asciminib, only 1-step dose reduction to total daily dose of 40 mg was allowed, and for bosutinib 2-step sequential dose reduction up to total daily dose of 300 mg was allowed.

Adequate methods for compliance control were addressed in the protocol and established in the study conduct.

Duration of treatment is planned as up to the EOsT defined as up to 96 weeks after the last patient received the first dose or up to 48 weeks after the last patient had switched to asciminib treatment (whichever was longer, unless patients had discontinued study treatment earlier).

The applicant justifies the decision to choose Bosutinib as comparator because, in contrast to dasatinib and nilotinib, it was specifically evaluated in patients R/I $\geq 2$ prior TKIs, and the dose of 500 mg q.d. was selected as it is the approved dose for $\geq 2$ lines (2L) of therapy in CML (Khoury et al 2012). Ponatinib was not selected as the comparator in Study A2301, because ponatinib's dose was being evaluated in a randomized study as a post-approval commitment due to the occurrence of arterial occlusive events at the approved dose of ponatinib (45 mg q.d.) at the time when the Study A2301 started (Cortes et al 2020).

The open-label conduct of the study is justified as, in addition to differences in dose adaptations, conditions for drug administration differ markedly for ABL001 and bosutinib (ABL001 needs to be taken in a fasted state, bosutinib should be taken with food), making blinding with double-dummy treatment complex and carrying the inherent risk of administration and dosing errors. This justification is accepted in principle; in particular, since an open label design was also used in the pivotal trials for other second or third generation TKIs in CML.

Concomitant treatment: The use of any concomitant medication/therapies deemed necessary for the supportive care of the patient were permitted; except as specifically prohibited due to potential PK or metabolic interaction with the products.

- **Objectives**

The primary clinical question of interest is: Is the efficacy of asciminib (40 mg bid) superior to bosutinib (500 mg qd) in CML patients in chronic phase, previously treated with 2 or more tyrosine kinase inhibitors, with regards to achieving MMR at 24 weeks while on study treatment and without meeting any treatment failure criteria (defined in section 5.4.4) prior to 24 weeks, regardless of dose modification, dose interruption, or deviation in any intake of concomitant medications. (**Superiority in efficacy of asciminib over bosutinib in the target population)**

In consequence, the **null hypothesis** is that there is no difference between the treatment groups with respect to MMR rate at 24 weeks.

The primary estimand is described by the following attributes:

- Population: CML patients in CP, previously treated with 2 or more tyrosine kinase inhibitors. Further details about the population are provided by in/exclusion criteria.

- Endpoint: MMR achieved at 24 weeks while on study treatment without meeting any treatment failure criteria (see below treatment failure criteria) prior to 24 weeks. A patient was counted as having achieved MMR at 24 weeks if he/she met the MMR criterion (*BCR-ABL1* ratio ≤ 0.1%) at 24 weeks while on study treatment unless the patient met any treatment failure criteria prior to 24 weeks.

- Intercurrent events:

  o Treatment discontinuation (i.e. having performed an EOT visit) prior to 24 weeks due to any reason (e.g. intolerance, treatment failure, death, etc.): non response

  o Meeting any treatment failure criteria prior to 24 weeks: non response

  o Dose modification: dose interruption, or deviation in any intake of concomitant medications: ignore (treatment policy strategy)

- Treatment of interest: the randomized treatment (the investigational treatment asciminib or the control treatment bosutinib) received for at least 24 weeks with or without dose modification, dose interruption or deviation in any intake of concomitant medications.

- Handling of remaining intercurrent events : no other intercurrent events foreseen

- The summary measure: difference in MMR rate and its 95% confidence interval at week 24 between the two treatment arms


- **Outcomes/endpoints**

*The following table provides an overview about the trial objectives and the related endpoints in the pivotal trial A2301:*

**Table 18**     *Objectives and the related endpoints in the pivotal trial A2301*

| Objective | Endpoint |
|---|---|
| **Primary** | |
| To compare the MMR rate at 24 weeks of asciminib versus bosutinib | **Major molecular response (MMR) rate at 24 weeks** |
| **Key secondary** | |

| Objective | Endpoint |
|---|---|
| To compare additional parameters of the efficacy of asciminib versus bosutinib | **MMR rate at 96 weeks** |
| **Other secondary** | |
| **To compare additional parameters of the efficacy of asciminib versus bosutinib** | • Cytogenetic response rate (complete, partial, major, minor, minimal, no response) at and by all scheduled data collection time points including 24, 48 and 96 weeks<br>• MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints)<br>• MMR rate by all scheduled data collection time points including 24, 48 and 96 weeks<br>• Time to MMR<br>• Duration of MMR<br>• Time to CCyR<br>• Duration of CCyR<br>• Time to treatment failure<br>• Progression free survival<br>• Overall survival |
| To compare the safety and tolerability profile of asciminib versus bosutinib | Type, frequency and severity of adverse events, changes in laboratory values that fall outside the pre-determined ranges and clinically notable ECG and other safety data (vital signs, physical examination) |
| To characterize the PK of asciminib in the CML-CP population | Trough plasma concentrations, PK parameters in full PK group: Cmax, Tmax, AUC0-12h, CL/F |
| **Exploratory** | |
| To explore the exposure-response relationships of asciminib; evaluate the effect of population covariates | • Exposure-safety and exposure-PD analyses |
| To characterize mutations in the *BCR-ABL1* gene at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment and examine their association with molecular and cytogenetic response for asciminib vs. bosutinib | • *BCR-ABL1* gene mutations at Week 1 Day 1, upon confirmed loss of molecular response and/or at end of treatment as determined by Sanger Sequencing |
| To compare the impact of treatment on patient reported outcomes (PRO) including CML-specific symptoms, patient quality of life, and impact on work productivity and activity impairment from baseline and EOT between treatment arms in all patients | • Change in symptom burden and interference from baseline over time according to the MDASI-CML PRO instrument<br>• Change in patient's impression of CML symptoms according to Patient Global Impression of Change (PGIC)<br>• Change in health utility from baseline over time according to EQ-5D-5L<br>• Change in work productivity and activity impairment over time according to WPAI |
| To compare the impact of treatment on health care resource utilization between treatment arms in all patients | • Health care resource burden over time |

- **Sample size**

It was assumed that asciminib has a 20% higher MMR rate at 24 weeks than bosutinib i.e. 35%

compared to 15%. To test the null hypothesis that the MMR rate at 24 weeks is equal in the two treatment arms, based on two-sided 5% level of significance and with 90% power, 222 patients were needed in total based on 2:1 randomization allocation.

- **Randomisation and Blinding (masking)**

Patients were assigned to asciminib or bosutinib in a ratio of 2:1. Randomization was stratified by cytogenetic response status at screening (MCyR or no MCyR). In this study, an open-label study design was considered appropriate, due to inherent difference in the conditions for drug administration for the two treatment arms and use of objective efficacy endpoints.

- **Statistical methods**

The statistical analysis plan was finalized prior to the conduct of the primary analysis and unblinding of the database.

The Full Analysis Set (FAS) comprised of all randomized patients. According to the intent to treat principle, patients were analyzed according to the treatment and stratum that were assigned at randomization. Unless otherwise stated, the FAS was used for the analysis of the primary efficacy endpoint and all other secondary efficacy endpoints.

The null hypothesis was that there is no difference between the treatment groups with respect to MMR rate at 24 weeks. The Cochrane-Mantel-Haenszel (CMH) chi-square test, stratified by the randomization stratification factor (MCyR vs no MCyR at screening), was used to compare MMR rate between the two treatment groups, at the two-sided 5% level of significance. Patients with missing PCR evaluations at 24 weeks were considered as non-responders.

The 95% CI for the difference in MMR rate between treatment groups was provided using the Wald method. In addition, the common risk difference and corresponding 95% CI were provided by using the Mantel-Haenszel method.

The analysis of the key secondary endpoint (MMR at week 96 while on study treatment without meeting any treatment failure criteria prior to 96 weeks) will be performed at 96-week analysis time point, which was not reached prior to submission.

No confirmatory statistical testing of non-key secondary efficacy endpoints was performed; however, nominal p-values were presented.

MMR and CCyR rate at and by time points were analysed using the same methods as for the primary endpoint.

Time to event endpoint were generally analysed and graphically displayed using the Kaplan-Meier (K-M) approach.

TTF was compared between the two treatment groups using stratified log-rank test stratified by the randomization strata. The hazard ratio and 95% confidence intervals were computed from a stratified Cox model. The same methods will be applied for PFS and OS, which were not mature yet.

In addition to the primary efficacy analysis, various supplementary and sensitivity analyses were performed to assess the overall robustness of the primary efficacy results.

Efficacy analyses in subgroups were exploratory and intended to investigate the consistency of treatment effect.

*Results*

- **Participant flow**
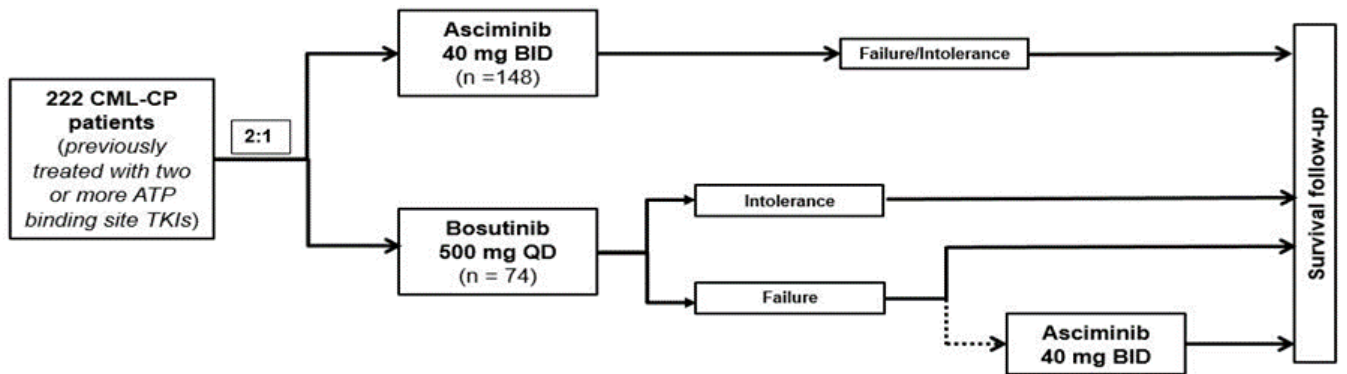


- **Recruitment**

Study initiation date: 26-Oct-2017 (first patient first visit).

Data cut-off date at submission: 25-May-2020 (primary endpoint completion date, study is ongoing).

**Current cut-off date: 06-Oct-2021 (week 96 assessment).**

- **Conduct of the study**

Three amendments were performed during the study conduct. In Amendment 3 a change was implemented which allows patients in the bosutinib arm into the asciminib arm according predefined conditions. The changes implemented are not likely to have impaired the integrity of trial A2301 in a relevant manner, which would allow presuming a decreased reliability of efficacy and safety outcome.

Protocol deviations were reported in 66.1% of patients; the proportion of patients with protocol deviation was higher in the asciminib arm (70.7%) compared to the bosutinib arm (56.6%). This may be explained at least partially by a longer duration of treatment exposure in patients randomized to asciminib compared to bosutinib (median 43.36 weeks vs. 29.21 weeks) and mainly caused to higher frequencies of deviations in the 'Other deviation' category in the asciminib arm (57.3%) vs. in the bosutinib arm (38.2%). Protocol deviations, specific to the COVID-19 pandemic, may have contributed also. They were reported in 61 patients (26.2%) with no significant imbalance between the two treatment arms (e.g. visit done outside of study site, change in drug supply method and change in assessment/procedure).

However, the assessment revealed a relevant difference of about 5 % more deviations in the asciminib arm with respect to not met inclusion and exclusion criteria. However, further assessment clarified that this issue is unlikely to have biased the outcome.

Stratification to the wrong stratum (15.3% vs. 13.2%) based on the sensitivity analysis this deviation did not have an impact on the primary analysis.

- **Baseline data**

Overall, the median age of patients in the study was 52 years (range: 19-83), 18.9% patients were $\geq$ 65 years and 2.6% patients were $\geq$ 75 years. 51.5% patients were female and 48.5% patients were male. A majority of the patients were White (74.7%), with 14.2% being Asian, and 4.3% being Black or African American. Almost all patients (98.7%) had a baseline ECOG performance status of 0 or 1

Considering the progress in CML treatment during the last twenty years and the hereby resulting intrinsic feasibility difficulties in the applied late line population, the two treatment arms can be seen as overall

balanced for the demographic characteristics. Differences noted were primary regarding ethnicity and sex. Patients in the asciminib arm (9.6%) compared fewer Hispanic/Latino to the bosutinib arm (22.4%). Similarly, the proportion of males was slightly higher in the asciminib arm (52.2%) compared to the bosutinib arm (40.8%).

Overall the included patients were heavily pre-treated, with approximately half of the patients receiving study treatment as 3rd-line therapy.

- **Numbers analysed**

233 patients with CML-CP were enrolled into the ITT analysis of this study, of whom 157 patients were randomized to treatment with asciminib and 76 patients to treatment with bosutinib (2:1).

As of the initial 25-May-2020 data cut-off, 119 patients (51.1%) continued to receive treatment. Twice the proportion of patients were ongoing in the asciminib arm (61.8%) relative to the bosutinib arm (28.9%). Overall, discontinuations in both treatment arms were predominantly due to lack of efficacy, followed by AEs and physician decision, although all were less frequent in the asciminib arm relative to the bosutinib arm (lack of efficacy: 21.0% vs. 31.6%; AE(s): 5.1% vs. 21.1%; physician decision: 6.4% vs. 7.9%). The majority of discontinuations before Week 24 were related to AEs while after Week 24, discontinuations were mainly due to lack of efficacy (Table below).

**Table 19 Patient disposition (FAS, cut-off 25-may-2020)**

| | Asciminib N=157 n (%) | Bosutinib N=76 n (%) | All Patients N=233 n (%) |
|---|---|---|---|
| **Patients randomized** | | | |
| Treated | 156 (99.4) | 76 (100.0) | 232 (99.6) |
| Not treated | 1 (0.6) | 0 | 1 (0.4) |
| **Reason for not being treated** | | | |
| Physician decision | 1 (0.6) | 0 | 1 (0.4) |
| **Treatment ongoing [1]** | 97 (61.8) | 22 (28.9) | 119 (51.1) |
| **Discontinued from treatment** | | | |
| < Week 24 | 59 (37.6) | 54 (71.1) | 113 (48.5) |
| ≥ Week 24 and < Week 48 | 26 (16.6) | 25 (32.9) | 51 (21.9) |
| ≥ Week 48 and < Week 96 | 22 (14.0) | 28 (36.8) | 50 (21.5) |
| **Reason for discontinuation** | | | |
| Lack of efficacy | 11 (7.0) | 1 (1.3) | 12 (5.2) |
| Adverse event | 33 (21.0) | 24 (31.6) | 57 (24.5) |
| Physician decision | 8 (5.1) | 16 (21.1) | 24 (10.3) |
| Patient/guardian decision | 10 (6.4) | 6 (7.9) | 16 (6.9) |
| Progressive disease | 4 (2.5) | 3 (3.9) | 7 (3.0) |
| Lost to follow-up | 1 (0.6) | 3 (3.9) | 4 (1.7) |
| Death | 1 (0.6) | 2 (2.6) | 3 (1.3) |
| Protocol deviation | 1 (0.6) | 0 | 1 (0.4) |
| **< Week 24** | | | |
| Adverse event | 1 (0.6) | 0 | 1 (0.4) |
| Lack of efficacy | 7 (4.5) | 11 (14.5) | 18 (7.7) |
| Physician decision | 7 (4.5) | 5 (6.6) | 12 (5.2) |
| Patient/guardian decision | 7 (4.5) | 4 (5.3) | 11 (4.7) |

| | | | |
|---|---|---|---|
| Progressive disease | 2 (1.3) | 2 (2.6) | 4 (1.7) |
| Death | 1 (0.6) | 3 (3.9) | 4 (1.7) |
| Protocol deviation | 1 (0.6) | 0 | 1 (0.4) |
| **≥ Week 24 and < Week 48** | | | |
| Lack of efficacy | 1 (0.6) | 0 | 1 (0.4) |
| Adverse event | 19 (12.1) | 18 (23.7) | 37 (15.9) |
| Patient/guardian decision | 1 (0.6) | 5 (6.6) | 6 (2.6) |
| Physician decision | 2 (1.3) | 1 (1.3) | 3 (1.3) |
| Lost to follow-up | 0 | 2 (2.6) | 2 (0.9) |
| **≥ Week 48 and < Week 96** | | | |
| Lack of efficacy | 7 (4.5) | 1 (1.3) | 8 (3.4) |
| Physician decision | 3 (1.9) | 0 | 3 (1.3) |
| Lost to follow-up | 1 (0.6) | 0 | 1 (0.4) |
| Switched to receive asciminib | NA | 22 (28.9) | 22 (9.4) |

- Twenty-two patients randomized to bosutinib switched to asciminib treatment after meeting lack of efficacy criteria as per protocol.

As of the Week 96 cut-off (06-Oct-2021), 99 of the 233 patients (42.5%) were continuing the study treatment with 84 patients (53.5%) and 15 patients (19.7%) still ongoing in the asciminib and bosutinib arms, respectively. Compared with the Week 24 cut-off (25-May-2020), 13 additional patients discontinued study treatment in the asciminib arm (5 patients discontinued due to lack of efficacy, 4 due to PI decision, 3 due to AE, and one due to patient/guardian decision), and 7 additional patients discontinued treatment in the bosutinib arm (3 patients discontinued due to lack of efficacy, 3 due to AE, and one due to patient/guardian decision).

- **Outcomes and estimation**

With respect to MMR:

**Primary endpoint: Major molecular response (MMR) rate at 24 weeks**

The **MMR rate at 24 weeks** was **25.5% in the asciminib** arm compared to **13.2% in the bosutinib** arm.

The treatment difference in the MMR rate was both statistically significant, 12.2% (95% CI: 2.19, 22.30, two-sided p-value: 0.029) (per the Cochran–Mantel–Haenszel two-sided test, stratified by the MCyR status at baseline). A clinically relevant two-fold increase in the MMR rate at 24 weeks was observed between the two treatment arms (Table below).

**Table 20      MMR rate at 24 weeks (FAS, cut-off cut-off 25-may-2020)**

| | Asciminib N=157 | | Bosutinib N=76 |
|---|---|---|---|
| Response - n (%) | 40 (25.48) | | 10 (13.16) |
| 95% CI for response 1 | (18.87, 33.04) | | (6.49, 22.87) |
| Unstratified difference in response rate (vs. bosutinib) (%) | | 12.32 | |

| 95% CI for difference in response rate 2 | | (2.11, 22.53) | |
|---|---|---|---|
| Common risk difference (%) 3 | | 12.24 | |
| 95% CI for difference | | (2.19, 22.30) | |
| CMH test p-value 4 | | 0.029 | |

Patients without PCR assessment at 24 weeks were considered as non-responders, unless both 16 and 36- week PCR assessments indicated that the patient was in MMR: no patients in the asciminib arm and in the bosutinib arm with missing PCR assessment at 24 weeks were imputed as having MMR at 24 weeks as they had MMR both at 16 and 36 weeks
1 -Clopper-Pearson 95% 2-sided CI.
2 Wald 95% 2-sided CI.
3 The common risk difference after adjusting for stratum: baseline major cytogenetic response status (based on randomization data) and its 95% CI were estimated using the Mantel-Haenszel method.
4 CMH 2-sided test was stratified by baseline major cytogenetic response status (based on randomization data).
Source: Table 14.2-1.1, Listing 14.2-1.1 0.029

Follow-up after longer treatment up to week 96 is shown in Tables below.

**Table 21        MMR rate at 60 weeks (updated, cut-off 06-Oct-2021)**

| | Asciminib N=157 | | Bosutinib N=76 |
|---|---|---|---|
| Response - n (%) | 51 (32.48) | | 10 (14.47) |
| 95% CI for response 1 | (25.24, 40.41) | | (7.45, 24.42) |
| Common risk difference (%) 3 | | 17.97 | |
| 95% CI for difference | | (7.27, 28.76) | |

At the new cut-off, clinical superiority versus bosutinib increased compared to the primary analysis, as reflected by a more than 2-fold improvement in MMR rate compared to bosutinib at Week 96; 37.6.% (95% CI: 29.99, 45.65) in the asciminib arm compared to 15.8 % (95% CI: 8.43, 25.96) in the bosutinib arm, corresponding to a common treatment difference (after adjusting for baseline MCyR status.

**Table 22        MMR rate at week 96 (updated, cut-off 06-Oct-2021)**

| | Asciminib N=157 | | Bosutinib N=76 |
|---|---|---|---|
| Response - n (%) | 59 (37.58) | | 12 (15.79) |
| 95% CI for response (1) | (29.99, 45.65) | | (8.43, 25.96) |
| Unstratified difference in response rate (vs bosutinib) (%) | | 21.79 | |
| 95% CI for difference in response rate (2) | | (10.63; 32.95) | |
| Common risk difference (%) (3) | | 21,74 | |
| 95% CI for difference | | (10.53; 32.95) | |

| CHM test p-value (4) | | 0.001 | |
|---|---|---|---|

Subjects without PCR assessment at 96 weeks were considered as non-responders, unless both 84 and 108 weeks PCR assessments indicated that the subject was in MMR: 0 subjects in the asciminib arm and 0 in the bosutinib arm with missing PCR assessment at 96 weeks were imputed as having MMR at 96 weeks.
(1) Clopper-Pearson 95% 2-sided CI. (2) Wald 95% 2-sided CI.
(3) The common risk difference after adjusting for stratum: baseline major cytogenetic response status (based on randomization data) and its 95% CI were estimated using the Mantel-Haenszel method.
(4) CMH 2-sided test was stratified by baseline major cytogenetic response status (based on randomization data).

Sensitivity analyses

Results of the predefined sensitivity analyses demonstrated consistency with the primary results and thereby claiming confirmation of their robustness.

Two patients (one from each arm) had missing data after 24 weeks. Statistical significance could not be concluded if patient in the bosutinib arm is assumed a responder but not the patient on asciminib arm, while statistical significance could be concluded for all other constellations. As both patients were MMR responders after week 96, no constellation is implausible. The true constellation must remain speculative such that the decision must rely on the pre-specified approach, however, the conclusion of statistical significance is not robust.

Discrepancies between stratum assigned at randomization (IRT) and that derived based on bone marrow aspirate data as reported in the CRF, had no significant impact on the interpretation of the efficacy results. The analysis of MMR rate at Week 24 adjusting by the stratum based on the CRF data demonstrated consistency with the primary results which adjusted by the stratum based on the randomization data. However, since interpretation of this data does not reflect the long term outcome, the relevance of this observations may be challenged.

The imputation rule in case of missing PCR evaluations at Week 24 was used however not applicable in the primary analysis as no patient with missing Week 24 assessment had both a 16-week and a 36-week assessment indicating MMR [Study A2301 CSR Primary endpoint analysis-Section 11.1.1.2]. Consequently, the results from the analysis of the primary endpoint not using the imputation rule were the same as those from for the primary analysis.

Off-note: Hypothesis testing for the primary and key secondary endpoints follows a hierarchical testing approach to preserve overall alpha level of 5% (two-sided). Therefore since the test of the primary endpoint was significant the key secondary endpoint can be tested at the 5% significance level at the 96-week analysis time point.

Subgroup Analysis:

**Figure 9 Forest plot of risk difference with 95% confidence interval for MMR at Week 24 from subgroup analysis (FAS)**

| Subgroup | Asciminib n/N (%) | Bosutinib n/N (%) | Favors Bosutinib | Favors Asciminib | Risk difference (95% CI) |
|---|---|---|---|---|---|
| All subjects | 40/157 (25.5) | 10/76 (13.2) | | | 12.3 (2.1 to 22.5) |
| Strata based on randomization data | | | | | |
|   Major cytogenetic response | 21/46 (45.7) | 4/22 (18.2) | | | 27.5 (5.9 to 49.1) |
|   No major cytogenetic response | 19/111 (17.1) | 6/54 (11.1) | | | 6.0 (-4.9 to 16.9) |
| Strata based on CRF data | | | | | |
|   Major cytogenetic response | 23/57 (40.4) | 7/25 (28.0) | | | 12.4 (-9.4 to 34.1) |
|   No major cytogenetic response | 17/100 (17.0) | 3/51 (5.9) | | | 11.1 (1.3 to 20.9) |
| Sex | | | | | |
|   Female | 22/75 (29.3) | 4/45 (8.9) | | | 20.4 (7.2 to 33.7) |
|   Male | 18/82 (22.0) | 6/31 (19.4) | | | 2.6 (-13.9 to 19.1) |
| Race | | | | | |
|   Asian | 6/22 (27.3) | 1/11 (9.1) | | | 18.2 (-7.0 to 43.4) |
|   White | 30/118 (25.4) | 8/56 (14.3) | | | 11.1 (-0.9 to 23.2) |
|   Others | 4/17 (23.5) | 1/9 (11.1) | | | 12.4 (-16.4 to 41.2) |
| Age category | | | | | |
|   18-65 years | 33/128 (25.8) | 8/61 (13.1) | | | 12.7 (1.3 to 24.0) |
|   ≥ 65 years | 7/29 (24.1) | 2/15 (13.3) | | | 10.8 (-12.4 to 34.0) |
|   ≥ 75 years | 3/4 (75.0) | 1/2 (50.0) | | | 25.0 (-56.3 to 100.0) |
| Reason for disc. of the last prior TKI | | | | | |
|   Failure | 20/95 (21.1) | 3/54 (5.6) | | | 15.5 (5.3 to 25.7) |
|   Intolerance | 20/59 (33.9) | 7/22 (31.8) | | | 2.1 (-20.8 to 25.0) |
| Number of prior TKI therapies | | | | | |
|   2 | 27/89 (30.3) | 6/33 (18.2) | | | 12.2 (-4.1 to 28.4) |
|   3 | 12/53 (22.6) | 4/33 (12.1) | | | 10.5 (-5.3 to 26.4) |
|   ≥ 4 | 1/15 (6.7) | 0/10 (0.0) | | | 6.7 (-6.0 to 19.3) |
| Line of therapy of randomized treatment | | | | | |
|   3 | 24/82 (29.3) | 6/30 (20.0) | | | 9.3 (-8.1 to 26.6) |
|   4 | 11/44 (25.0) | 4/29 (13.8) | | | 11.2 (-6.7 to 29.1) |
|   ≥ 5 | 5/31 (16.1) | 0/17 (0.0) | | | 16.1 (3.2 to 29.1) |
| BCR-ABL1 mutation at day 1 of week 1 | | | | | |
|   Unmutated | 31/125 (24.8) | 7/63 (11.1) | | | 13.7 (2.8 to 24.5) |
|   Mutated | 6/17 (35.3) | 2/8 (25.0) | | | 10.3 (-27.3 to 47.9) |
| BCR-ABL1 transcript level (IS) at basel. | | | | | |
|   ≥ 1% | 34/142 (23.9) | 8/72 (11.1) | | | 12.8 (2.7 to 22.9) |
|   < 1% | 6/15 (40.0) | 2/4 (50.0) | | | -10.0 (-64.9 to 44.9) |

-50   0   50   100

MMR: Major molecular response.
n: The number of patients who responded.
N: The total number of patients in the subgroup and treatment arm with response variable defined.
95% Wald CI for Risk Difference. Risk Difference is asciminib vs bosutinib.
Strata based on CRF data: patients with missing baseline bone marrow aspirate and baseline BCR-ABL1 levels ≤ 10% (IS) were considered in MCyR.
BCR-ABL1 ratio at baseline <1%: Protocol amendment 3 allowed the inclusion of patients intolerant to most recent TKI and BCR-ABL1 ratio >0.1%.
Patients with T315I and V299L BCR-ABL1 mutations or non-evaluable mutation assessment were excluded from the BCR-ABL1 mutation at Week 1 Day 1 subgroup analysis. Source: [Study A2301 Primary endpoint analysis-Figure 14.2-1.3]

The provided subgroup analyses demonstrated a homogeneous and consistent treatment effect in favor of asciminib across most major demographic and prognostic subgroups reported in Figure OE 2 above.

The MMR rate at Week 24 was higher in patients on asciminib regardless of baseline cytogenetic response (MCyR or no MCyR) or the detection of BCR-ABL1 mutations.

The subgroup analysis by line of therapy of randomized treatment confirmed the benefit of asciminib in heavily pretreated patients. A consistent treatment benefit with respect to the primary endpoint MMR rate at Week 24 was observed with asciminib compared to bosutinib whether given as 3rd-line therapy (29.3% vs. 20.0%), 4th-line therapy (25.0% vs. 13.8%), or ≥ 5th-line therapy (16.1% vs. 0%).

According to the applicant these results may demonstrate the efficacy of asciminib irrespective of the number of previous lines of treatment with TKIs.

**Other secondary efficacy results**

<u>MMR rate at and by all scheduled data collection time points</u>

The MMR rate at each scheduled time point was higher for the asciminib arm compared to the bosutinib arm, with relevant differences starting to be noted at Week 12 (17.8% in the asciminib arm compared to 9.2% in the bosutinib arm; common treatment difference after adjusting for the baseline MCyR status was 8.58%, (95% CI: -0.18, 17.34) (CSR Table 11-5).

<u>Time to MMR</u>

Among patients who achieved MMR, responses were achieved faster in patients treated with asciminib (median time to MMR: 15.6 weeks) compared to bosutinib (median time to MMR: 24.0 weeks)

<u>Duration of MMR</u>

**The majority of patients who achieved MMR continued in MMR: only 2 patients (5.6%) in the asciminib arm versus one subject in the bosutinib arm subsequently lost their response.**

The KM estimated proportion of patients maintaining their MMR for at least 48 weeks was 96.1% (95% CI: 85.4, 99.0) in the asciminib arm vs 90.0% (95% CI: 47.3,98.5) in the bosutinib arm.

**With respect to Cytogenetic Response:**

<u>Cytogenetic response rate (complete, partial, major, minor, minimal, no response) at and by all scheduled data collection time points including 24, 48 and 96 weeks</u>

The CCyR rates at Week 24 and by Week 24 (based on patients who were not in CCyR at baseline) were both 40.8% in the asciminib arm compared to 24.2% in the bosutinib arm. The treatment difference in the CCyR rate was 17.3% (95%: 3.62, 30.99, nominal p value= 0.019) (Table below). By the cut-off, CCyR rates were 42.7% in the asciminib arm and 30.7% in the bosutinib arm.

**Table 23 CCyR rate at and by Week 24 (CCyR analysis set)**

| | At week 24 | | By week 24 | |
|---|---|---|---|---|
| | Asciminib N=103 | Bosutinib N=62 | Asciminib N=103 | Bosutinib N=62 |
| Response - n (%) | 42 (40.78) | 15 (24.19) | 42 (40.78) | 15 (24.19) |
| 95% CI for response1 | (31.20, 50.90) | (14.22, 36.74) | (31.20, 50.90) | (14.22, 36.74) |
| Unstratified difference in response rate (vs. bosutinib) (%) | 16.58 | | 16.58 | |
| 95% CI for difference in response rate2 | (2.31, 30.86) | | (2.31, 30.86) | |
| Common risk difference (%)3 | 17.30 | | 17.30 | |
| 95% CI for difference | (3.62, 30.99) | | (3.62, 30.99) | |
| CMH test p-value4 | 0.019 | | 0.019 | |

(1) Clopper-Pearson 95% 2-sided CI.
(2) Wald 95% 2-sided CI
(3) The common risk difference after adjusting for stratum: baseline major cytogenetic response status (based on randomization data) and its 95% CI were estimated using the Mantel-Haenszel method.
(4) CMH 2-sided test was stratified by baseline major cytogenetic response status based on randomization data. Nominal p-values are presented for descriptive purpose only.
Patients with MMR or better were counted as CCyR if no valid cytogenetic assessment was available at that specific time-point.
Source: Table 14.2-2.3, Table 14.2-2.4

The **CCyR rates** continued to be higher in the asciminib arm compared to the bosutinib arm **at Week 48** (39.8% vs 21.0%) and by Week 48 (45.6% vs 35.5%). By the time of the 30-day update cut-off, overall CCyR rates were 47.6% (compared to 42.7% at the previous cut-off) in the asciminib arm and 35.5% (compared to 30.7% at the previous cut-off) in the bosutinib arm.

The **CCyR rate at Week 96** (based on patients who were not in CCyR at baseline) was 39.8% in the asciminib arm and 16.1% in the bosutinib arm, corresponding to a common treatment difference (after adjusting for baseline MCyR status) of 23.9% (95% CI: 10.3, 37.4).

Time to CCyR

Time to CCyR among subjects who achieved CCyR was the same between the two treatment arms, with medians of approximately 24 weeks (Median: Asciminib 24.3 weeks versus Bosutinib 24. 2 weeks) in the recent updated interim analysis.

Duration of CCyR

The majority of patients who achieved CCyR continued to be in CCyR at the time of their last assessment (48/49 in the asciminib arm and 21/22 in the bosutinib arm).

The KM estimated proportion of patients maintaining CCyR for at least 48 weeks was 97.6% (95% CI: 84.3, 99.7) in the asciminib arm vs 91.7% (95% CI: 53.9, 98.8) in the bosutinib arm.

The KM estimated median duration of CCyR has not been reached in either treatment arm.

The majority of patients who achieved CCyR continued to be in CCyR at the time of the 96 weeks assessment (50/51 in the asciminib arm and 20/22 in the bosutinib arm). The KM estimated proportion of patients maintaining CCyR for at least 72 weeks was 97.8% (95% CI: 85.6, 99.7) in the asciminib arm vs 81.3% (95% CI: 41.5, 95.2) in the bosutinib arm.

Time to treatment failure

The probability of patients experiencing treatment failure (defined as not meeting efficacy criteria or treatment discontinuation due to any reason) continued to be lower in the asciminib arm with a 60% relative risk reduction in favor of asciminib (Hazard ratio=0.4; 95% CI: 0.3, 0.6; p<0.0001). The proportion of patients experiencing treatment failure by the 30-day update cut-off date was 48.4% (compared to 45.2% at the previous cut-off) in the asciminib arm versus 80.3% (compared to 73.7% at the previous cut-off) in the bosutinib arm. The median time to treatment failure was not reached for the asciminib arm while it was 0.5 years in the bosutinib arm.

In the week 96 evaluation, the risk of experiencing a treatment failure (defined as meeting a lack of efficacy criteria based on ELN 2013 recommendations or discontinuing treatment due to any reason) was 56% still lower in the asciminib arm than in the bosutinib arm (Hazard ratio=0.44; 95% CI: 0.3, 0.6; p<0.0001).

The median time to treatment failure was 2 years in the asciminib arm and 6 months in the bosutinib arm.

Progression free survival

The median follow-up time for progression free survival (PFS) extends to 14.4 months in the asciminib arm and 13.2 months in the bosutinib arm.

The KM estimated PFS rate at 1 year was 96.3% (95% CI: 91.3, 98.5) in the asciminib arm and 91.1% (95% CI: 79.5, 96.3) in the bosutinib arm

Recent updated results are shown in the following Figure below:
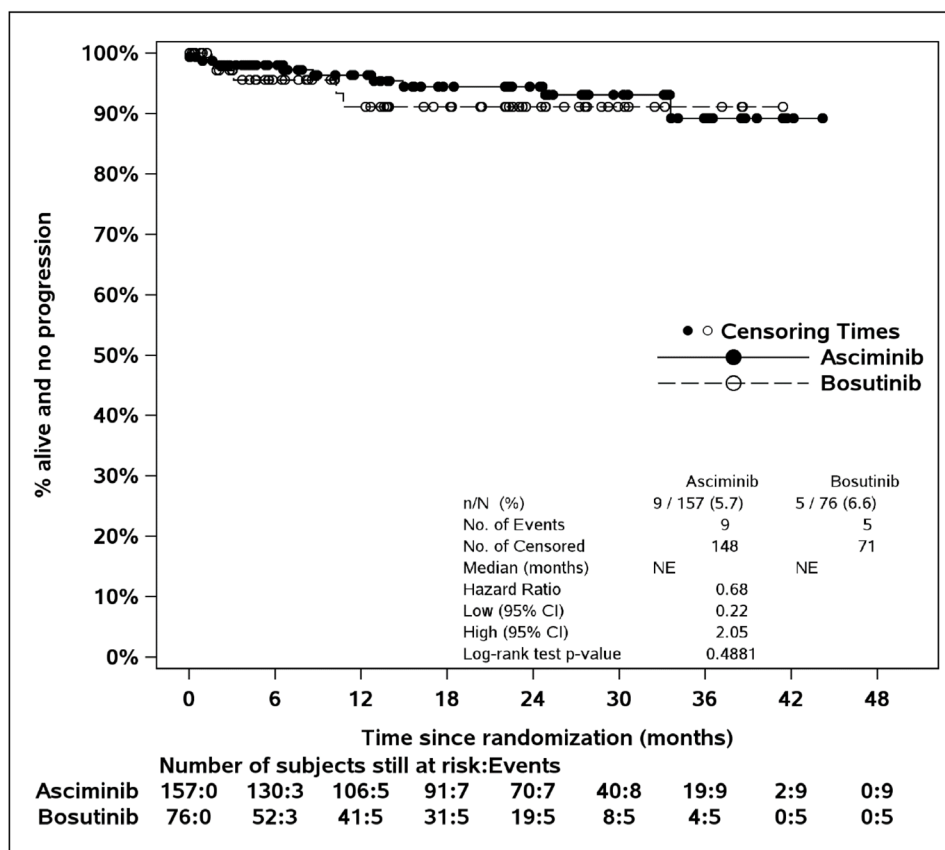


Caution: Median follow-up was 21.6 months in the asciminib arm and 13.2 months in the bosutinib arm. The tails of the curves should be interpreted with caution when the number of patients still at risk becomes low.

**Figure 10: Kaplan-Meier plot of progression-free survival (Study A2301, FAS)**

PFS at week 96 is reported with a median follow-up time for PFS of 1.8 years in the asciminib arm and 1.1 years in the bosutinib arm. Overall, by the cut-off date, 9 patients (5.7%) in the asciminib arm and 5 patients (6.6%) in the bosutinib arm either experienced a disease progression to AP/BC or died during the study. The KM estimated PFS rate at 2 years was 94.4% (95% CI: 88.6, 97.3) for the asciminib arm and 91.1% (95% CI: 79.5, 96.3) for the bosutinib arm.

Overall survival

A total of five patients (3.2%; two on-treatment and three during survival follow-up) in the asciminib arm and two patients (2.6%, one on-treatment and one during survival follow-up) in the bosutinib arm died on-study, including two additional deaths (one in each treatment arm) during survival follow-up reported after the previous cut-off date (06-Jan-2021).

The 1-year survival rates were 98.0% (95% CI: 93.8, 99.3) in the asciminib arm and 98.6% (95% CI: 90.2, 99.8) in the bosutinib arm and the 2-year survival rates were 97.3% (95% CI: 92.9, 99.0) in the asciminib arm and 98.6% (90.2, 99.8) in the bosutinib arm.
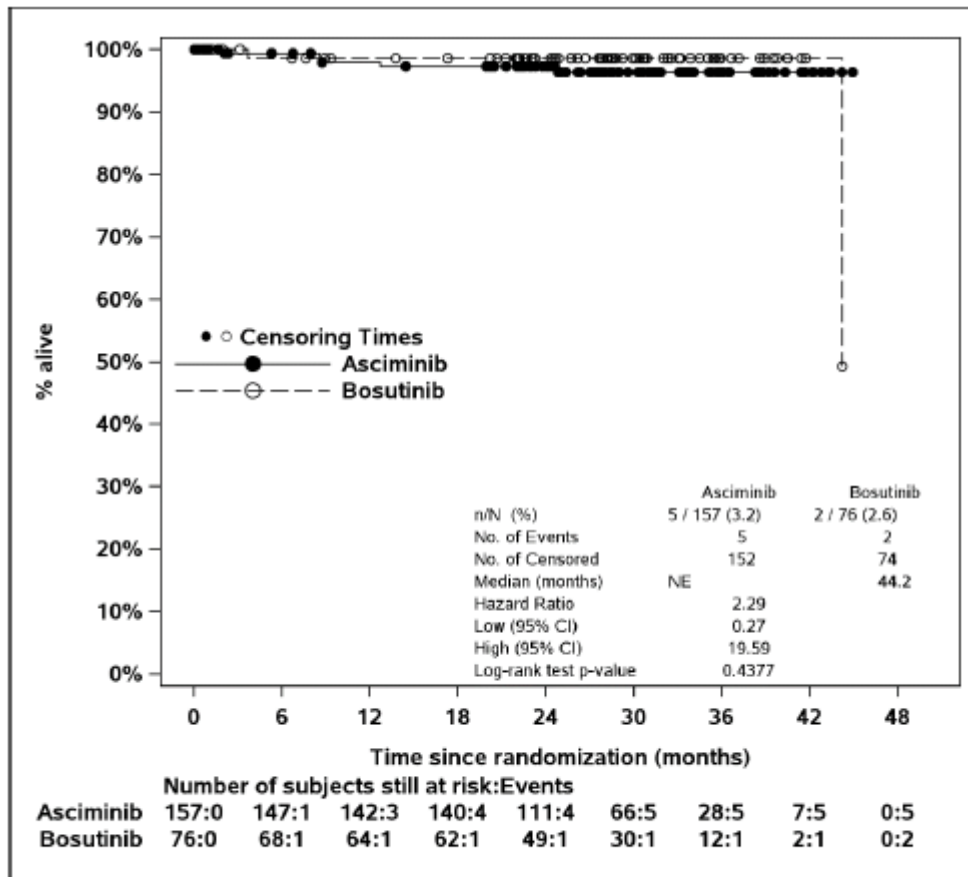


Caution: the drop in the estimated survival rate in the bosutinib arm after Month 42 should be interpreted with caution due to the very low number of patients still at risk.

**Figure 11     Kaplan-Meier plot of overall survival (Study A2301, FAS)**

At the Week 96 cut-off date, a total of 7 patients died: 5 in the asciminib arm and 2 in the bosutinib arm. The KM estimated OS rate at 2 years was 97.3% (95% CI: 92.9, 99.0) for the asciminib arm and 98.6% (95% CI: 90.2, 99.8) for the bosutinib arm.

- **Ancillary analyses**

Impact of COVID-19

The COVID-19 pandemic had minimal effect on the primary study results. 191/233 patients had planned 24-week visit before the COVID-19 pandemic (started from 1-Jan-2020).

**The primary endpoint assessment (*BCR-ABL1* level at Week 24 only assessed at central testing laboratory) was missed for 2 patients due to the COVID-19 pandemic. These patients were considered as non-responders in the primary analysis**.

The results from the sensitivity analysis excluding patients (29 patients in the asciminib arm and 13 patients in the bosutinib arm) with a planned Week 24 visit after the start of the COVID-19 pandemic were consistent with the results from the primary analysis:

- The MMR rate at Week 24 was 28.9% in the asciminib arm compared to 12.7% in the bosutinib arm.

The common treatment difference after adjusting for the baseline MCyR status was 16.1% (95% CI: 4.91, 27.36) (Cochran-Mantel-Haenszel chi-square test, stratified by MCyR status at baseline, two-sided).

- **Summary of main efficacy results**

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

**Table 24        Summary of Efficacy for the pivotal trial A2301**

| **Title:** *A ongoing Phase III, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with chronic myelogenous leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors. (Study CABL001A2301, A2301)* | | | |
|---|---|---|---|
| Study identifier | Protocol identification: CABL001A2301 EudraCT number 2016-002461-66 | | |
| Design | Ongoing, Open-label, (2:1)-randomised, parallel, fixed-dose response, mutlicenter trial | | |
| | Duration until PEP: Duration of main phase: Duration of Follow-up phase: Study initiation date: | | 24 weeks treatment (prim. endpoint assess.) 96 weeks (key secondary endpoint assess. 5 years 26-Oct-2017 (first patient first visit) |
| Hypothesis | **Superiority** | | |
| Treatments groups *{add as many rows as needed to describe the treatment groups}* | Asciminib | | **Posology:** 40 mg BID to be taken in fasted state; food was to be avoided for at least 2 hours before the dose and for at least 1 hour after the dose (water was permitted); Dose escalation beyond the standard doses of 40 mg BID for asciminib was not permitted. allowed. **Duration:** Duration of treatment is planned as up to the EOsT defined as up to 96 weeks after the last patient received the first dose or up to 48 weeks **Number randomized**: 157 |
| | Bosulif | | **Posology:** Bosutinib 500 mg QD was to be taken in in fed state. For bosutinib, dose escalation to 600 mg QD was permitted according the approved posology. **Duration:** Duration of treatment is planned as up to the EOsT defined as up to 96 weeks after the last patient received the first dose or up to 48 weeks **Number randomized:** 76 |
| Endpoints and definitions | **Primary endpoint** | **MMR rate at 24 weeks** | Major molecular response (MMR) rate at 24 weeks |
| | **Key Secondary Endpoint**: | **MMR rate at 96 weeks** | MMR rate at 96 weeks |
| | **Other Secondary** Endpoints | CCyR rate at all collection weeks | Cytogenetic response rate (complete, partial, major, minor, minimal, no response) at and by all scheduled data collection time points including 24, 48 and 96 weeks |

| | Other Secondary Endpoints | MMR rate at all collection weeks | MMR rate at all scheduled data collection time points (except 24 and 96 weeks which are already covered by primary and key secondary endpoints) |
|---|---|---|---|
| | Other Secondary Endpoints | MMR rate at week 24,48,96 | MMR rate by all scheduled data collection time points including 24, 48 and 96 weeks |
| | Other Secondary Endpoints | TtMMR | Time to MMR |
| | Other Secondary Endpoints | DoMMR | Duration of MMR |
| | Other Secondary Endpoints | TCCyR | Time to CCyR |
| | Other Secondary Endpoints | DoCCyR | Duration of CCyR |
| | Other Secondary Endpoints | TTF | Time to treatment failure |
| | Other Secondary Endpoints | PFS | Progression free survival |
| | Other Secondary Endpoints | OS | Overall survival |
| | | | |
| Database lock | Data cut-off date: 25-May-2020 (primary endpoint completion date, study is ongoing) | | |

**Results and Analysis**

| Analysis description | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Intent to treat time poin: primary analysis at week 26 of treatment | | |
| Descriptive statistics and estimate variability | Treatment group | Asciminib | Bosutinib |
| | Number of subject | N= 157 | N=76 |
| | **Primary endpoint: MMR rate at 24 weeks** | N=40/157 25.48% | N=10/76 13.16% |
| | 95% CI for response Unstratified difference in response rate (vs. bosutinib) CMH test p-value | (18.87, 33.04) 12.32 %  0.029 | |
| | **Key secondary endpoint: MMR rate at 96 weeks** | N=59/157 (37.58%) | N=12/76 (15.79%) |
| | 95% CI for response Unstratified difference in response rate (vs. bosutinib) CMH test p-value | (29.99, 45.65) 21.79  0.001 | (8.43, 25.96) |
| | **Other secondary endpoint:** Time to MMR | Median: 15.6 weeks | Median: 24.0 weeks |
| | **Other secondary endpoint:** Duration of MMR | 96.1% (85.4-99.0) | 90 % |
| | **Other secondary endpoint:**  CCyR-rate at week 24 | N=42/103 40.78% (31.20-50.90) | N=14/62 24.29% 14.22, 36,74) |
| | CCyR-rate at week 48 | 39.8 % | 21.0% |
| | CCyR rate at week 96 | 39.8 % | 16.1% |

| | | |
|---|---|---|
| **Other secondary endpoint:** Time to CCyR | 24.3 weeks | 24.3 weeks |
| **Other secondary endpoint:** Duration of CCyR | The majority of patients who achieved CCyR continued to be in CCyR at the time of the 96 weeks assessment (50/51 in the asciminib arm and 20/22 in the bosutinib arm). The KM estimated proportion of patients maintaining CCyR for at least 72 weeks was 97.8% (95% CI: 85.6, 99.7) in the asciminib arm vs 81.3% (95% CI: 41.5, 95.2) in the bosutinib arm. | |
| **Other secondary endpoint:** Time to treatment failure | The risk of experiencing a treatment failure (defined as meeting a lack of efficacy criteria based on ELN 2013 recommendations or discontinuing treatment due to any reason) was 56% lower in the asciminib arm than in the bosutinib arm (Hazard ratio=0.44; 95% CI: 0.3, 0.6; p<0.0001). The median time to treatment failure was 2 years in the asciminib arm and 6 months in the bosutinib arm. | |
| **Other secondary endpoint:** Progression free survival | 1.8 years | 1.1 years |
| **Other secondary endpoint:** Overall survival | The KM estimated OS rate at 2 years was 97.3% (95% CI: 92.9, 99.0) for the asciminib arm and 98.6% (95% CI: 90.2, 99.8) for the bosutinib arm. | |
| **Including updated information from D180 AR regarding outcome at Week 96, cut-off 06-Oct-2021** | | |

### 2.6.5.3. Clinical studies in special populations

| | Age 65-74 (Older subjects number /total number) | Age 75-84 (Older subjects number /total number) | Age 85+ (Older subjects number /total number) |
|---|---|---|---|
| **Controlled Trials** | | | |
| **Non Controlled Trials** | | | |

### 2.6.5.4. In vitro biomarker test for patient selection for efficacy

MMR is selected as a surrogate endpoint based on Current guidelines which agree regarding the response definitions as well as with respect to the monitoring of treatment response and treatment selections. Similarly, analytical standards and clinical strategies in patient handling are adequately validated and agreed as detailed in the recently updated European LeukemiaNet guideline (Hochhaus et al., 2020).

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

No combined efficacy analyses, were performed for studies A2301 and X2101 as intra-patient dose escalation was allowed in Study X2101 and different drug combinations were allowed in the Phase 1 trial.

### 2.6.5.6. Supportive study(ies)

**Supportive study: Study X2101**

The Study X2101 is an ongoing, multi-center, open-label dose finding Phase 1 study (First in patient) to define the MTD and/or RDE(s), safety, tolerability, PK and to provide preliminary evidence of efficacy of asciminib given as single agent or in combination with either nilotinib or imatinib or dasatinib.

The study was designed to include 5 arms:

**Arm 1: asciminib as single agent in patients with CML-CP/-AP**

Arm 2: asciminib in combination with nilotinib in patients with CML-CP/-AP (introduced with protocol amendment 4)

Arm 3: asciminib in combination with imatinib in patients with CML-CP/-AP (introduced with protocol amendment 6)

Arm 4: asciminib in combination with dasatinib in patients with CML-CP/-AP (introduced with protocol amendment 6)

Arm 5: asciminib as single agent in patients with CML-BP and Ph+ ALL

A total of 330 patients were planned and 317 patients were enrolled and analyzed as of the cut-off date. The study is still enrolling patients in Arm 4.

**With respect to the applied indication, this AR focuses mainly on the subset of patients from Study X2101, receiving single agent asciminib for CML-CP <u>not harboring the T315I</u> mutation (subset of Arm 1).**

Study population

In Study X2101, a subset of 115 enrolled patients received single agent asciminib at any dose for CML-CP not harboring the T315I mutation. The various asciminib single agent treatment cohorts into which these patients with CML-CP not harboring the T315I were enrolled, were: 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) [CSR Study X2101 Primary analysis-Table 14.1-1.1.1.2].

Treatment

The starting dose of asciminib for patients with CML-CP/-AP selected for the dose escalation part of this study was set at 10 mg orally administered b.i.d. under fasted conditions. The selection of the starting dose of asciminib was based on 4-week GLP toxicology studies conducted in rats and dogs. In addition, the PK-pharmacodynamic (PD) mouse model suggested a b.i.d. regimen was required to maintain PD effect. The starting dose of 10 mg b.i.d. was expected to be safe and tolerated in adult patients with CML-CP/-AP. Based on further PK modeling and pre-clinical studies which suggested response in *BCR-ABL1* transcripts also when a q.d. regimen was considered in Study X2101, decision was taken to open a cohort of patients dosed on a q.d. regimen at 120 mg q.d. as starting dose level.

The dose range covered were initially based on the projections for the human PK of asciminib and projections for the relationship between asciminib systemic exposure and toxicity. The dose levels were updated as more PK and safety data became available and clinical experience was used to elucidate the relationships between dose, systemic exposure, and toxicity.

Based on the above, actual dose levels evaluated in patients with CML-CP/-AP included 10 mg b.i.d., 20 mg b.i.d., 40 mg b.i.d., 80 mg b.i.d., 150 mg b.i.d., 160 mg b.i.d., 200 mg b.i.d., 80 mg q.d., 120 mg q.d., and 200 mg q.d.

**Results**

MMR rate at scheduled time-point

Among 86 evaluable CML-CP patients not harboring the T315I mutation, **50 (58.1%) patients achieved MMR at any time-point. The MMR rate at Week 24 was 23.3%**; an increasing MMR rate (for patients who were not in MMR at baseline) over time was observed [SCE-Table 3-22]. A similar trend of increasing MMR rate over time was observed across all lines of therapy for all patients evaluable for MMR with CML-CP not harboring the T315I mutation [CSR SCE-Figure 3-8].

Time to MMR and duration of response

**Time of MMR:** Overall, among 50/86 patients with CML-CP without the T315I mutation who achieved MMR, the **median time to first MMR was 38.3 weeks**, ranging from 2 to 192 weeks after starting treatment with single agent asciminib. Similarly, a wide range of time to response was observed across all dose levels with the majority of responses being observed within the first 48 weeks of treatment [CSR Study X2101 Primary analysis-Table 14.2-6.2].

**Duration of MMR:** Overall, among 50/86 patients with CML-CP without the T315I mutation who achieved MMR, most (46 patients) maintained this response level or improved it to a deeper level of response at the time of their last assessment. Given the median (maximum) duration of treatment exposure of 183.4 (302) weeks, this indicates that the responses achieved were highly durable. The KM estimated proportion of patients maintaining their first MMR for at least 48 weeks was 96% (95% CI: 89.5, 100.0) and for at least 96 weeks was 93% (95% CI: 85.7, 100.0) [CSR Study X2101 Primary analysis-Table 14.2-5.2].

## 2.6.6. Discussion on clinical efficacy

Asciminib (ABL001) is an inhibitor that targets the myristoyl pocket of BCR-ABL1, in contrast to the currently available TKIs that target the BCR-ABL1 ATP binding site. By virtue of asciminib not interacting with the ATP-binding site, asciminib maintains activity against cells expressing clinically observed ATP-binding TKI resistant mutations. Therefore, in a first step, approval in adult patients for the treatment of Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors is applied.

***Design and conduct of clinical studies***

**Efficacy claim** for the applied indication "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" is based on the results of the primary analysis of the **pivotal Phase III study Study A2301** (data cut-off date of 06-Jan 2021/ 06-Oct 2021).

**Supportive evidence** from the **first phase 1 trial in patients (Study X2101)** is available. Cut -off date is 02-Apr-2020. However, since the primary endpoint of trial X2101 was the incidence of dose limiting toxicities (DLTs) during the first cycle of study treatment, the main focus of this data is clearly

safety and evaluation of MTD. Due to the mix-up of several dosages as well as drug combinations and diseases (Ph+ALL, CML-CM+AP) information regarding efficacy in the small cohorts remains limited and mainly supportive regarding outcome after longer treatment.

**No combined efficacy analyses could be performed for studies A2301 and X2101 as intra-patient dose escalation was allowed in Study X2101.**

**The pivotal Study A2301** is an ongoing, randomized, open-label, active-controlled (bosutinib), multi-center Phase III study to compare the efficacy and safety of asciminib with that of bosutinib in patients with CML-CP, previously treated with at least 2 prior TKIs. A total of 233 patients were randomized in a 2:1 ratio to receive either asciminib 40 mg b.i.d. (n=157) or bosutinib 500 mg q.d. (n=76), stratified by the patient's cytogenetic response status at baseline.

Twice as many patients were ongoing in the asciminib arm (61.8%) relative to the bosutinib arm (28.9%) at the time of the data cut-off. Median duration of exposure to study treatment was approximately 50% longer in the asciminib 40 mg b.i.d. arm (43.4 vs. 29.2 weeks) compared to the bosutinib 500 mg q.d. indicating a higher probability for treatment discontinuation (and switch to asciminib in patients meeting protocol defined lack of efficacy criteria) in the bosutinib arm. However, also other reasons may have contributed to the higher treatment discontinuation rate considering the open trial design.

The proposed dose of 40 mg BID in fasting state was selected based on preclinical evidence, the results of the PopPK-exposure Analysis and the pharmacokinetic, efficacy and safety data available from the first in-human study phase 1 trial X2101. According to the results of this trial, a signal for an increased toxicity was observed at doses ≥ 80 mg BID, although the maximum tolerated dose (MTD) for asciminib monotherapy in patients with CML-CP was not achieved. Thus, the applicant selected the dose of 40 mg b.i.d. for the pivotal trial A2301, taken orally on an empty stomach, with no food to be consumed for at least 2 hour before the dose was taken, and for at least 1 hour after the dose was taken.

However, the applicant applied also for a different posology than administered in the pivotal trial: a dose of 80 mg q.d. is proposed as an *alternative regimen* to the 40 mg b.i.d. Since this dose was only preliminary investigated in 17 subjects in trial X2101, definitive conclusions on comparative efficacy and particularly regarding safety cannot be reliably drawn. In conclusion, the benefit risk balance for the 80 mg q,d posology may be different and  this recommendation should not be included in the product information.  The applicant has accepted to remove the 80 mg q.d. as an alternative dosing regimen, as recommended by the CHMP. The already initiated trial CABL001A2302 , that was regarded as PASS to evaluate the benefit risk balance for the 80 mg q,d posology, is now considered as PASS for long-term safety, important identified and important potential risks in currently proposed dosing regimen of 40 mg BID.

Bosutinib and not ponatinib was selected as comparator for trial A2301, since this product was specifically evaluated and approved in the EU in patients R/I ≥ 2 prior TKIs at the recommended dose of 500 mg q.d.. Insofar this comparator is fully acceptable, as already agreed during CHMP's previous scientific advice.

Similarly, an open-label conduct of the study is acceptable. It was justified since in addition to differences in dose adaptations, conditions for drug administration differ markedly for asciminib and bosutinib (asciminib needs to be taken in a fasted state, bosutinib should be taken with food). It was agreed that these issue making blinding with double-dummy treatment complex and probably carrying the inherent risk of administration and dosing errors. Moreover, acceptance is in accordance with CHMP's previous decision to accept open label designs already for pivotal trials for previous second or third generation TKIs in this disease. However, it needs to be considered that issues as treatment discontinuation and

particularly the switch to a treatment alternative may be more reliably assessed in a double-blinded trial design.

Inclusion and exclusion criteria were adequately chosen in order to select the intended target population of adult patients (>18 years of age) with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors. No specific concern became obvious regarding the selected study population from the inclusion and exclusion criteria.

Major molecular response (MMR) in principle is an acceptable surrogate-marker in CML. However, selection of MMR at week 24 as primary endpoint needs to be supplemented by long-term surrogate data as MMR at week 96, which was meanwhile provided.

Moreover, assessment of the treatment duration and other secondary endpoints, which are standard in CML trials and thus fully acceptable, is also not fully mature and need an update as far as available during this procedure and late on. Nevertheless, the issue remains that the high discontinuation rate in the bosutinib arm due to non-response may had affected the reported efficacy outcome also at the end.

The statistical methods are standard and generally considered acceptable.

The randomisation stratification factor was adequately taken into account by a correspondingly stratified analysis. Using the common risk difference and corresponding 95% CI using Mantel-Haenszel method is considered as the appropriate method for summarizing the treatment effect as risk differences can be easier interpreted (compared to e.g. odds ratios) and as the method is consistent with the hypothesis test.

Adjustment for multiplicity was pre-planned only for the key secondary endpoint, which had not yet been analysed. Analyses of additional endpoints were not consistently confirmatory.

In accordance with the primary estimand, patients who discontinued treatment before week 24 were considered as treatment failures such that these do not cause a missing data problem for the primary analysis. Although only few patients still on treatment had missing data at week 24, considering that one more responder in the bosutinib group would change the conclusion regarding statistical significance, handling of missing data is of relevance. Considering the tipping point analysis after 96 weeks, more responders in the bosutinib arm among patients with intercurrent events are required to change the conclusion with regard to statistical significance (at least more than 5, if no additional responders occurred under asciminib). However, the supplementary analyses demonstrate that this is not implausible such that the tipping point analysis provides also no conclusive support for the robustness of the conclusion of statistical significance after 96 weeks, if other estimands than the pre-specified are of interest.

The two treatment arms were overall balanced for the demographic characteristics assessed, with differences observed in ethnicity and sex. Patients in the asciminib arm (9.6%) included fewer Hispanic/Latino patients compared to the bosutinib arm (22.4%). Similarly, the proportion of males was slightly higher in the asciminib arm (52.2%) compared to the bosutinib arm (40.8%). No evidence for bias is observed.

The studied population in study A2301 consisted of heavily pre-treated CML patients with half of the patients (52.4%) receiving study treatment as 3rd-line therapy and the other half as 4,5 or 6th line of treatment. Sixty-four percent (64%) of the patients entered the study due to lack of efficacy on last TKI and 35% due to tolerability issues with last TKI. Imbalances between the treatment arms were noted with respect to prior lines of TKI treatment (pts with 2 prior TKIs (57% asci vs 43% bosu), discontinuation of prior treatment due to lack of efficacy (60% in asci arm vs 71% bosu) and a lower proportions of

patients received nilotinib and ponatinib in the asciminib arm than in the bosutinib arm (66.2% vs. 73.7% and 14.6% vs. 23.7%). The requested additional information revealed no evidence for bias.

The applicant clarified that it is not intended to allow asciminib also for treatment of Ph+ CML-CP patients harboring a T315I mutation who have received two or more TKIs.

**Supportive data from Trial X2101**

**Study X2101**, is an ongoing Phase I, first-in-patients, multicenter, open-label, dose escalation study to define the maximum tolerated dose and/or recommended dose for expansion (MTD/RDEs), to characterize safety and tolerability, and to assess the pharmacokinetic (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 CML or Ph+ acute lymphoblastic leukemia (ALL) [5 arm-trial].

Supportive efficacy data from a small cohort of CML-CP and AP patients was submitted from trial X2101. In this first-in-patients, phase 1 trial, efficacy from CML patients exposed to the applied dose of 40 mg b.i.d. (n=30) an alternative dose of 80 mg q.d. (n=17) is evaluable.

This data allow at preliminary evaluation of efficacy after longer exposure and seems to be the only source for the proposed alternative posology of 80 mg asciminib o.d.. However, the presented outcome analyses among 86 evaluable CML patients not harboring the T315I mutation include also patients that were treated with a higher (and probably lower) doses of asciminib due to the design. This heterogeneity precludes any pooling of the data and impeded interpretation of the results and makes further conclusions a priori difficult. Thus, the pivotal relevance of the data is seen as limited compared with that derived from trial A2301.

*Efficacy data and additional analyses*

It is agreed that study A2301 indicate efficacy of asciminib in the target population applied for and the trial met its primary objective. Thus, formal statistical superiority regarding this outcome was demonstrated for asciminib 40 mg BID relative to bosutinib 500 mg QD with respect to the primary endpoint of MMR at 24 weeks while on study treatment without meeting any treatment failure criteria as pre-specified in the study protocol.

A MMR rate of 25.5% is reported in the asciminib arm (nearly twice as high) compared to 13.2% in the bosutinib arm after 24 weeks of treatment. It is acknowledged that this result is statistically significant and may indicate a potentially clinical meaningful difference in the heavily pre-treated study population of 12.2% (95% CI: 2.19, 22.30, two-sided p-value: 0.029) (per the Cochran–Mantel–Haenszel two-sided test stratified by the MCyR status at baseline) in favour for asciminib.

MMR rate seems to be consistent also at later time points up to week 48/60/96 according the recent interim update of data submitted after start of procedure.

Sensitivity analyses and subgroup analysis presented for the outcome MMR at week 24 are in line with the primary outcome. The efficacy of asciminib is irrespective of the number of previous lines of TKIs as demonstrated in MMR rate at 24 weeks (asciminib compared to bosutinib) as 3rd-line therapy (29.3% vs. 20.0%), 4th-line therapy (25.0% vs. 13.8%), or  5th-line therapy (16.1% vs. 0%).

Other secondary endpoints support also the primary analysis as demonstrated in favour of asci with a shorter median time to MMR (12.7 weeks vs 14.3 weeks for bosutinib), a higher duration of MMR (KM estimated proportion of patients maintaining their MMR for at least 48 weeks was 96.1% (95% CI: 85.4, 99.0) in the asci arm vs 90.0% (95% CI: 47.3, 98.5) in the bosutinib arm). However, it is considered that current database is affected by the issue that only few participants are remaining in the bosutinib arm.

Loss of response has been observed in both treatment arms in the current study and has also been described previously in a small subset of the bosutinib treated patients as part of the compassionate use program (source bosutinib EPAR). As loss of response has only been seen in a limited number of subjects, both CHMP agreed that this is not a reason to question the benefit of asciminib treatment in principle. The initially requested further information on reasons for loss of response in these patients (i.e. was loss of response determined objective through assessment, or due to another reason) together with an update of the cases of loss of response in the asciminib arm was provided and does not lead to major changes in the assessment outcome.

From a methodological point of view it is important, that for the primary estimand, treatment discontinuation and meeting any treatment failure criteria were included as components in the primary endpoint by considering these as non-response (i.e. a composite strategy was applied in accordance with ICH E9 (R1)), which implies that these events are considered as clinically relevant and of equal importance than not achieving MMR at week 24. This is generally appropriate for meeting treatment failure criteria. While it is also agreed that treatment discontinuation can be considered as a negative outcome considering that long-term disease control is possible only under continuous treatment, the reasons for treatment discontinuation should also be taken into account, particularly considering the open-label design. However, response received on the initial concerns and the increase of the difference in MMR at week 96 in favour for asciminib modifies the issues regarding the relevance of the discontinuation reasons, since superiority no longer depends from a single patient between the arms.

Moreover, imbalances between the treatment arms with respect to prior lines of TKI treatment, the higher proportions of patients discontinued the prior TKI due to intolerance in the asciminib arm vs. the bosutinib arm and particularly the fact that lower proportions of patients received nilotinib and ponatinib in the asciminib arm than in the bosutinib arm in combination were noted. Although these baseline imbalances could have favored all asciminib at the end, the effect seems not so pronounced that it may have affect the efficacy outcome significantly. In conclusion, the main uncertainty which remains is caused by the higher discontinuation rate due to a lack of efficacy or adverse events in the bosutinib arm. Overall, the potential impact of baseline imbalances was sufficiently clarified with the response and no longer raise concern regarding the described benefit.

A difference was observed between patients discontinuing last prior TKI due to intolerance (2.1%; 95%CI -20.8 - 25.0) or due to resistance on their last TKI (15.5%; 95%CI 5.3 - 25.7). Further analysis revealed that this is not due to the unbalanced baseline distribution of prognostic factors. It was suggested that this is due to limited efficacy of bosunitinib in patients with prior failure of their last TKI (MMR rate: 5.6% patients with failure compared to 31.8% patients intolerant to last TKI). However, the applicant clarified that at the time of primary endpoint assessment at Week 24, by treatment arms, the responder group in the asciminib arm had the same proportion of patients with intolerance or resistance to last TKI (50% each). However, in the bosutinib arm, the responder group had more patients who were intolerant to last TKI (70%).

Given the trial was open-label and patients who withdrew from the study were considered non-responders, it could be that the discrepancy between patients with prior failure or intolerance was due to the withdrawal of patients rather than a difference in response. For these subgroups, the Applicant is requested to provide the number of patients who had an assessment at 24 weeks and the outcomes for these patients by treatment arm. For those patients who did not have an assessment at 24 weeks, a detailed summary of reasons for discontinuation was provided and clarified that prior failure or intolerance is not explained by non-response due to withdrawal/missing data.

Supportive data from Trial X2101

Among 86 evaluable CML-CP (-AP?) patients not harboring the T315I mutation results may be assessed as in-line with the outcome in the pivotal trial A2301. The MMR rate at Week 24 is reported with 23.3%

(compared with 25 % in A2301). As could be expected, the MMR rate increases over time: 50 (58.1%) patients achieved MMR at any time-point. The duration of MMR among the 50/86 patients with CML-CP who achieved MMR the KM estimated proportion of patients maintaining their first MMR for at least 48 weeks was 96% (95% CI: 89.5, 100.0) and for at least 96 weeks was 93% (95% CI: 85.7, 100.0). However, since only 47 of the 86 subjection analysed received the applied posology [40 mg b.i.d. (n=30) an alternative dose of 80 mg q.d. (n=17)], the interpretability of the reported outcome is critical due to several reasons. In particular, since also patients treated with higher doses (up to 200 mg bid) were included.

Nevertheless, the data presented seems be support the efficacy in CML in principle and particularly allow a first glance on efficacy after longer exposure, since treatment duration is significantly longer (183.4 weeks in 115 CML-CP patients) than in the pivotal trial A2301. Moreover, efficacy data from X2101 is the only source for the proposed, but rejected alternative posology of 80 mg asciminib o.d..

Further conclusions from this data source are difficult due to the highly heterogeneous phase I population included and the probable differences in disease-stage (including CML-AP) and the primary dose-finding aim of the design.

## 2.6.7. Conclusions on the clinical efficacy

Efficacy of asciminib in patients with Ph+ CML-CP not harboring the T315I mutation and treated with two or more TKIs has been demonstrated in the pivotal study A2301 supported with data from study X2101. Outcome after longer treatment duration with the surrogate endpoint MMR at week 96 was also provided and confirms the superiority in efficacy against bosutinib. The currently available data set with Week 96 efficacy is seen as mature.

## 2.6.8. Clinical safety

The safety profile of asciminib has been characterized based on the safety data from Study A2301 (pivotal study), Study X2101 (supportive study) and pooled analysis data (in total 356 patients). The overall safety database is small. For comparison to other approved TKIs, dasatinib database comprised 511 patients when the product was approved; bosutinib database comprised 1209 patients who received at least 1 dose of oral bosutinib alone or in combination with another anticancer agent.

The safety evaluation of asciminib monotherapy in patients with Ph+ CML-CP is based on the data from the primary analysis (data cut-off date: 25-May-2020) of an ongoing Phase III, multi-center, open-label, randomized, active-controlled Study – Study A2301 (asciminib group; N=156 and bosutinib group; N=76). The safety population exposed to asciminib in the pivotal phase III study (n=156) is smaller than in bosutinib (n=248), dasatinib (n=258) or nilotinib (n=556) pivotal trials.

The safety data from the Study X2101 (data cut-off date: 02-Apr-2020) provides supportive evidence of asciminib safety in patients with CML-CP.

A 30-day update was submitted as well, that provided an updated evaluation of efficacy and safety. Updated data were analysed included longer follow-up data with a cut-off date 6-Jan-2021, corresponding to approximately 7.5 months and 9 months additional follow-up for study A2301 and Study X2101, respectively. In general, these updated safety results seem consistent with the safety results submitted in the original CO and SCS.

Based on previous regulatory experience on TKIs the safety database in the target population could be considered overall large enough to allow safety assessment. However, as the product is intended for

long-term treatment in a heavily pre-treated CML population, updated longer follow-up safety data is to be provided to allow the assessment of the long-term risk.

Therefore, as a response to Day 120 List of Questions, an updated safety analysis of the pivotal Study A2301, at cut-off date 06-Oct-2021 and with 9 months additional follow-up, was presented and discussed.

Furthermore, the Week 96 interim CSR for Study A2301 was provided with the responses to the Day 180 List of Outstanding Issues, with an additional safety update.

Pooled data from Study A2301 and Study X2101 enable an evaluation of the impact of asciminib treatment at different doses and different treatment regimens. Safety pools are defined as follow:

- Pool A (asciminib All patients Safety Pool; N=356): Data from all patients treated with asciminib in the Study A2301 (N=156) along with data from all patients with CML-CP/-AP (regardless of T315I mutation) treated with single agent asciminib at any dose from Study X2101 (N=200).

- Pool C (asciminib 40 mg b.i.d. Safety Pool; N=187): Data from all patients treated with asciminib in the Study A2301 (N=156) along with data from patients with CML-CP (regardless of T315I mutation) treated with a starting dose of single agent asciminib 40 mg b.i.d. in Study X2101 (N= 31).

In this Assessment Report, safety assessment focuses mainly on the pivotal trial Study A2301 and information from Study X2101.

The safety population in each study included subjects who received at least one dose of study drug.

Of note, patients on bosutinib treatment in the study were offered the option to receive asciminib treatment within 96 weeks after the last patient was randomized on study, and if investigator considered this treatment to be in the best interest of the patient. Patients intolerant to bosutinib were not allowed to switch to asciminib.

As of the primary analysis cut-off (25-May-2020), 22 patients had switched treatment from bosutinib to asciminib, with additional two at the data cut-off date of 06-Oct-2021. The safety profile of asciminib observed in the patients who switched from bosutinib to asciminib is consistent with that observed in patients receiving asciminib in the randomization phase of the study.

### 2.6.8.1. Patient exposure

In the pivotal Study A2301, as of the data cut off of 6-Jan-2021, the median duration of exposure to asciminib was 67.1 weeks (approximately 15.6 months), which was longer by 23.8 weeks from 43.4 weeks at the previous cut-off on 25-May 2020; 67.3% of patients were exposed for at least 48 weeks of asciminib treatment. The longest duration of exposure was approximately 6.5 years in Asciminib All Patients Pool and approximately 3 years in the study A2301.

The median duration of exposure to bosutinib at the data cut off of 6-Jan-2021, remained similar at 29.7 weeks compared to 29.2 weeks at the previous cut-off. The reason for this is that majority of patients had discontinued bosutinib by the time of primary analysis cut-off. The maximum exposure to bosutinib increased to 149 weeks. Total exposure was 204.3 patient-years and 61.2 patient-years for patients randomised to asciminib treatment group and the bosutinib treatment group, respectively.

An updated safety analysis with a cut-off date of 06-Oct-2021 increased the median duration of exposure in Study A2301 to 23.7 months, and in asciminib All patients Pool to 26.6 months .

There is a substantial difference in exposure between asciminib and bosutinib treatment groups. The median duration of exposure to study drug was approximately three times longer in the asciminib arm (103.14 weeks; range: 0.1 to 201.1) compared to that in the bosutinib arm (30.50 weeks; range: 1.0 to 188.3). This is due to the fact that more patients discontinued study medication in the bosutinib vs asciminib treatment group.

The per-protocol doses of asciminib and bosutinib in the study A2301 were 40 mg b.i.d. and 500 mg q.d. respectively. In case of toxicities, the dose of asciminib could be reduced to 20 mg b.i.d. For bosutinib, two levels of dose reduction were allowed: 400 mg q.d. and 300 mg q.d. Doses below 20 mg b.i.d. for asciminib and below 300 mg q.d. for bosutinib were not allowed. In Study A2301, median dose intensities were 79.8 mg/day (minimum-maximum: 33-80) and 478.6 mg (minimum-maximum: 181-566) for the asciminib and bosutinib treatment groups, respectively.

The Study A2301 included patients with a diagnosis of Ph+ CML-CP (n = 157 patients); however 1 patient (in the asciminib arm) was not included in the Safety set (n = 156 patients), as this patient developed cytopenia after randomization and subsequently did not receive study treatment per Investigator's decision. As of the 25-May-2020 data cut-off date, 119 patients (51.1%) continued to receive treatment. Treatment discontinuation was less frequent in the asciminib treatment group compared to the bosutinib treatment group (37.6% versus 69.7%). Lack of efficacy and AEs were the primary reasons for discontinuation in both treatment groups, and both were less frequent in the asciminib treatment group compared to the bosutinib treatment group (lack of efficacy: 21.0% versus 31.6%; AE(s): 5.1% versus 21.1%). As of updated 06-Jan-2021 data cut-off date, 106 of the 233 patients (45.5%) were continuing the study treatment with 89 patients (56.7%) and 17 patients (22.4%) still ongoing in the asciminib and bosutinib arms, respectively. Since the previous cut-off, 8 additional patients discontinued study treatment in the asciminib arm (4 patients discontinued due to lack of efficacy, one due to AE, and 3 due to PI decision), and 5 additional patients in bosutinib arm (3 patients discontinued due to lack of efficacy and 2 due to AE). Lack of efficacy (27.5%) and AEs (11.6%) remained the primary reasons for discontinuation, and both were less frequent in the asciminib treatment group compared to the bosutinib treatment group (lack of efficacy: 23.6% versus 35.5%; AE(s): 5.7% versus 23.7%). At the Week 96 cut-off, the frequency of AEs leading to study treatment discontinuation continued to be lower in the asciminib arm; 7.7% on asciminib and 26.3% on bosutinib.

In Study X2101, as of the 02-Apr-2020 data cut-off date, 123 patients (61.5%) were continuing treatment with single-agent asciminib and 77 patients (38.5%) had their treatment discontinued. The most frequent reasons for discontinuation of treatment were physician's decision (16.0%) and AE(s) (9.5%). Of the 32 patients (16%) who discontinued due to physician's decision, 29 patients discontinued due to lack of efficacy (including 8 who received transplantation and one who was re-assigned to Arm 4), 1 patient due to both intolerance and lack of efficacy and 2 patients due to other reasons. As of updated 06-Jan-2021 data cut-off date, 113 patients (56.5%) were continuing treatment with single-agent asciminib and 87 patients (43.5%) had discontinued study treatment, with 10 additional patients (6 patients in 200 mg b.i.d. dose group and 1 patient each in 40 mg b.i.d., 160 mg b.i.d., 80 mg q.d. and 120 mg q.d. dose groups) having discontinued the study relative to the previous data cut-off. The most frequent reasons for discontinuation of treatment remained physician's decision (16.5%) and AE(s) (10.0%).

In the study A2301, the proportion of patients with at least one dose reduction (39.1% vs. 46.1%) at least one dose interruption (53.2% vs. 73.7%), and discontinuation (43.6% vs. 78.9%) was lower in the asciminib group compared to bosutinib group.

Dose reductions were primarily attributable to AEs in both the treatment groups; 23.1% in the asciminib treatment group and 44.7% in the bosutinib treatment group. Dosing errors (17.9%) were the second common reason for dose reduction in the asciminib treatment group in comparison to bosutinib arm

(1.3%). The higher frequency for dosing errors as the cause of dose reductions in the asciminib arm is attributable to the difference in dosing regimen between both arms; asciminib was administered twice daily, therefore any missed dose was reported as a dose reduction.

Dose interruptions were primarily attributable to AEs (60.5% vs, 40.4%) and dosing errors (17.1% vs. 12.2%); the incidence of both reasons was higher in the bosutinib treatment group than asciminib treatment group.

Permanent discontinuation were primarily due to lack of efficacy in both the treatment groups (23.7% in the asciminib treatment group compared to 35.5% in the bosutinib treatment group). Permanent discontinuation due to AEs was less frequently reported in the asciminib group (6.4%) as compared with the bosutinib group (25.0%).

In Study A2301, demographic characteristics were well balanced between the asciminib and bosutinib treatment groups with the exception of gender and ethnicity.

### 2.6.8.2. Adverse events

Overall, in the pivotal study 2301, the incidence of AEs in all categories was lower in the asciminib treatment group compared to the bosutinib treatment group, with the exception of fatal SAEs, where no difference was apparent.

In Study X2101, all patients who received 80 mg q.d. dose had experienced at least one AE (regardless of study treatment relationship). Eight (44.4%) patients had experienced SAEs and 1 patient had fatal SAE that was not suspected to be study treatment related as assessed by the investigator. Three patients had AEs that led to study treatment discontinuation. Although the number of patients who received 80 mg q.d. in this study is too small to draw a certain conclusion, nevertheless the incidence of AE for all categories is evidently higher in comparison to asciminib 40 mg b.i.d in the study A2301.

The incidence of AEs for all AE categories in the Asciminib safety pools was consistent with the asciminib treatment group in Study A2301. The treatment –related AEs and SAEs, however, were experienced by a higher number of patients (> 10%) in the asciminib All Patients Safety Pool compared to asciminib treatment group in Study A2301 which was attributed to the longer exposure.

**Table 25        Overview of adverse events – Safety set (cut-off date 6-Jan-2021)**

| Category | Study A2301 | | | | Study X2101 | | Safety Pool | | | |
| | Bosutinib 500 mg q.d. N=76 | | Asciminib 40 mg b.i.d. N=156 | | Asciminib 80 mg q.d. (CP) N=18 | | Asciminib 40 mg b.i.d. (CP) N=187 | | Asciminib All Patients N=356 | |
| | All grades n (%) | Grade ≥ 3 n (%) | All grades n (%) | Grade ≥ 3 n (%) | All grades n (%) | Grade ≥ 3 n (%) | All grades n (%) | Grade ≥ 3 n (%) | All grades n (%) | Grade ≥ 3 n (%) |
| Adverse events | 74 (97.4) | 51 (67.1) | 142 (91.0) | 85 (54.5) | 18 (100) | 14 (77.8) | 173 (92.5) | 109 (58.3) | 342 (96.1) | 222 (62.4) |
| Treatment-related | 68 (89.5) | 40 (52.6) | 103 (66.0) | 50 (32.1) | 16 (88.9) | 12 (66.7) | 131 (70.1) | 66 (35.3) | 279 (78.4) | 145 (40.7) |
| SAEs | 18 (23.7) | 16 (21.1) | 24 (15.4) | 19 (12.2) | 8 (44.4) | 7 (38.9) | 35 (18.7) | 27 (14.4) | 108 (30.3) | 83 (23.3) |
| Treatment-related | 9 (11.8) | 7 (9.2) | 5 (3.2) | 4 (2.6) | 1 (5.6) | 1 (5.6) | 6 (3.2) | 4 (2.1) | 26 (7.3) | 20 (5.6) |
| Fatal SAEs | 1 (1.3) | 1 (1.3) | 2 (1.3) | 2 (1.3) | 1 (5.6) | 1 (5.6) | 2 (1.1) | 2 (1.1) | 8 (2.2) | 8 (2.2) |
| Treatment-related | 1 (1.3) | 1 (1.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| AEs leading to discontinuation | 19 (25.0) | 14 (18.4) | 11 (7.1) | 10 (6.4) | 3 (16.7) | 1 (5.6) | 14 (7.5) | 12 (6.4) | 34 (9.6) | 28 (7.9) |
| Treatment-related | 16 (21.1) | 11 (14.5) | 8 (5.1) | 7 (4.5) | 1 (5.6) | 0 | 11 (5.9) | 9 (4.8) | 21 (5.9) | 17 (4.8) |

A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 23.1, CTCAE version 4.03.
Source: [SCS30du Appendix 3-Table 2.1-23]

Since fewer patients in the asciminib treatment group discontinued study medication compared to the bosutinib treatment group which resulted in marked differences in the median exposure to the two treatment groups (67.14 weeks vs 29.21 weeks, respectively), in order to adjust for the imbalance in

treatment exposure when comparing the crude frequency of AEs between asciminib and bosutinib in Study A2301 and between asciminib treatment group in Study A2301 and the asciminib Safety Pools, the applicant provided also summary tables calculating exposure-adjusted incidence rates (EAIRs) and cumulative incidence proportions at Week 8, 24 and 48. The AEs assessed based on the EAIRs were consistent for both the asciminib 40 mg b.i.d. Safety Pool and the asciminib All Patients Safety Pool and were generally also consistent with the asciminib treatment group in Study A2301. However, the EAIR for the asciminib 80 mg q.d. treatment group in the Study X2101 was significantly higher (AEs 1557.9; treatment related AEs 255.4) in comparison to other groups/safety pools.

**Table 26        Overview of adverse events by EAIR – Safety set (cut-off date 6-Jan-2021)**

| | Study A2301 | | | | Study X2101 | | Safety Pool | | | |
| | Bosutinib 500 mg q.d. N=76 | | Asciminib 40 mg b.i.d. N=156 | | Asciminib 80 mg q.d. (CP) N=18 | | Asciminib 40 mg b.i.d. (CP) N=187 | | Asciminib All Patients N=356 | |
| Category | All grades n (IR per 100 PTY) | Grade ≥ 3 n (IR per 100 PTY) | All grades n (IR per 100 PTY) | Grade ≥ 3 n (IR per 100 PTY) | All grades n (IR per 100 PTY) | Grade ≥ 3 n (IR per 100 PTY) | All grades n (IR per 100 PTY) | Grade ≥ 3 n (IR per 100 PTY) | All grades n (IR per 100 PTY) | Grade ≥ 3 n (IR per 100 PTY) |
|---|---|---|---|---|---|---|---|---|---|---|
| Adverse events | 74 (1379.0) | 51 (126.9) | 142 (411.9) | 85 (67.7) | 18 (1557.9) | 14 (63.9) | 173 (481.9) | 109 (68.2) | 342 (700.9) | 222 (54.4) |
|    Treatment-related | 68 (590.9) | 40 (84.4) | 103 (119.2) | 50 (30.2) | 16 (255.4) | 12 (38.7) | 131 (122.6) | 66 (27.6) | 279 (149.9) | 145 (26.0) |
| SAEs | 18 (30.4) | 16 (26.8) | 24 (12.8) | 19 (9.7) | 8 (18.4) | 7 (15.6) | 35 (13.2) | 27 (9.5) | 108 (17.2) | 83 (12.2) |
|    Treatment-related | 9 (14.4) | 7 (11.1) | 5 (2.4) | 4 (1.9) | 1 (1.7) | 1 (1.7) | 6 (1.9) | 4 (1.2) | 26 (3.4) | 20 (2.5) |
| AEs leading to discontinuation | 19 (30.2) | 14 (22.1) | 11 (5.3) | 10 (4.8) | 3 (4.9) | 1 (1.6) | 14 (4.3) | 12 (3.7) | 34 (4.2) | 28 (3.5) |

IR = exposure-adjusted incidence rate: number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in 100 PTY is counted up to the first qualifying event (or end of time at risk for patients without event).
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 23.1, CTCAE version 4.03.
Source: [SCS30du Appendix 3-Table 2.1-9], [SCS30du Appendix 3-Table 2.1-10], [SCS30du Appendix 3-Table 2.1-11], [SCS30du Appendix 3-Table 2.1-12], [SCS30du Appendix 3-Table 2.1-13]

In the pivotal study A2301, the SOCs in which AEs were reported more frequently in asciminib group (≥ 10% difference relative to the bosutinib group) were infections and infestations (+16.0%), musculoskeletal and connective tissue disorders (+12.2%), and nervous system disorders (+11.6%) and vascular disorders (+10.0%) On the other hand, AEs were less frequently reported in the asciminib group relative to bosutinib group for the SOCs of GI disorders (-38.6%) and investigations (-19.2%).

All patients who were treated with asciminib 80 mg q.d. in the study X2101 had at least one AE, and in majority of patients (88.9%) AEs reported were treatment-related. The incidence of AEs in majority of SOC was much higher than for the asciminib 40 mg b.i.d group in pivotal study.

In Responses to D120 LoQ, the applicant presented both the detailed descriptive analysis of adverse events by dose cohort in the Study X2101, as well as the comprehensive exposure-safety analysis (data not shown here).

AEs by preferred term

Thrombocytopenia (23.1%), neutropenia (19.2%), headache (18.6%), fatigue (13.5%). arthralgia (12.2%), hypertension (12.2%), diarrhoea (11.5%), nausea (11.5%), and nasopharyngitis (10.9%) were the AEs (all grades, regardless of study treatment relationship) that occurred most frequently (≥ 10%) in the asciminib treatment group in the Study A2301. The most frequently (≥ 10%) reported AEs in the bosutinib treatment group included diarrhoea (71.1%), nausea (46.1%), ALT increase (28.9%), vomiting (26.3%), rash (23.7%), AST increase (21.1%), neutropenia (17.1%), abdominal pain (15.8%), headache (14.5%), and thrombocytopenia (14.5%).

In the asciminib treatment group, 54.5% of the patients had at least one grade $\geq$ 3 AE with the majority of the grade $\geq$ 3 AEs occurring in either 1 or 2 patients per preferred term. The incidence of most frequently occurring grade $\geq$ 3 AEs ($\geq$ 5%) were thrombocytopenia (17.9%), neutropenia (15.4%), and hypertension (5.8%). The incidence of grade $\geq$ 3 AEs (regardless of study treatment relationship) was lower in the asciminib treatment group, relative to bosutinib treatment group (54.5% vs. 67.1%).

All patients who received 80 mg q.d. dose in the Study X2101 had experienced at least one AE. The most frequently reported AEs (all grades) were upper respiratory tract infection (44.4%; 8 patients), fatigue (38.9%; 7 patients), headache (33.3%), arthralgia (33.3%), hypertension (33.3%), and diarrhoea (33.3%). Except for hypertension (22.2%; 4 patients) and lipase increase (16.7%; 3 patients), all grade $\geq$ 3 AEs were reported infrequently in either 1 or 2 patients.

For Asciminib Safety pools, in general, the nature and frequency of the AEs were largely consistent (difference of $\leq$ 10%) with those from the asciminib treatment group in Study A2301. Higher incidence (of $\geq$ 10%) was observed for lipase increase (+13.2%) in the asciminib All Patients Safety Pool compared to asciminib treatment group in Study A2301.

**Table 27     Adverse events by preferred term and grade - (Safety set) (cut-off date 6-Jan-2021)**

| | Study A2301 | | | | Study X2101 | | Safety Pool | | | |
| | Bosutinib 500 mg q.d. N=76 | | Asciminib 40 mg b.i.d. N=156 | | Asciminib 80 mg q.d. (CP) N=18 | | Asciminib 40 mg b.i.d. (CP) N=187 | | Asciminib All Patients N=356 | |
| Preferred term | All grades n (%) | Grade ≥ 3 n (%) | All grades n (%) | Grade ≥ 3 n (%) | All grades n (%) | Grade ≥ 3 n (%) | All grades n (%) | Grade ≥ 3 n (%) | All grades n (%) | Grade ≥ 3 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of patients with at least one event | 74 (97.4) | 51 (67.1) | 142 (91.0) | 85 (54.5) | 18 (100) | 14 (77.8) | 173 (92.5) | 109 (58.3) | 342 (96.1) | 222 (62.4) |
| Headache | 11 (14.5) | 0 | 29 (18.6) | 3 (1.9) | 6 (33.3) | 2 (11.1) | 37 (19.8) | 4 (2.1) | 84 (23.6) | 7 (2.0) |
| Fatigue | 7 (9.2) | 1 (1.3) | 21 (13.5) | 1 (0.6) | 7 (38.9) | 0 | 34 (18.2) | 1 (0.5) | 81 (22.8) | 4 (1.1) |
| Thrombocytopenia | 11 (14.5) | 5 (6.6) | 36 (23.1) | 28 (17.9) | 5 (27.8) | 2 (11.1) | 42 (22.5) | 30 (16.0) | 81 (22.8) | 54 (15.2) |
| Arthralgia | 3 (3.9) | 0 | 19 (12.2) | 0 | 6 (33.3) | 2 (11.1) | 29 (15.5) | 0 | 76 (21.3) | 4 (1.1) |
| Nausea | 35 (46.1) | 0 | 18 (11.5) | 1 (0.6) | 5 (27.8) | 0 | 24 (12.8) | 1 (0.5) | 72 (20.2) | 4 (1.1) |
| Diarrhoea | 54 (71.1) | 8 (10.5) | 18 (11.5) | 0 | 6 (33.3) | 0 | 27 (14.4) | 0 | 71 (19.9) | 2 (0.6) |
| Lipase increased | 5 (6.6) | 4 (5.3) | 8 (5.1) | 6 (3.8) | 4 (22.2) | 3 (16.7) | 23 (12.3) | 13 (7.0) | 65 (18.3) | 38 (10.7) |
| Hypertension | 4 (5.3) | 3 (3.9) | 19 (12.2) | 9 (5.8) | 6 (33.3) | 4 (22.2) | 28 (15.0) | 12 (6.4) | 63 (17.7) | 30 (8.4) |
| Neutropenia | 13 (17.1) | 9 (11.8) | 30 (19.2) | 24 (15.4) | 4 (22.2) | 2 (11.1) | 34 (18.2) | 27 (14.4) | 55 (15.4) | 42 (11.8) |
| Vomiting | 20 (26.3) | 0 | 11 (7.1) | 2 (1.3) | 3 (16.7) | 1 (5.6) | 19 (10.2) | 3 (1.6) | 55 (15.4) | 9 (2.5) |
| Rash | 18 (23.7) | 3 (3.9) | 12 (7.7) | 0 | 3 (16.7) | 0 | 21 (11.2) | 0 | 53 (14.9) | 0 |
| Abdominal pain | 12 (15.8) | 1 (1.3) | 9 (5.8) | 0 | 4 (22.2) | 1 (5.6) | 19 (10.2) | 0 | 47 (13.2) | 5 (1.4) |
| Pain in extremity | 5 (6.6) | 0 | 13 (8.3) | 1 (0.6) | 3 (16.7) | 0 | 19 (10.2) | 1 (0.5) | 47 (13.2) | 2 (0.6) |
| Upper respiratory tract infection | 4 (5.3) | 0 | 11 (7.1) | 1 (0.6) | 8 (44.4) | 0 | 17 (9.1) | 1 (0.5) | 46 (12.9) | 1 (0.3) |
| Cough | 5 (6.6) | 0 | 12 (7.7) | 0 | 2 (11.1) | 0 | 19 (10.2) | 0 | 44 (12.4) | 0 |
| Pruritus | 5 (6.6) | 1 (1.3) | 8 (5.1) | 0 | 3 (16.7) | 0 | 12 (6.4) | 0 | 44 (12.4) | 1 (0.3) |
| Anaemia | 6 (7.9) | 3 (3.9) | 15 (9.6) | 2 (1.3) | 3 (16.7) | 0 | 21 (11.2) | 6 (3.2) | 43 (12.1) | 19 (5.3) |
| Back pain | 2 (2.6) | 1 (1.3) | 11 (7.1) | 1 (0.6) | 3 (16.7) | 1 (5.6) | 16 (8.6) | 1 (0.5) | 41 (11.5) | 4 (1.1) |
| Nasopharyngitis | 3 (3.9) | 0 | 17 (10.9) | 0 | 0 | 0 | 21 (11.2) | 0 | 41 (11.5) | 0 |
| Dizziness | 2 (2.6) | 0 | 11 (7.1) | 0 | 5 (27.8) | 0 | 16 (8.6) | 0 | 40 (11.2) | 1 (0.3) |

| | Study A2301 | | | | Study X2101 | | Safety Pool | | | |
| | Bosutinib 500 mg q.d. N=76 | | Asciminib 40 mg b.i.d. N=156 | | Asciminib 80 mg q.d. (CP) N=18 | | Asciminib 40 mg b.i.d. (CP) N=187 | | Asciminib All Patients N=356 | |
| Preferred term | All grades n (%) | Grade ≥ 3 n (%) | All grades n (%) | Grade ≥ 3 n (%) | All grades n (%) | Grade ≥ 3 n (%) | All grades n (%) | Grade ≥ 3 n (%) | All grades n (%) | Grade ≥ 3 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Amylase increased | 4 (5.3) | 0 | 9 (5.8) | 1 (0.6) | 2 (11.1) | 0 | 16 (8.6) | 4 (2.1) | 38 (10.7) | 8 (2.2) |
| Myalgia | 2 (2.6) | 0 | 8 (5.1) | 0 | 2 (11.1) | 0 | 14 (7.5) | 1 (0.5) | 38 (10.7) | 3 (0.8) |
| Constipation | 4 (5.3) | 0 | 7 (4.5) | 0 | 5 (27.8) | 0 | 11 (5.9) | 0 | 37 (10.4) | 0 |
| Dyspnoea | 4 (5.3) | 0 | 8 (5.1) | 0 | 3 (16.7) | 0 | 13 (7.0) | 0 | 33 (9.3) | 2 (0.6) |
| Pyrexia | 6 (7.9) | 1 (1.3) | 6 (3.8) | 2 (1.3) | 1 (5.6) | 0 | 10 (5.3) | 3 (1.6) | 33 (9.3) | 3 (0.8) |
| Alanine aminotransferase increased | 22 (28.9) | 11 (14.5) | 6 (3.8) | 1 (0.6) | 1 (5.6) | 1 (5.6) | 7 (3.7) | 1 (0.5) | 32 (9.0) | 9 (2.5) |
| Abdominal pain upper | 5 (6.6) | 1 (1.3) | 7 (4.5) | 0 | 3 (16.7) | 0 | 10 (5.3) | 0 | 31 (8.7) | 0 |
| Insomnia | 1 (1.3) | 0 | 11 (7.1) | 0 | 0 | 0 | 16 (8.6) | 0 | 31 (8.7) | 2 (0.6) |
| Oedema peripheral | 2 (2.6) | 0 | 9 (5.8) | 0 | 1 (5.6) | 0 | 15 (8.0) | 0 | 31 (8.7) | 2 (0.6) |
| Aspartate aminotransferase increased | 16 (21.1) | 5 (6.6) | 8 (5.1) | 3 (1.9) | 1 (5.6) | 0 | 9 (4.8) | 4 (2.1) | 29 (8.1) | 7 (2.0) |
| Dyspepsia | 3 (3.9) | 0 | 11 (7.1) | 0 | 1 (5.6) | 0 | 11 (5.9) | 0 | 26 (7.3) | 0 |
| Non-cardiac chest pain | 1 (1.3) | 0 | 8 (5.1) | 2 (1.3) | 2 (11.1) | 0 | 11 (5.9) | 2 (1.1) | 26 (7.3) | 4 (1.1) |
| Hypertriglyceridaemia | 0 | 0 | 5 (3.2) | 2 (1.3) | 4 (22.2) | 2 (11.1) | 9 (4.8) | 2 (1.1) | 25 (7.0) | 7 (2.0) |
| Oropharyngeal pain | 2 (2.6) | 0 | 7 (4.5) | 0 | 5 (27.8) | 0 | 9 (4.8) | 0 | 25 (7.0) | 0 |
| Decreased appetite | 6 (7.9) | 0 | 7 (4.5) | 0 | 0 | 0 | 8 (4.3) | 0 | 24 (6.7) | 1 (0.3) |
| Hyperuricaemia | 2 (2.6) | 0 | 5 (3.2) | 2 (1.3) | 3 (16.7) | 2 (11.1) | 6 (3.2) | 3 (1.6) | 24 (6.7) | 6 (1.7) |
| Dry skin | 6 (7.9) | 0 | 7 (4.5) | 0 | 2 (11.1) | 0 | 9 (4.8) | 0 | 23 (6.5) | 0 |
| Muscle spasms | 0 | 0 | 8 (5.1) | 1 (0.6) | 1 (5.6) | 0 | 13 (7.0) | 1 (0.5) | 23 (6.5) | 1 (0.3) |
| Anxiety | 1 (1.3) | 0 | 5 (3.2) | 1 (0.6) | 2 (11.1) | 1 (5.6) | 7 (3.7) | 1 (0.5) | 22 (6.2) | 3 (0.8) |
| Hyperglycaemia | 0 | 0 | 6 (3.8) | 3 (1.9) | 3 (16.7) | 1 (5.6) | 9 (4.8) | 3 (1.6) | 22 (6.2) | 6 (1.7) |
| Blood creatinine increased | 5 (6.6) | 0 | 5 (3.2) | 0 | 0 | 0 | 8 (4.3) | 0 | 20 (5.6) | 0 |
| Bone pain | 1 (1.3) | 0 | 2 (1.3) | 0 | 2 (11.1) | 1 (5.6) | 7 (3.7) | 0 | 20 (5.6) | 1 (0.3) |
| Gamma-glutamyltransferase increased | 0 | 0 | 1 (0.6) | 1 (0.6) | 1 (5.6) | 1 (5.6) | 4 (2.1) | 2 (1.1) | 20 (5.6) | 7 (2.0) |
| Platelet count decreased | 4 (5.3) | 2 (2.6) | 10 (6.4) | 7 (4.5) | 2 (11.1) | 1 (5.6) | 13 (7.0) | 10 (5.3) | 20 (5.6) | 15 (4.2) |
| Dry eye | 2 (2.6) | 0 | 3 (1.9) | 0 | 1 (5.6) | 0 | 6 (3.2) | 0 | 19 (5.3) | 0 |
| Hyperhidrosis | 0 | 0 | 3 (1.9) | 0 | 3 (16.7) | 0 | 4 (2.1) | 0 | 19 (5.3) | 0 |
| Hypophosphataemia | 4 (5.3) | 3 (3.9) | 2 (1.3) | 1 (0.6) | 1 (5.6) | 1 (5.6) | 4 (2.1) | 2 (1.1) | 19 (5.3) | 6 (1.7) |
| Neutrophil count decreased | 4 (5.3) | 3 (3.9) | 7 (4.5) | 6 (3.8) | 1 (5.6) | 1 (5.6) | 9 (4.8) | 8 (4.3) | 18 (5.1) | 16 (4.5) |
| Rash maculo-papular | 2 (2.6) | 1 (1.3) | 8 (5.1) | 0 | 2 (11.1) | 0 | 10 (5.3) | 0 | 18 (5.1) | 0 |
| Asthenia | 1 (1.3) | 0 | 9 (5.8) | 0 | 1 (5.6) | 0 | 10 (5.3) | 0 | 16 (4.5) | 0 |
| Migraine | 0 | 0 | 0 | 0 | 3 (16.7) | 2 (11.1) | 1 (0.5) | 1 (0.5) | 6 (1.7) | 4 (1.1) |
| Memory impairment | 0 | 0 | 3 (1.9) | 0 | 4 (22.2) | 0 | 3 (1.6) | 0 | 15 (4.2) | 0 |

[1]With at least 5% incidence in Study A2301 or asciminib Safety Pool or at least 15% incidence in Study X2101 (due to small sample size of 80 mg q.d. dose group).
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 23.1, CTCAE version 4.03.
Source: [SCS30du Appendix 3-Table 2-3]

Treatment-related AEs

In the study A2301, similar to the previous data presented, proportion of patients having treatment related AEs was lower in asciminib treatment group (66.0%) compared to bosutinib treatment group (89.5%). The most frequently reported AEs associated with asciminib therapy were thrombocytopenia (19.9%), neutropenia (15.4 %) and headache (9.0%). Adverse event that was reported more frequently in the asciminib group (with a ≥ 5% difference relative to the bosutinib group) was thrombocytopenia (+5.4%). The incidence of grade ≥ 3 treatment related AEs were 50.0% and 29.5% in the bosutinib and asciminib treatment groups respectively with thrombocytopenia and neutropenia being most frequent in asciminib treatment group and ALT increased, diarrhoea, neutropenia in bosutinib treatment group.

In the Study X2101 80 mg q.d., majority of the patients (88.9%; 16/18 patients) had treatment related AEs. The most frequently reported were fatigue and thrombocytopenia (each 27.8%; 5 patients). 4

patients (22.2%) had lipase increased. For comparison in the 40 mg b.i.d safety pool, lipase increased was reported in 9.1% of patients. Eleven patients (66.7%; 12/18 patients) had grade ≥ 3 AEs which were suspected to be study treatment related.

The frequently reported suspected AEs (all grades and grade ≥ 3) and their incidence in both the asciminib 40 mg b.i.d. Safety Pool and the asciminib All Patients Safety Pool were largely similar (difference of ≤ 10%) with those observed in the asciminib treatment group in Study A2301, except for lipase increased in asciminib All Patients Safety Pool (+10.8%).

Majority of the AEs reported in the asciminib and bosutinib groups (76.9% vs. 85.5%) occurred within the first 2 months of start of the treatment. The incidence rate of AEs decreased over time (post 8 weeks and up to 24 weeks) with the exception of incidence of haematological AEs that remained same, and higher incidence of ALT/AST increase and lipase increase in the bosutinib group.

ADRs

In the Study A2301, the most frequent ADRs occurring in asciminib treatment group with an incidence rate of ≥ 20% were thrombocytopenia (29.5%), neutropenia (23.1%), and upper respiratory tract infection (24.4%). The most frequent grade ≥ 3 ADRs, with an incidence rate of ≥ 5%, were thrombocytopenia (22.4%), neutropenia (18.6%), and hypertension (5.8%).

All patients in the Study X2101 (asciminib 80 mg q.d.) experienced at least one ADR and 13 patients experienced at least one grade ≥ 3 ADR. The most frequent ADRs (all grades) occurring in asciminib treatment group with an incidence rate of ≥ 20% were upper respiratory tract infection, musculoskeletal pain and fatigue (each 44.4%), thrombocytopenia and dyslipidemia (each 33.3%), headache, hypertension, abdominal pain and pancreatic enzyme increase (each 27.8%), neutropenia, anaemia, dizziness, nausea, diarrhoea, rash, arthralgia (each 22.2%).

As to the asciminib safety pools, the incidence of majority of the ADRs was similar to the ADRs observed in Study A2301, the ADRs with a higher incidence of ≥ 20% were musculoskeletal pain (36.2%), thrombocytopenia (27.5%), upper respiratory tract infection (28.1%), fatigue (25.8%), headache (23.6%) and pancreatic enzyme increase (21.3%).

Of note, in several categories the frequency of ARDs has shifted to a higher frequency category due to the fact that frequency in Asciminib All patients safety pool was higher than in the pivotal study (40 mg b.i,d treatment group).

AEs of special interest

The AESIs identified with asciminib treatment are: myelosuppression, pancreatic toxicity, hypersensitivity, hepatotoxicity, hepatitis B virus reactivation, reproductive toxicity, GI toxicity, phototoxicity, QTc prolongation, cardiac failure, edema and fluid retention, ischemic heart disease and CNS conditions, and haemorrhage.

The key categories of AESI with similar incidence between the asciminib group and the bosutinib group in Study A2301 were: myelosuppression (37.8% vs. 36.8%, with the exception of thrombocytopenia (part of the myelosuppression grouped AESIs; 29.5% vs. 19.7%), pancreatic toxicity (8.3% vs. 9.2%), and QTc prolongation (3.8% vs. 1.3%). Hypersensitivity related events (19.2% vs. 34.2%), and hepatotoxicity events (including laboratory terms) (9.0% vs. 31.6%) are less frequently reported in the asciminib group compared to the bosutinib group.

In Study X2101 80 mg q.d. dose group, myelosuppression, pancreatic toxicity, hypersensitivity, and QTc prolongation were reported in 44.4%, 27.8%, 38.9%, and 22.2% of patients, respectively.

*Myelosuppression*

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 Study A2301, the incidence of myelosuppression-related events was comparable in both treatment groups (37.8% vs. 36.8% in the asciminib and bosutinib groups respectively) with the exception of thrombocytopenia (part of the myelosuppression grouped AESIs; 29.5% vs. 19.7%). Events leading to treatment discontinuation were infrequent (3.8% vs. 5.3%). Thrombocytopenia was more frequently observed in the asciminib group (see above), but was generally manageable with dose adjustments/interruptions and required treatment discontinuations in only a small proportion of patients (3.2% vs. 1.3%).

Eight of 18 patients (44.4%) in the 80 mg q.d. group had myelosuppression-related events, with 3 patients having grade ≥ 3 events. The overall incidence of myelosuppression events in both asciminib Safety Pools was mostly consistent with that reported for the asciminib group in Study A2301.

Myelosuppression related events are generally reversible and manageable with appropriate monitoring, and dose interruption/modification.

The overall incidence of thrombocytopenia (all grades) was higher in the asciminib treatment group (28.8%) relative to the bosutinib treatment group (18.4%). The cumulative incidence of thrombocytopenia events was higher at week 8 (by 11.9%) and at Week 24 (by 9.8%) in the asciminib treatment group compared to the bosutinib treatment group. Thrombocytopenia events were suspected to be treatment related (per investigator determination) in 24.4% and 17.1% of patients in the asciminib and the bosutinib treatment groups, respectively.

Grade ≥ 3 events were reported in higher proportion of patients in the asciminib treatment group relative to the bosutinib treatment group (21.8% vs. 9.2%). The incidence of SAEs was low (1.3%) in the asciminib treatment group and none in the bosutinib treatment group. Five patients (3.2%) discontinued the study drug due to thrombocytopenia in the asciminib treatment group compared to 1 patient (1.3%) in the bosutinib treatment group. Dose interruptions were required in 18.6% in the asciminib and 9.2% in the bosutinib treatment group. Despite a higher frequency of thrombocytopenia in the asciminib group, the frequency of haemorrhage was relatively similar between asciminib and bosutinib (10.3% vs 9.2%). The EAIR for thrombocytopenia, was 37.1 per 100 PTY in the asciminib treatment group and 31.5 per 100 PTY in the bosutinib treatment group.

*Pancreatic toxicity*

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. In Study A2301, pancreatic toxicity AEs occurred in 8.3% of patients in the asciminib group and 9.2% in the bosutinib group. All pancreatic events were related to laboratory findings (lipase/amylase increases) with no co-existing clinical events. None of events were considered as serious.

In the asciminib 80 mg q.d. group, 1 patient had pancreatitis (suspected). Three patients (1.6%) in the 40 mg b.i.d. Safety Pool and 9 patients (2.5%) in the asciminib All Patients Safety Pool experienced clinical events of pancreatitis or acute pancreatitis (all suspected). Two patients discontinued study treatment (1 × pancreatitis and 1 × acute pancreatitis).

Overall, pancreatic toxicity events (including clinical events) were of low severity and were reversible; and were managed by dose reduction or interruptions.

Caution is nevertheless recommended in patients with previous history of pancreatitis and a warning has been included in section 4.4 of the SmPC.

*Hypersensitivity*

Hypersensitivity represents a known risk with approved TKIs. As hypersensitivity events can potentially be life-threatening, patients with known allergies to TKIs were excluded from Study A2301.

In Study A2301, hypersensitivity events (including skin reactions) were seen less frequently in the asciminib group (19.2% vs. 34.2% in the bosutinib group) and no patient discontinued treatment with asciminib due to hypersensitivity. In the asciminib 80 mg q.d. dose group, 7 patients had hypersensitivity events (all skin disorders). Within the asciminib All Patients Safety Pool, with the exception of 2 index cases (bronchospasm and hypersensitivity) in Study X2101, the majority of hypersensitivity events were skin disorders (primarily rash), that were either mild or moderate (grade 1/2) in nature, were transient, and were manageable.

*Hepatotoxicity*

In Study A2301 the incidence of hepatotoxicity events (including laboratory terms) was lower in the asciminib treatment group (8.3%) compared to the bosutinib treatment group (30.3%). No clinical events related to hepatotoxicity AESI were reported, only laboratory/enzyme elevations were noted. The incidence of the most frequently occurring events: ALT increase and AST increase were lower in the asciminib treatment group (each 3.8%) compared to bosutinib treatment group (27.6% and 21.1% respectively).

*Hepatitis B virus infection reactivation*

One patient in the asciminib All Patients Safety Pool, had hepatitis B virus infection reactivation. This patient was from the Study X2101, 120 mg q.d. dose cohort and had grade 1 event of viral hepatitis carrier, which was considered as a SAE.

*Reproductive toxicity*

Nonclinical studies provide evidence towards foetal malformation due to in-utero exposure to asciminib. Information regarding the human implications are not available due to limited exposure in this population.

In study A2301 three patients (1.9%) in the asciminib treatment group and 1 patient (1.3%) in the bosutinib treatment group had reproductive toxicity events. The reproductive toxicity events reported in the asciminib treatment group were spontaneous abortion and maternal exposure during pregnancy (both grade 3 and both occurring in the same patient), a congenital cardiovascular anomaly (1 patient) and maternal exposure during pregnancy (post confirmation of pregnancy, patient opted for an elective termination by mifepriston). These events therefore were not related to any inborn anomaly detected in a newborn of a patient treated with the study drugs.

*Gastrointestinal toxicity*

Overall, GI toxicity events occurred in a considerably lower proportion of patients in the asciminib treatment group (31.4%) compared to the bosutinib treatment group (78.9%).

There were no fatal GI toxicity events. Neither of the treatment groups had any grade 4 events. Grade ≥ 3 events were reported in 1.9% of patients in the asciminib treatment group and 11.8% of patients in the bosutinib treatment group. Serious AEs were noted in 2 patients (1 patient with non-cardiac chest pain and the second patient with vomiting and nausea) in the asciminib treatment group and 1 patient (vomiting) in the bosutinib treatment group. No patient discontinued in the asciminib treatment group compared to 2 patients (2.6%) in the bosutinib treatment group who discontinued study treatment due to GI toxicity events.

In Study X2101 (asciminib 80 mg q.d. dose group) eleven of 18 patients had events related to GI toxicity. Two patients had a grade 3 event and one SAE (vomiting).

*Ischemic heart and CNS conditions*

Cases of ischemic heart and CNS conditions were reported in 9 and 4 patients in the asciminib and bosutinib treatment groups, respectively. Of note, 3 patients in the asciminib treatment group had new events at the follow-up cut-off date 06-Jan-2021 as compared to previous cut-off date (25-May-2020) cerebral infarction (grade 3), myocardial infarction (grade 1) and CPK increase (grade 4).

Three patients in the asciminib treatment group (blood creatine phosphokinase increase, myocardial infraction and cerebral infarction) and 1 patient in the bosutinib treatment group (blood creatine phosphokinase increase) had events suspected to be in treatment related (per investigator's assessment).

One patient experienced a fatal ischemic stroke (which was not considered to be treatment related by the investigator, medical history included hypertension and left ventricular hypertrophy as per ECG) and leading to patient discontinuation.

Overall, 36 patients (10.1%) in asciminib all patients safety pool has ischemic heart and CNS condition events.

The observed incidence of ischemic heart and CNS condition events could be explained by the multiple confounding factors/underlying conditions in these patients and the role of asciminib in the development of these events is not possible to determine at this point.

An updated information on ischemic heart and CNS conditions, based on the updated Safety Pool with Week 96 cut-off date (06-Oct-2021) has been provided. Two additional events (i.e., Troponin increased, Vascular graft occlusion) were included in the updated Week 96 output and presented. Due to MedDRA version update, the PT "arterial bypass occlusion" was demoted to a LLT, and is linked to a PT "vascular graft occlusion". The patient presented is not a new patient with PT (narrative provided as part of X2101 primary analysis CSR) but this patient is now captured as part of the ischemic heart and CNS output due to a MedDRA version change from 23.1 to 24.1. The event of troponin increase was not related to asciminib by the investigator, there was no dose change and the patient recovered the same day.

Overall, the frequency of ischemic heart and CNS conditions was comparable in asciminib and bosutinib treatment group in the study A2301 (6.4% vs 5.3%; EIAR per 100PTY 3.8% vs 5.9%).


*Cardiac failure*

In the Study A2301 asciminib 40 mg b.i.d. dose, cardiac failure occurred in 1.3% (2 patients) and 1.3% (1 patients; grade 3) in the asciminib treatment group and the bosutinib treatment group, respectively, with no risk difference between groups. The cardiac events in the asciminib treatment group were cardiac failure and ejection fraction decrease (each occurring in 1 patient); both were of grade 3 severity and were considered as SAEs. Three of 18 patients in the Study X2101 (asciminib 80 mg q.d. dose group) had events related to cardiac failure with all 3 patients having grade ≥ 3 events. All were considered as SAEs and all required medication or therapy. As of updated data cut-off date 06-Jan-2021, one additional patient (congestive hepatopathy, ejection fraction decreased) had cardiac failure event in the asciminib All Patients Safety Pool (200 mg b.i.d.). 40 days after the last dose of asciminib (discontinuation due to COVID 19 pneumonia), the patient died due to pneumonia. The occurrence of heart failure reported in patients receiving asciminib was strongly confounded by predisposing classic cardiovascular risks.

*QTc prolongation*

In Study A2301, QTc prolongation related events were reported in 4 patients in the asciminib group and 1 patient in the bosutinib group. No grade 4 events were reported and none of the events led to study discontinuation. In the asciminib group, two cases of ECG QTc prolonged were reported as AEs; one of these patients experienced QTcF > 500 ms with > 60 ms increase – the event resolved with dose interruption and did not reoccur after asciminib was resumed at the reduced dose of 20 mg b.i.d.

At therapeutic doses, asciminib appears not to have a relevant effect on cardiac repolarization as the estimated mean and upper bound of the 90% CIs ΔQTcF at 40 mg b.i.d., 80 mg q.d., 200 mg b.i.d. and at the HCRE (which is the worst case scenario for Cmax at 200 mg b.i.d.) were below 10 ms, which is the threshold that is considered clinically significant.

The findings for the assessment of QT prolongation showed an asciminib dose dependent increase in the QT prolongation, although not clinically significant in the therapeutic doses. These QT prolongation findings are addressed in the current proposed SmPC and RMP.

*Cardiac arrhythmias*

The EAIR for cardiac arrhythmias was similar between patients in the bosutinib (EAIR = 4.7, 3 patients of 76) and the asciminib (EAIR = 5.1, 10 of 156 patients) 40 mg b.i.d. arms in Study A2301 as well as in the asciminib 40 mg b.i.d. (EAIR = 5.0, 15 of 187 patients) and asciminib All patients (EAIR = 6.8, 48 of 356 patients) Safety Pools.

In the Study A2301 asciminib 40 mg b.i.d arm, ten (6.4%) patients reported the following arrhythmia PTs: palpitations (four (2.6%) patients); electrocardiogram QT prolonged, syncope (two (1.3%) patients each); tachycardia, bradycardia, sinus bradycardia, arrhythmia, cardiac arrest, ventricular tachycardia, heart rate decreased (one (0.6%) patient each). The following additional arrhythmias were identified in the asciminib 40 mg b.i.d. and asciminib All patients Safety Pools only: Atrial fibrillation (two (1.1%) and seven (2.0%) patients, respectively); cardiac flutter, sinus tachycardia (one (0.5% and 0.3%, respectively) patient each). The following arrhythmias were identified in the asciminib All patients Safety Pool only: Bundle branch block right, extrasystoles, heart rate irregular, sinus arrhythmia, supraventricular tachycardia, tachyarrhythmia, ventricular extrasystoles (one (0.3%) patient each).

Treatment-related arrhythmias as assessed by the investigator occurred in four (2.6%) patients in the asciminib 40 mg b.i.d. arm of Study A2301, in six (3.2%) patients in the asciminib 40 mg b.i.d. patient Safety Pool, and in 13 (3.7%) patients in the asciminib All patients Safety Pool. Treatment-related arrhythmias which occurred in ≥2 patients in either of the groups were palpitations, atrial fibrillation, electrocardiogram QT prolonged, and tachycardia.

Grade 3 arrhythmias occurred as follows:

Two (1.3%) patients with the reported PTs of syncope and electrocardiogram QT prolonged (one (0.6%) patient each) from the asciminib 40 mg b.i.d. arm of Study A2301;

three (1.6%) patients with the reported PTs of atrial fibrillation, syncope, and electrocardiogram QT prolonged (one (0.5%) patient each) in the asciminib 40 mg b.i.d Safety Pool;

eleven (3.1%) patients with the reported PTs of atrial fibrillation (four (1.1%) patients); syncope (three (0.8%) patients); and arrythmia, electrocardiogram QT prolonged, extrasystoles, tachyarrhythmia, ventricular tachycardia (one (0.3%) patient each) in the asciminib All patients Safety Pool.

Grade 4 arrhythmias occurred in one (0.6%) patient with the reported PT of cardiac arrest originating from the 40 mg b.i.d. arm of Study A2301; the same patient was represented in the asciminib 40 mg b.i.d. (0.5%) and All patients (0.3%) Safety Pools.

Grade 5 arrhythmias occurred in one (0.3%) patient with the reported PT of cardiac arrest in the asciminib All patients Safety Pool and represented a patient from Study X2101.

Arrhythmias reported as SAEs occurred as follows: One (0.6%) patient with the reported PT of cardiac arrest originating from the 40 mg b.i.d. arm of Study A2301; two (1.1%) patients reported the PTs of atrial fibrillation and cardiac arrest (one (0.5%) patient each) from the asciminib 40 mg b.i.d. Safety Pool; seven (2.0%) patients reported the PTs atrial fibrillation (three (0.8%) patients), cardiac arrest (two (0.6%) patients), and arrhythmia and ventricular tachycardia (one (0.3%) patient each) in the asciminib All patients Safety Pool.

*Oedema and fluid retention*

Oedema and fluid retention adverse events were reported in 8.3% (13 patients) and 7.9% (6 patients) in the asciminib and bosutinib treatment groups, respectively, and most patients experienced grade 1 or 2 events.

Four of 18 patients in the Study X2101 (asciminib 80 mg q.d. dose group) had events related to oedema and fluid retention however none having grade $\geq$ 3 events.

The edema and fluid retention events in the asciminib 40 mg b.i.d. Safety Pool were consistent with those in the asciminib treatment group in Study A2301, whereas the incidence was higher (+6.9%) in the asciminib All Patients Safety Pool (15.2%), compared to the asciminib treatment group in Study A2301 (8.3%). As of updated data cut-off date 06-Jan-2021, two additional patients (pleural effusion (grade 3 and oedema peripheral (grade 2)) had oedema and fluid retention events in the asciminib All Patients Safety Pool.

Relevant events related to edema and fluid retention (oedema, including oedema peripheral, and pleural effusion) are already listed as ADRs of 'common' frequency in Section 4.8 of the proposed SmPC.

*Phototoxicity*

In the asciminib 40 mg b.i.d. Safety Pool, 2 patients (1.1%) and in the asciminib All Patients Safety Pool 12 patients (3.4%) had phototoxicity events. None of these events was of grade $\geq$ 3 severity and none was SAE. Events in the asciminib 40 mg b.i.d. Safety Pool were photosensitivity reaction and sunburn (each in 1 patient), of which photosensitivity reaction was suspected to be treatment related (by the investigator). The events in the asciminib All Patients Safety Pool were photosensitivity reaction (2.5%; 9 patients), sunburn (0.8%; 3 patients) and retinal phototoxicity (0.3%, 1 patient). Treatment-related AEs were noted in 6 patients (5 patients with photosensitivity and 1 retinal phototoxicity).

No new photosensitivity/phototoxicity findings were reported in the Week 96 cut-off data from Study A2301.

*Haemorrhage*

In the pivotal study, haemorrhage events occurred with relatively similar incidence (+2.3%) in patients in the asciminib and the bosutinib treatment groups, despite the fact that thrombocytopenia was much more frequently observed in asciminib treatment group. No pattern for a specific site of bleeding has been identified.

## 2.6.9. Serious adverse events, deaths, and other significant events

### 2.6.9.1. Serious adverse event/deaths/other significant events

Serious adverse events were reported in a lower proportion of patients in the asciminib treatment group (15.4%) compared to the bosutinib treatment group (23.7%). The incidence of SAEs (by PTs) suspected to be treatment related was also lower in the asciminib treatment group compared to the bosutinib arm. Overall, the number of individual SAEs in the pivotal study was too low to conclude on the trend. In

asciminib Safety Pool A (All Patients) pleural effusion and pneumonia were reported in 9 and 8 patients, respectively, and all cases of pneumonia were grade 3.

Overall, 5 deaths occurred in the pivotal study A2301, 4 in asciminib and 1 in bosutinib treatment group. On-treatment deaths were reported for 3 patients with a similar frequency between treatment groups: 2 patients (1.3%) in the asciminib treatment group (embolism arterial and ischaemic stroke) and 1 (1.3%) in the bosutinib treatment group (septic shock). Although, deaths in the asciminib group were not suspected to be study treatment-related, as discussed before, under ischemic heart and CNS conditions the role of asciminib in the development of these events is not possible to completely rule out at this point. Similarities to ponatinib may be discussed.

In Study X2101 asciminib 80 mg q.d. dose one on-treatment death has occurred due to cardiac arrest and wasn't either reported as treatment related, however, as commented above, whether or not there was a connection with the asciminib treatment is still considered uncertain.

Overall, 14 patients died in the asciminib All Patients Safety pool, including two patients who died due to COVID-19.

### 2.6.9.2. Laboratory findings

Haematological abnormalities, as was expected were very commonly experienced by the patients in all treatment groups. Most common AEs was thrombocytopenia in asciminib treatment groups and anaemia in bosutinib treatment group.

In Study A2301, the incidences of new or worsened grade 3 hematologic laboratory abnormalities were similar (difference < 5%) in both the treatment groups. Incidence of grade 4 were higher (difference > 5%) in the asciminib treatment group for platelets decrease (+6.5%) and neutrophils decrease (+6.1%) relative to the bosutinib treatment group.

Study X2101 asciminib 80 mg dose group: The most frequently ($\geq$ 40%) noted new or worsened hematologic laboratory abnormalities (all grades) were lymphocytes decrease (50%) and platelets decrease (44.4%).

All the post-baseline hematologic laboratory abnormalities in both the asciminib 40 mg b.i.d. Safety Pool and the asciminib All Patients Safety Pool were consistent with those in the asciminib treatment group in Study A2301, with the exception of lymphocytes decrease; 17.1% in the asciminib treatment group in Study A2301 and 38.6% in the asciminib All Patients Safety Pool.

**Table 28        New or worsened hematology abnormalities based on CTC grades – Safety set**

| | Study A2301 | | | | | | Study X2101 | | | Safety Pool | | | | | |
| | Bosutinib 500 mg q.d. N=76 | | | Asciminib 40 mg b.i.d. N=156 | | | Asciminib 80 mg q.d. (CP) N=18 | | | Asciminib 40 mg b.i.d. (CP) N=187 | | | Asciminib All Patients N=356 | | |
| | All grades n/m (%) | G 3 n/m (%) | G 4 n/m (%) | All grades n/m (%) | G 3 n/m (%) | G 4 n/m (%) | All grades n/m (%) | G 3 n/m (%) | G 4 n/m (%) | All grades n/m (%) | G 3 n/m (%) | G 4 n/m (%) | All grades n/m (%) | G 3 n/m (%) | G 4 n/m (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Platelet count decrease | 27/75 (36.0) | 5/74 (6.8) | 4/75 (5.3) | 67/153 (43.8) | 17/153 (11.1) | 18/153 (11.8) | 8/18 (44.4) | 0 | 2/18 (11.1) | 83/184 (45.1) | 18/183 (9.8) | 22/184 (12.0) | 150/353 (42.5) | 27/352 (7.7) | 40/353 (11.3) |
| Leukocyte count decrease | 18/76 (23.7) | 4/76 (5.3) | 0 | 66/153 (43.1) | 12/150 (8.0) | 1/153 (0.7) | 6/18 (33.3) | 1/18 (5.6) | 1/18 (5.6) | 82/184 (44.6) | 18/181 (9.9) | 1/184 (0.5) | 147/353 (41.6) | 28/348 (8.0) | 4/353 (1.1) |
| Neutrophil count decrease | 24/76 (31.6) | 9/74 (12.2) | 1/75 (1.3) | 58/150 (38.7) | 13/145 (9.0) | 11/148 (7.4) | 6/18 (33.3) | 1/17 (5.9) | 2/18 (11.1) | 71/181 (39.2) | 16/176 (9.1) | 15/179 (8.4) | 142/350 (40.6) | 28/339 (8.3) | 29/348 (8.3) |
| Hemoglobin decrease | 40/76 (52.6) | 4/76 (5.3) | 0 | 54/153 (35.3) | 3/151 (2.0) | 0 | 7/18 (38.9) | 0 | 0 | 67/184 (36.4) | 7/182 (3.8) | 0 | 143/353 (40.5) | 18/351 (5.1) | 0 |
| Lymphocyte count decrease | 25/76 (32.9) | 1/75 (1.3) | 0 | 26/152 (17.1) | 3/152 (2.0) | 0 | 9/18 (50.0) | 2/18 (11.1) | 0 | 48/183 (26.2) | 10/183 (5.5) | 1/183 (0.5) | 136/352 (38.6) | 23/347 (6.6) | 5/352 (1.4) |

m=Total = number of patients who had less than grade x at baseline and with at least one post-baseline value for the lab parameter.
n=number of patients who had less than grade x at baseline, and worsened to grade x post-baseline
Patients are counted only for the worst grade observed post-baseline.
'New' means 'grade 0' at baseline and 'grade ≥1' after baseline.
Baseline is defined as the last non-missing value prior to the first dose.
Grades based on CTCAE version 4.03.
Source: [SCS Appendix 1-Table 3.3-1]

New or worsened post-baseline clinical chemistry laboratory abnormalities occurred in similar proportions of patients in the two treatment groups, with only few notable differences. Most of these abnormalities were mild-to-moderate (grade 1 or 2) in both treatment group.

The most frequently ($\geq 40\%$) noted new or worsened post-baseline biochemical laboratory abnormalities (all grades) in patients receiving 80 mg q.d. dose were pancreatic lipase increase, phosphate decrease (each 55.6%), triglycerides increase (52.9%), and potassium increase (50.0%). Except for grade 3 phosphate decrease and grade 4 urate increase each (16.7%; n=3), new or worsened post-baseline biochemical laboratory abnormalities grade $\geq 3$ were only seen in either 1 or 2 patients.

The biochemical laboratory abnormalities which were noted with $\geq 10\%$ higher incidence in the asciminib All Patients Safety Pool compared to asciminib treatment group in Study A2301 were pancreatic lipase increase (+19%), potassium increase (+17.9%), phosphate decrease (+17.4%), ALT increase (+13.1%), albumin decrease (+12.6%) AST increase (+11.3%), calcium corrected decrease (+11.2%) and amylase increase (+11%). The longer exposure to asciminib treatment in Study X2101 than in Study A2301 is claimed to be the reason for these higher frequencies.

**Table 29      New or worsened biochemistry abnormalities based on CTC grades – Safety set**

| | Study A2301 | | | | | | Study X2101 | | | Safety Pool | | | | | |
| | Bosutinib 500 mg q.d. N=76 | | | Asciminib 40 mg b.i.d. N=156 | | | Asciminib 80 mg q.d. (CP) N=18 | | | Asciminib 40 mg b.i.d. (CP) N=187 | | | Asciminib All Patients N=356 | | |
| | All grades n/m (%) | G 3 n/m (%) | G 4 n/m (%) | All grades n (%) | G 3 n/m (%) | G 4 n/m (%) | All grades n (%) | G 3 n/m (%) | G 4 n/m (%) | All grades n (%) | G 3 n/m (%) | G 4 n/m (%) | All grades n (%) | G 3 n/m (%) | G 4 n/m (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Triglycerides increase | 21/76 (27.6) | 2/76 (2.6) | 0 | 65/156 (41.7) | 6/150 (4.0) | 2/156 (1.3) | 9/17 (52.9) | 2/16 (12.5) | 0 | 77/187 (41.2) | 7/181 (3.9) | 3/187 (1.6) | 147/354 (41.5) | 13/341 (3.8) | 4/354 (1.1) |
| Pancreatic lipase increase | 13/76 (17.1) | 4/76 (5.3) | 0 | 21/155 (13.5) | 5/155 (3.2) | 1/155 (0.6) | 10/18 (55.6) | 1/17 (5.9) | 1/18 (5.6) | 41/186 (22.0) | 13/186 (7.0) | 3/186 (1.6) | 115/354 (32.5) | 34/351 (9.7) | 9/354 (2.5) |
| Alanine aminotransferase increase | 38/76 (50.0) | 12/76 (15.8) | 0 | 29/155 (18.7) | 1/155 (0.6) | 0 | 7/18 (38.9) | 1/18 (5.6) | 0 | 42/186 (22.6) | 1/186 (0.5) | 0 | 113/355 (31.8) | 8/355 (2.3) | 0 |
| Phosphate decrease | 14/76 (18.4) | 4/76 (5.3) | 0 | 22/156 (14.1) | 9/156 (5.8) | 0 | 10/18 (55.6) | 3/18 (16.7) | 0 | 35/187 (18.7) | 13/186 (7.0) | 0 | 112/356 (31.5) | 24/354 (6.8) | 0 |
| Aspartate aminotransferase increase | 35/76 (46.1) | 5/76 (6.6) | 0 | 24/155 (15.5) | 1/155 (0.6) | 0 | 5/18 (27.8) | 0 | 0 | 33/186 (17.7) | 2/186 (1.1) | 0 | 95/355 (26.8) | 4/355 (1.1) | 1/355 (0.3) |
| Potassium increase | 4/76 (5.3) | 0 | 0 | 12/156 (7.7) | 0 | 0 | 9/18 (50.0) | 0 | 0 | 22/187 (11.8) | 0 | 1/187 (0.5) | 91/356 (25.6) | 3/356 (0.8) | 1/356 (0.3) |
| Urate increase | 12/76 (15.8) | 0 | 1/75 (1.3) | 29/156 (18.6) | 0 | 8/154 (5.2) | 5/18 (27.8) | 0 | 3/18 (16.7) | 37/187 (19.8) | 0 | 9/183 (4.9) | 90/356 (25.3) | 0 | 17/349 (4.9) |
| Calcium corrected decrease | 15/76 (19.7) | 0 | 0 | 22/156 (14.1) | 1/156 (0.6) | 0 | 7/18 (38.9) | 0 | 0 | 32/187 (17.1) | 1/187 (0.5) | 1/187 (0.5) | 90/356 (25.3) | 1/356 (0.3) | 1/356 (0.3) |
| Amylase increase | 10/76 (13.2) | 0 | 0 | 18/156 (11.5) | 1/156 (0.6) | 1/156 (0.6) | 4/18 (22.2) | 1/18 (5.6) | 0 | 31/187 (16.6) | 3/187 (1.6) | 2/187 (1.1) | 80/355 (22.5) | 12/355 (3.4) | 4/355 (1.1) |
| Creatinine increase | 18/76 (23.7) | 0 | 0 | 21/156 (13.5) | 0 | 0 | 3/18 (16.7) | 0 | 0 | 29/187 (15.5) | 0 | 0 | 68/356 (19.1) | 0 | 0 |

| | Study A2301 | | | | | | Study X2101 | | | Safety Pool | | | | | |
| | Bosutinib 500 mg q.d. N=76 | | | Asciminib 40 mg b.i.d. N=156 | | | Asciminib 80 mg q.d. (CP) N=18 | | | Asciminib 40 mg b.i.d. (CP) N=187 | | | Asciminib All Patients N=356 | | |
| | All grades n/m (%) | G 3 n/m (%) | G 4 n/m (%) | All grades n (%) | G 3 n/m (%) | G 4 n/m (%) | All grades n (%) | G 3 n/m (%) | G 4 n/m (%) | All grades n (%) | G 3 n/m (%) | G 4 n/m (%) | All grades n (%) | G 3 n/m (%) | G 4 n/m (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cholesterol increase | 4/76 (5.3) | 0 | 0 | 16/156 (10.3) | 0 | 0 | 6/17 (35.3) | 0 | 0 | 23/187 (12.3) | 0 | 0 | 64/354 (18.1) | 1/354 (0.3) | 0 |
| Alkaline phosphatase increase | 8/76 (10.5) | 0 | 0 | 20/156 (12.8) | 0 | 0 | 3/18 (16.7) | 0 | 0 | 27/187 (14.4) | 0 | 0 | 64/356 (18.0) | 0 | 0 |
| Bilirubin increase | 3/71 (4.2) | 0 | 0 | 16/145 (11.0) | 0 | 0 | 5/18 (27.8) | 0 | 0 | 22/176 (12.5) | 0 | 0 | 60/345 (17.4) | 1/345 (0.3) | 0 |
| Magnesium increase | 18/76 (23.7) | 0 | 0 | 23/156 (14.7) | 1/156 (0.6) | 0 | 4/18 (22.2) | 0 | 0 | 26/186 (14.0) | 1/186 (0.5) | 0 | 61/354 (17.2) | 5/354 (1.4) | 0 |
| Albumin decrease | 1/76 (1.3) | 0 | 0 | 1/156 (0.6) | 0 | 0 | 2/18 (11.1) | 0 | 0 | 10/187 (5.3) | 0 | 0 | 47/356 (13.2) | 2/356 (0.6) | 0 |
| Magnesium decrease | 0 | 0 | 0 | 5/156 (3.2) | 0 | 1/156 (0.6) | 4/18 (22.2) | 0 | 0 | 16/186 (8.6) | 0 | 2/186 (1.1) | 43/354 (12.1) | 0 | 2/354 (0.6) |
| Potassium decrease | 7/76 (9.2) | 0 | 0 | 16/156 (10.3) | 0 | 0 | 5/18 (27.8) | 1/18 (5.6) | 0 | 22/187 (11.8) | 0 | 0 | 41/356 (11.5) | 4/356 (1.1) | 0 |
| Sodium decrease | 1/76 (1.3) | 0 | 1/76 (1.3) | 6/156 (3.8) | 1/155 (0.6) | 0 | 4/18 (22.2) | 1/18 (5.6) | 0 | 7/169 (4.1) | 1/168 (0.6) | 0 | 33/298 (11.1) | 5/297 (1.7) | 1/298 (0.3) |
| Sodium increase | 8/76 (10.5) | 0 | 1/76 (1.3) | 7/156 (4.5) | 0 | 0 | 4/18 (22.2) | 0 | 0 | 10/169 (5.9) | 0 | 0 | 32/298 (10.7) | 0 | 1/298 (0.3) |
| Calcium corrected increase | 0 | 0 | 0 | 2/156 (1.3) | 0 | 0 | 1/18 (5.6) | 0 | 0 | 5/187 (2.7) | 0 | 0 | 15/356 (4.2) | 0 | 0 |

m=Total = number of patients who had less than grade x at baseline and with at least one post-baseline value for the lab parameter.
n=number of patients who had less than grade x at baseline, and worsened to grade x post-baseline
Patients are counted only for the worst grade observed post-baseline.
'New' means 'grade 0' at baseline and 'grade ≥1' after baseline.
Baseline is defined as the last non-missing value prior to the first dose.

Triglycerides increase was noted in >50% of patients in both the treatment groups (70.5% vs. 53.9% in the asciminib and bosutinib treatment group respectively).

Hyperglycaemia was more frequently reported as AEs in patients on asciminib (in 83.3% of patients vs. 68.4% in the bosutinib arm), However, after treatment initiation, worsening of glycated hemoglobin was observed with similar frequency in patients on bosutinib (5.8%) vs. asciminib (4.9%).

The majority of glucose concentration increases were grade 1/2 and did not result in HbA1c increase.

**Table 30 Worst post-baseline clinical chemistry abnormalities based on CTC grades (Safety set)**

| | Asciminib N = 156 | | Bosutinib N = 76 | |
|---|---|---|---|---|
| | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) |
| Glucose - increase | 130 (83.3) | 6 (3.8) | 52 (68.4) | 3 (3.9) |
| Triglycerides - increase | 110 (70.5) | 11 (7.1) | 41 (53.9) | 2 (2.6) |
| Alanine aminotransferase - increase | 46 (29.5) | 1 (0.6) | 42 (55.3) | 12 (15.8) |
| Creatine kinase – increase | 39 (25.0) | 3 (1.9) | 18 (23.7) | 4 (5.3) |
| Urate - increase | 38 (24.4) | 10 (6.4) | 19 (25.0) | 2 (2.6) |
| Aspartate aminotransferase - increase | 32 (20.5) | 1 (0.6) | 39 (51.3) | 5 (6.6) |
| Creatinine - increase | 29 (18.6) | 0 | 20 (26.3) | 0 |
| Magnesium - increase | 28 (17.9) | 1 (0.6) | 21 (27.6) | 0 |
| Alkaline phosphatase - increase | 22 (14.1) | 0 | 11 (14.5) | 0 |
| Amylase - increase | 22 (14.1) | 2 (1.3) | 13 (17.1) | 0 |
| Calcium corrected - decrease | 22 (14.1) | 1 (0.6) | 15 (19.7) | 0 |
| Phosphate - decrease | 22 (14.1) | 9 (5.8) | 15 (19.7) | 4 (5.3) |
| Lipase, pancreatic - increase | 21 (13.5) | 6 (3.8) | 13 (17.1) | 4 (5.3) |
| Glucose - decrease | 18 (11.5) | 0 | 8 (10.5) | 0 |
| Bilirubin - increase | 16 (10.3) | 0 | 6 (7.9) | 0 |
| Cholesterol - increase | 16 (10.3) | 0 | 6 (7.9) | 0 |
| Potassium - decrease | 16 (10.3) | 0 | 8 (10.5) | 0 |
| Potassium - increase | 13 (8.3) | 0 | 5 (6.6) | 0 |
| Sodium - increase | 8 (5.1) | 0 | 8 (10.5) | 1 (1.3) |
| Sodium - decrease | 7 (4.5) | 1 (0.6) | 1 (1.3) | 1 (1.3) |
| Magnesium - decrease | 5 (3.2) | 1 (0.6) | 0 | 0 |
| Calcium corrected - increase | 2 (1.3) | 0 | 0 | 0 |
| Albumin - decrease | 1 (0.6) | 0 | 1 (1.3) | 0 |

'All grades' represents patients with any grade 1, 2, 3 or 4 post-baseline.
Grades based on CTCAE version 4.03.
Source: Table 14.3-3.3

Increases in ALT or AST > 3×ULN were noted in lower numbers of patients in the asciminib treatment group (3.8%) compared to in the bosutinib treatment group (30.3%).

**Table 31          Hepatic laboratory values – Study A2301 (Safety set)**

| Peak post-baseline values | Bosutinib N=76 n (%) | Asciminib N=156 n (%) |
|---|---|---|
| ALT > 3 × ULN | 22 (28.9) | 6 (3.8) |
| ALT > 5 × ULN | 12 (15.8) | 1 (0.6) |
| ALT > 10 × ULN | 2 (2.6) | 1 (0.6) |
| AST > 3 × ULN | 11 (14.5) | 2 (1.3) |
| AST > 5 × ULN | 5 (6.6) | 1 (0.6) |
| ALT or AST > 3 × ULN | 23 (30.3) | 6 (3.8) |
| ALT or AST > 5 × ULN | 12 (15.8) | 1 (0.6) |
| ALT or AST > 8 × ULN | 4 (5.3) | 1 (0.6) |
| ALT or AST > 10 × ULN | 2 (2.6) | 1 (0.6) |
| ALT or AST > 20 × ULN | 0 | 0 |
| Total bilirubin (BILI) > 2 × ULN | 0 | 1 (0.6) |
| **Combined elevations post-baseline** | | |
| ALT or AST > 3 × ULN & BILI > 2 × ULN | 0 | 0 |
| ALT or AST > 3 × ULN & BILI > 2 × ULN & ALP ≥ 2 × ULN | 0 | 0 |
| ALT or AST > 3 × ULN & BILI > 2 × ULN & ALP < 2 × ULN | 0 | 0 |

Combined elevations based on the peak values at any post-baseline time for a patient.
Source: [Study A2301 Primary endpoint analysis-Table 14.3-3.5]

### 2.6.9.3. Safety in special populations

<u>Age</u>

**Table 32 Representation of elderly patient age groups in ascminib studies**

|  | Age 65-74 (Older subjects number /total number) | Age 75-84 (Older subjects number /total number) | Age 85+ (Older subjects number /total number) |
|---|---|---|---|
| Controlled Trials | 63 / 356 | 18 / 356 | 3 / 356 |
| Non Controlled trials | NA | NA | NA |

The number of patients ≥65 years of age in the pivotal Study A2301 (n=29) and the number of patients ≥75 years of age in the All patients Safety Pool (n=21) were low.

The proportion of patients having treatment related AEs in Study A2301 was higher (+18.6%) in 18 to < 65 years (66.9%) age category compared to ≥ 65 years (48.3%) age category. The proportion of patients having AEs requiring additional therapy was higher (+16.3%) in ≥ 65 years (79.3%) age category compared to 18 to < 65 years (63.0%) age category. The incidence of SAEs and AEs leading to discontinuation were higher (>10% difference) in the 65-74 year old age group compared to the <65 year old age group.

The incidence of majority of AEs in both the age subgroups in the asciminib arm were consistent (difference of < 10%). Largest differences were observed in the incidence of (cerebro)vascular disorders and accidents and injuries, as could be expected to increase with advanced age. No new, age specific safety risks were identified in the elderly population (65-74 vs. <65 years of age) treated with asciminib. Due to the low numbers, no meaningful conclusions could be drawn in the >75 year-old age categories.

<u>Gender</u>

The overall safety was similar for both genders in the asciminib and bosutinib treatment groups in Study A2301. However, in the asciminib treatment group higher incidence of AEs suspected to be treatment related was observed in females (74.7%) compared to males (53.1%) and higher incidence AEs requiring additional therapy was observed in females (74.7%) compared to males (58.0%); whereas for the AEs (grade ≥ 3) males (55.6%) had a higher frequency compared to females (45.3%). In the bosutinib treatment group, females had higher incidence of grade ≥ 3 treatment related AEs compared to males (55.6% vs. 41.9%).

<u>Race</u>

No clinically relevant differences were observed amongst ethnic sub-groups. However, due to small sub-group size the data should be interpreted with caution.

<u>Safety in patients with Ph+ CML-CP harbouring the T315I mutation</u>

Patients with a T315I "gatekeeper" mutation were excluded from the pivotal study as bosutinib has no inhibitory activity against this mutation. Protocol Amendment 9 of supportive study X2101 incorporated an expansion of Arm 1 to further assess asciminib as a single agent in patients with Ph+ CML-CP or -AP harbouring the T315I mutation.

Overall, 70 patients with CML-CP harboring the T315I mutation were treated with asciminib single agent across 10 dose levels (10 to 200 mg b.i.d. and 80 to 200 mg q.d.), and the median duration of exposure was 80.8 weeks (84.3% were exposed for at least 24 weeks).

In 48 patients treated with asciminib 200 mg b.i.d., which is the RDE for this population, the median duration of exposure was 69.8 weeks (83.3% were exposed for at least 24 weeks). Results summarized below represent data from 200 mg b.i.d. cohort.

All 48 patients (100%) had at least one AE during the study. Fatigue (29.2%), nausea (27.1%), diarrhoea and increased lipase (20.8% each) were the most frequent AEs. Grade ≥3 AEs were reported in 56.3% of patients. SAEs were reported in 10/48 (20.8%) patients, of whom 1/48 (2.1%) had a SAE that was suspected to be treatment related. SAEs were infrequent with no event reported in more than 2 patients. Study treatment discontinuation due to AEs was reported in 3/48 (6.3%) patients including 2/48 (4.2%) patients with AEs that were suspected to be treatment related. Pancytopenia and increased lipase (both treatment related) and thrombocytosis were the AEs that led to treatment discontinuation in one patient each.

Renal impairment

There is a limited safety data in patients with renal impairment and no patient with severe renal impairment was included in the asciminib studies. From the safety data of the pivotal (A2301) and supportive study (X2101) a worse safety profile for patients with moderate renal impairment compared to patients with normal renal function or mild renal impairment may be suggested. Grade ≥3 events, SAEs, and AEs leading to discontinuation were reported with higher frequencies. Due to the small sample size (n=10 in pivotal study and n=30 in Asciminib all safety pool) these results should be interpreted with caution.

The effect of renal impairment on the PK of asciminib is extensively discussed in PK section of this report, in particularly the comparability of asciminib 80 mg q.d. vs 40 mg b.i.d dose. The median predicted $AUC_{0-24}$ and $C_{max}$ for severely impaired patients are 60% and 40% higher than that of a typical individual with normal renal function, respectively, for either a dose of 80 mg q.d. or 40 mg b.i.d. The applicant concluded that this difference in median AUC or $C_{max}$ in subjects with normal and severe renal impairment is not considered to be clinically relevant given the relatively flat exposure-safety relationship over a 5-fold difference in exposure. Furthermore, glucuronidation amounts only up to 7% of the elimination. Based on this, inhibition of M30.5 formation due to renal impairment status is considered to be not clinically relevant. According to the applicant that no dose adjustment is needed for subjects with renal impairment, including severe renal impairment.

Hepatic impairment

The applicant recommends no dose adjustment based on results from a dedicated hepatic impairment study [Study A2103], considering results of this study showed no relevant impact of mild or moderate hepatic impairment on the PK of asciminib. Asciminib AUCinf was increased by 22%, 3% and 66% in subjects with mild, moderate and severe hepatic impairment, respectively, compared to subjects with normal hepatic function, following oral administration of a single 40 mg dose of asciminib.

Patients with mild hepatic impairment were included in the development program of asciminib. At the 06-Jan-2021 cut-off date, the data showed that the safety in patients with mild hepatic impairment was comparable to patients with normal hepatic function. When analysing AESIs, although most of the safety topics of interest were well balanced between the subgroups in both 40 mg b.i.d. Safety Pool and All patients Safety Pool, myelosuppression and Pancreatic toxicity-laboratory events were reported with >10% higher incidence in the mild hepatic impairment group compared to the group of patients with normal hepatic function. The relevance of this finding is hard to assess, considering the low number of patients with mild hepatic impairment at baseline (47 out of 345 patients in the All patients Safety Pool).

Reassuring is that no increase of hepatic toxicity clinical events was detected in patients with mild hepatic impairment, the events were with low frequency and were well balanced between the subgroups.

Furthermore, in clinical studies with asciminib the majority of the reported events were mild to moderate, reversible hepatic enzyme or bilirubin level abnormalities, with no evidence of irreversible liver damage with the use of asciminib monotherapy for treatment of CML-CP/AP. There was no case related to DILI (drug induced liver injury) and none of the reported events were fatal or life-threatening.

Paediatric population

No clinical study with asciminib has been completed in children so far. A PIP has been agreed for asciminib.

Pregnancy, birth, and lactation

Based on findings from animal studies and it's mechanism of action, asciminib can cause foetal harm when administered to a pregnant woman. The pregnancy status of females of reproductive potential should be verified prior to starting treatment with asciminib. Asciminib can be used during pregnancy only if the expected benefit to the patient justifies the potential risk to the foetus. However, sexually-active females of reproductive potential should use effective contraception during treatment with asciminib and for at least 3 days after the last dose. The risk for adverse effects to a developing embryo/foetus in female partner of male patients is negligible and male contraception use is not required.

It is not known whether asciminib is transferred into human milk after administration. There are no data on the effects of asciminib on the breastfed child or on milk production. Because of the potential for serious adverse drug reactions in the breastfed child, breastfeeding is not recommended during treatment and for at least 3 days after stopping treatment with asciminib.

### 2.6.9.4. Immunological events

In preclinical studies with asciminib no signs of immunotoxicity were seen. In Study A2301, exploratory biomarker analysis will use flow cytometry to characterize defined immune cell populations, including those implicated in immunomodulatory effects of other TKIs (bosutinib, imatinib, dasatinib). In order to provide an insight into immunomodulatory effects of asciminib, exploratory biomarkers will be analysed at study end and reported at the time of the final CSR. This is considered acceptable, and data awaited.

### 2.6.9.5. Safety related to drug-drug interactions and other interactions

*Food effect*

Food decreases the oral bioavailability of asciminib, therefore it needs to be taken in the fasted state. Food consumption should be avoided for at least 2 hours before and 1 hour after taking asciminib.

*Drug interactions*

Asciminib is a substrate of CYP3A4, UGT2B7 and UGT2B17, contributing with 36%, 13.3% and 7.8% to its clearance, respectively. It is estimated that the efflux transporter BCRP contributes to total systemic clearance by 31.1%.

Co-administration with the strong CYP3A4 inhibitor clarithromycin resulted in an asciminib AUC and Cmax increase of 36% and 19%. No dose adjustment is needed. Co-administration with the strong CYP3A4 inducer rifampicin resulted in an asciminib AUCinf decrease of 14.9%. Therefore, co-administration with strong CYP3A4 inducers should be used with caution at all recommended doses.

Asciminib is a low affinity substrate of P-gp. In a clinical DDI study with the strong P-gp inhibitor quinidine no exposure increase of asciminib was observed confirming that P-gp is of low importance for the disposition of asciminib. No dose adjustment is proposed.

Asciminib can be administered with acid reducing agents without dose adjustments.

Clinical DDI studies demonstrated that asciminib (40 mg b.i.d.) is a weak inhibitor of CYP3A4, CYP2C9 and no inhibitor of CYP2C8. Co-administration with substrates of CYP3A4 with a narrow therapeutic window should be used with caution at all recommended doses.

At asciminib 40 mg b.i.d./ 80 mg q.d., substrates of CYP2C9 with a narrow therapeutic index should be used with caution. If co-administration cannot be avoided, the CYP2C9 substrates dose should be reduced. If co-administration with warfarin cannot be avoided, the frequency of international normalized ratio (INR) monitoring should be increased as the anti-coagulant effect of warfarin may be enhanced.

Based on PBPK simulations asciminib was characterized to result in no clinical relevant inhibition of P-gp, BCRP and OATP1B1/OATP1B3 substrates (AUC increase < 25%). No dose adjustment is proposed when co-administering asciminib with P-gp, BCRP and OATP substrates.

### 2.6.9.6. Discontinuation due to adverse events

The frequency of AEs leading to study treatment discontinuation reported in the study A2301 was lower in the asciminib group compared to the bosutinib group. Overall, 11 patients discontinued treatment in the asciminib treatment group in the study A2301. Reasons for discontinuation were thrombocytopenia (3 patients), neutropenia /neutrophil count decreased, platelet count decreased, lipase increased, amylase increased, cerebral disorder, ejection fraction decreased and ischaemic stroke. In eight out of eleven patents, the AEs resolved upon discontinuation of asciminib. In two patients, in whom AEs leading to discontinuation were still ongoing did not accept survival follow-up) and in the third patient neutrophil count decreased was still ongoing. Of note, two patents died, one on-treatment (ischemic stroke) and one during survival follow-up (cerebral disorder).

### 2.6.9.7. Exposure- safety analyses

The applicant provided an exposure-safety analyses where exposure-safety relationship was explored using various safety endpoints such as laboratory and vital signs abnormalities and AEs. The exposure metrics were based on daily predictions of AUC, Cmax and Cmin from the population PK model and a 5-day-average prior to safety event. In all safety endpoints analysed (except Grade 2 or Higher AST increase), no significant relationship was found between probability of safety events and increase in exposure within the range of dose levels and regimens investigated.

### 2.6.9.8. Post marketing experience

Asciminib has been approved by FDA in 10/2021, but post marketing data are not yet available.

## 2.6.10.  Discussion on clinical safety

The safety evaluation of asciminib was primarily based on the data from the pivotal Phase III trial (Study A2301) in adults patients with Ph+ CML-CP previously treated with ≥ ATP-competitive TKIs. The supportive safety information was collected from the Phase 1 study X2101 in heavily pre-treated patients

with CML-CP/-AP. The population enrolled from these studies is considered to adequately represent the target population.

The safety data from the Study 2301 and Study X2101 has been pooled to enable evaluation of the impact of asciminib treatment at different doses and different treatment regimens. The pooling strategy is based on the similarity of the study populations (patients treated with at least two prior TKIs) in these studies. Furthermore, the consistency of the safety results between Study A2301 and the asciminib Safety Pool reinforces the safety profile of asciminib across different dose levels. In addition, the asciminib All patients Safety Pool enables an informed assessment of the safety profile of asciminib, judgment of the overall benefit-risk of the drug in the treatment of Ph+ CML-CP and a more robust safety evaluation based on a larger pool of patients with a longer duration of follow-up. Overall, this approach is considered acceptable. An updated ADR table for the section 4.8 of the SmPC has been submitted with the responses to the Day 180 List of Outstanding Issues . Since frequencies of adverse reactions at Week 96 cut-off for the Study A2301 were unchanged in comparison to Week 48, there was no change in AR frequencies in the updated Safety Pool.

This application was submitted with the interim results from an ongoing studies Study 2301 and Study X2101 with the data cut-off dates 25-May-2020 and 2-Apr-2020, respectively. Additionally, an updated data analysis, including longer follow-up data with a cut-off date of 06-Jan-2021, corresponding to approximately 7.5 months and 9 months additional follow-up for Study A2301 and Study X2101, respectively, has been provided. As a response to Day 120 List of Questions, an updated safety analysis of the pivotal Study A2301, at cut-off date 06-Oct-2021 and with 9 months additional follow-up was presented and discussed.

The Week 96 interim CSR for Study A2301 was submitted with the responses to the Day 180 List of Outstanding Issues.

The safety database is small (n=356 in the pool A, asciminib all patients safety pool). The applicant argues that, based on previous regulatory experience on TKIs the safety database in the target population could be considered overall large enough to allow the initial safety assessment. Furthermore, the applicant is planning to collect the additional safety data for asciminib, with relevant studies described in the RMP section. Overall, this approach is acceptable. The long-term safety data of the probably life-long treatment in the target population is, however, considered essential.

In Study A2301, demographic characteristics were well balanced between the asciminib and bosutinib treatment groups with the exception of gender and ethnicity. This is acknowledged and probably not avoidable in a late line population.

Regarding the prior antineoplastic therapy in the study A2301, the imbalances between the treatment arms were noted with respect to prior lines of TKI treatment, reasons of discontinuation of prior treatment and prior TKIs received, however, it is considered that these imbalances do not bias in favour of asciminib.

The median duration of exposure to asciminib in Study A2301 was 43.4 weeks (range 0.1 to 129) compared to 29.2 weeks (range:1.0-117.0) for bosutinib group at the data cut-off date 25-May-2020. With the longer follow-up at the data cut-off date 6-Jan-2021, the difference in the exposure to study treatment between asciminib and bosutinib treatment groups was further increased (67.1 weeks for asciminib arm compared to 29.7 weeks for bosutinib arm).

An updated safety analysis with a cut-off date of 06-Oct-2021 increased the median duration of exposure in Study A2301 to 23.7 months and to 26.6 moths in asciminib All patients Safety Pool.

There is a substantial difference in exposure between asciminib and bosutinib treatment groups. The median duration of exposure to study drug was approximately three times longer in the asciminib arm

(103.14 weeks; range: 0.1 to 201.1) compared to that in the bosutinib arm (30.50 weeks; range: 1.0 to 188.3). This is because more patients discontinued study medication in the bosutinib vs asciminib treatment group.

The per-protocol dose of asciminib in the study A2301 was 40 mg b.i.d. In case of toxicities, the dose of asciminib could be reduced to 20 mg b.i.d. Doses below 20 mg b.i.d. for asciminib were not allowed. At the data cut-off date of 06-Jan-2021, at least one dose reduction was reported for 39.1% of patients in on asciminib and in 23.1% of patients the reason was AE. In the section 4.2 of the SmPC the dose reductions to 50% of dose were proposed. However, considering the lack of significant and clinically relevant safety-exposure relationships, as discussed in the responses to the D120 LoQ this recommendation needed clarification. In the response to D180 LoOI, the applicant clarified the issue regarding dose modification. A dose reduction is not the recommended first step to manage ARs, therefore, the former table 1 in the SmPC has been removed to not cause misunderstanding regarding dose modifications steps to be followed, which is endorsed. Dose reduction is only a conservative measure to minimize the risk of AE recurrence when asciminib treatment was resumed after AE resolution. The former table 2 (now table 1 of the proposed SmPC) adequately reflects the proposed management of ARs and is considered appropriate.

In the asciminib treatment group, overall, 11 patients discontinued treatment due to AEs. Reasons for discontinuation were thrombocytopenia (3 patients), neutropenia /neutrophil count decreased, platelet count decreased, lipase increased, amylase increased, cerebral disorder, ejection fraction decreased and ischaemic stroke. In eight out of eleven patents, the AEs resolved upon discontinuation of asciminib.

Overall 91.0% of patients in the asciminib group experienced AEs compared to 97.4% in the bosutinib treatment group. Grade $\geq$ 3 AEs were lower in patients on asciminib (54.5%) as compared to bosutinib (67.1%). Furthermore, AEs suspected to be study treatment related, AEs requiring dose interruption, dose adjustments, and additional therapies were also reported less frequently in the asciminib treatment group compared to the bosutinib treatment group. Also the overall incidence of fatal SAEs was comparable between the groups. Considering the lower overall exposure in the bosutinib arm due to discontinuation, these findings seemed in line with claims for a more favourable safety profile of asciminib compared with bosutinib.

Due to the early discontinuation of a higher proportion of patients from the bosutinib group, EAIRs were calculated for AEs. Results indicated lower EAIRs in the asciminib group for overall AEs irrespective of relationship to study treatment and treatment-related AEs.

The EAIR for the asciminib 80 mg q.d. treatment group in the Study X2101 was significantly higher (AEs 1557.9; treatment related AEs 255.4) in comparison to other groups/safety pools. This would suggest a less favourable safety profile when compared to the 40 mg b.i.d dosing. Furthermore, since data for patients treated at higher then currently proposed doses (> 80 mg per day) is integrated in the all patients safety pool and therefore not discussed separately (except for the safety data in patients harbouring the T315I mutation, discussed below) the applicant additionally discussed the safety profile of the patients treated at higher daily doses. The extensive exposure analysis showed lack of association between higher doses/regimens of asciminib and occurrence of AEs (in particular TEAEs and SAEs).

To further assess the safety profile of asciminib given at 80 mg q.d. dose, the applicant has initiated a phase IIIb treatment optimisation study of 80 mg asciminib total daily dose in third-line CML-CP. This data should provide additional information regarding 80 mg q.d. dosing regimen, the regimen that is considered to represent more convenient alternative for the patients. Following the request by the CHMP, the applicant has removed the 80 mg q.d. posology throughout the proposed product information.

The most commonly reported AEs in the asciminib treatment group were related to myelosuppression, specifically thrombocytopenia and neutropenia. The frequency of neutropenia was relatively similar

between patients on asciminib (19.2%) and bosutinib (17.1%), however, the frequency of thrombocytopenia was higher in patients in the asciminib group (23.1% vs 14.5% in bosutinib group). Other commonly AEs reported in the asciminib treatment group were headache, fatigue, arthralgia, hypertension, nausea, diarrhoea and nasopharyngitis. Thrombocytopenia, neutropenia and hypertension were the most frequent grade ≥ 3 events in asciminib treatment group. This could be probably explained due to the more rapid action on the target in the haematopoietic cells and is in line with previous findings in 2G-TKIs pivotal trials were the first generation product imatinib was the comparator.

AEs related to thrombocytopenia were mostly reported within the first 6 months of therapy in both the treatment groups, although at a higher frequency in the asciminib group and treatment discontinuation due to thrombocytopenia AESIs was low: 3.2% in the asciminib group and 1.3% in the bosutinib group. Despite the higher frequency of thrombocytopenia events in patients on asciminib, the observation of haemorrhagic events was similar between both treatment groups (11.5% vs. 9.2%)

In general, the safety events observed for bosutinib are well known and the reported incidences of drug related TEAEs are overall considered in accordance with the known safety profile of this drug.

An increased mortality was reported in the asciminib arm in comparison to the bosutinib arm in the pivotal trial: overall, 5 deaths occurred, 4 in asciminib and 1 in bosutinib treatment group. On-treatment deaths were reported for 3 patients with similar frequencies in both treatment groups: 2 patients (1.3%) in the asciminib treatment group (embolism arterial and ischaemic stroke) and 1 (1.3%) in the bosutinib treatment group (septic shock).

In Study X2101 asciminib 80 mg q.d. dose one on-treatment death has occurred due to cardiac arrest, which might also have been the sequela of a thromboembolic event. Overall, 14 patients died in the asciminib All Patients Safety pool, including two patients who died due to COVID-19.The adverse events of special interest identified with asciminib treatment are: myelosuppression, pancreatic toxicity, hypersensitivity, hepatotoxicity, hepatitis B virus reactivation, reproductive toxicity, GI toxicity, phototoxicity, QTc prolongation, cardiac failure, oedema and fluid retention, ischemic heart disease and CNS conditions, and haemorrhage.

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 Study A2301, the incidence of myelosuppression-related events was comparable in both treatment groups (37.8% vs. 36.8% in the asciminib and bosutinib groups respectively) with the exception of thrombocytopenia (part of the myelosuppression grouped AESIs; 29.5% vs. 19.7%). Events leading to treatment discontinuation were infrequent (3.8% vs. 5.3%). Thrombocytopenia was more frequently observed in the asciminib group (see above), but was generally manageable with dose adjustments/interruptions and required treatment discontinuations in only a small proportion of patients (3.2% vs. 1.3%). A dose dependence of these AEs was discussed since in the 80 mg q.d. group the frequency of myelosuppression-related events increased (44.4% of the 18 patients), with 3 patients having grade ≥ 3 events. The overall incidence of myelosuppression events in both asciminib Safety Pools was mostly consistent with that reported for the asciminib group in Study A2301. However, in general it is acknowledged that myelosuppression related events are generally reversible and manageable with appropriate monitoring, and dose interruption/modification in TKI treatment of CML.

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 Study A2301, pancreatic toxicity AEs occurred in 8.3% of patients in the asciminib group and 9.2% in the bosutinib group. All pancreatic events were related to laboratory findings (lipase/amylase increases) with no co-existing clinical events. None of events were considered as serious. Two patients discontinued study

treatment (1 × pancreatitis and 1 × acute pancreatitis). Overall, pancreatic toxicity events (including clinical events) were of low severity and were reversible; and were managed by dose reduction or interruptions. Caution is nevertheless recommended in patients with previous history of pancreatitis.

Hypersensitivity events (including skin reactions) were seen less frequently in the asciminib group (19.2% vs. 34.2% in the bosutinib group) and no patient discontinued treatment with asciminib due to hypersensitivity. In the asciminib 80 mg q.d. dose group, 7 patients had hypersensitivity events (all skin disorders). Within the asciminib All Patients Safety Pool, with the exception of 2 index cases (bronchospasm and hypersensitivity) in Study X2101, the majority of hypersensitivity events were skin disorders (primarily rash), that were either mild or moderate (grade 1/2) in nature, were transient, and were manageable.

In Study A2301 the incidence of hepatotoxicity events (including laboratory terms) was lower in the asciminib treatment group (8.3%) compared to the bosutinib treatment group (30.3%). No clinical events related to hepatotoxicity AESI were reported, only laboratory/enzyme elevations were noted. The incidence of the most frequently occurring events: ALT increase and AST increase were lower in the asciminib treatment group (each 3.8%) compared to bosutinib treatment group (27.6% and 21.1% respectively). There was no evidence of irreversible liver damage with the use of asciminib monotherapy for treatment of CML-CP/AP.

The applicant presented a comprehensive analysis of arterial occlusive events (AOEs) and asciminib. As vascular adverse events (including AOCs) are known problem in patients with CML receiving TKIs (especially ponatinib) is the analysis and applicant's discussion on this issue considered very important in characterisation of the risk pertinent to asciminib treatment.

AOEs represent off-target relevant complications of TKIs. The AOEs observed with other TKIs used to treat CML are considered to result from the inhibition of one or more kinases, other than ABL1 and ABL2. Considering asciminib inhibits only the tyrosine kinase activity of ABL1, ABL2 and BCR::ABL1 by specifically targeting the ABL myristate binding pocket and hence does not engage the orthosteric ATP-binding site, it is unlikely that it would cause off-target kinase pharmacological effects resulting from the inhibition of protein kinases other than ABL1 and ABL2. Nilotinib and ponatinib interact with a considerable number of clinically relevant vascular targets implicated in endothelial cell survival and angiogenesis. Of note, ponatinib inhibits a large number of kinases, including VEGFR kinases that are strongly associated with causing AOEs. Nevertheless, the exact mechanisms associated with the onset of vascular occlusive events observed with ponatinib treatment, are still unknown.

Thorough assessment of AOE events in clinical trials A2301 and X2101 is much appreciated. It is reassuring that ischemic heart and central nervous system events, that could be considered important arterial occlusive events, have been reported with similar frequencies in the asciminib arm and the bosutinib arm of Study A2301 (Week 96 update 6.4% vs. 5.3%).

Grade 3 AOEs were reported in 0.6% of patients in the asciminib arm (cerebral infarction) and Grade 5 in 1.3% (ischaemic stroke and mesenteric artery thrombosis). Furthermore, in asciminib All patients pool there were 28 patients (7.9%) that experienced AOEs. Grade 3 AOEs were reported in 3.1% of patients, grade 4 in 0.3% and grade 5 in 0.6%. When indirectly compared, frequencies were substantially lower than in the pivotal study for registration of ponatinib.

In the Week 96 cut-off for study A2301, no additional AOE was reported in patients randomized to asciminib. Most patients who experienced AOEs with asciminib had baseline cardiovascular risk factors and unfavourable cardiovascular medical history along with the prior exposure to multiple other TKIs including nilotinib and/or ponatinib. The assessment of an association between the occurrence of AOEs with duration of exposure, cumulative dose, and daily dose intensity did not reveal a clear trend. This while in the 5-year analysis of the PACE study such a trend has been found for ponatinib.

There was one additional patient who experienced AOEs (mesenteric arterial occlusion and mesenteric artery thrombosis) in the week 96 cut-off for study A2301. This 52-year-old female patient was initially randomised to bosutinib, but switched to asciminib after meeting lack of efficacy criteria on bosutinib. The Investigator did not suspect a relationship between the events of mesenteric artery thrombosis and mesenteric artery occlusion and asciminib. However, a possible causal relationship between mesenteric arterial occlusion and the use of asciminib, from the assessors' point of view, could not be completely ruled out.

In an updated information on AOEs, based on the updated Safety Pool with Week 96 cut-off date, in comparison to the previous Week 48 cut-off date, one additional patient was reported to experience AOE in the asciminib All patients Safety Pool (Troponin increased – Grade 1; not related).

Nevertheless, currently available safety data has provided no evidence that asciminib increased the risk of occurrence of AOEs among patients who have prior history of cardiovascular events and therefore patients with a medical history of previous episodes of AOEs should only be carefully followed up in line with the standard care guidelines. In line with this, the applicant has proposed a general statement as conservative approach to be added to the "Hypertension" paragraph in the Warning and Precautions section of the SmPC, which is endorsed.

In Study A2301, QTc prolongation related events were reported in 4 patients in the asciminib group and 1 patient in the bosutinib group. No grade 4 events were reported and none of the events led to study discontinuation. In the asciminib group, two cases of ECG QTc prolonged were reported as AEs; one of these patients experienced QTcF > 500 ms with > 60 ms increase – the event resolved with dose interruption and did not re-occur after asciminib was resumed at the reduced dose of 20 mg b.i.d. In this context, it is reassuring that at therapeutic doses, asciminib appears not to have a relevant effect on cardiac repolarization. AEs related to QT prolongation were mostly confounded by other factors including concurrent medical conditions, and concomitant medications but the additive role of asciminib cannot be fully excluded. Appropriate warnings regarding QT prolongation and combination with drugs known to cause Torsade de Pointes have been included in the SmPC.

Cardiac failure occurred with similar frequencies (1.3%) in both treatment arms. The cardiac events in the asciminib treatment group were cardiac failure and ejection fraction decrease (each occurring in 1 patient); both were of grade 3 severity and were considered as SAEs. Ejection fraction decrease (1 patient) was the only event suspected to be treatment related in the asciminib treatment group and this patient discontinued the study due to this event. The occurrence of heart failure reported in patients receiving asciminib was confounded by predisposing classic cardiovascular risks. It is agreed that this does not support including heart failure as an adverse drug reaction in SmPC section 4.8.

Apart from QT prolongation and palpitations (already included in section 4.8), it is agreed that there is no reasonable evidence of a causal association of asciminib for one of the other single events of arrhythmia warranting inclusion as adverse drug reaction in the SmPC. PSURs will provide data from the post-marketing setting on the safety of asciminib.

Fluid retention (including cases of pleural effusion) have been reported in patients treated with asciminib. Relevant events related to oedema and fluid retention (oedema, including oedema peripheral, and pleural effusion) are already listed as ADRs of 'common' frequency in Section 4.8 of the proposed SmPC. Considering that most of the events were mild to moderate (grade < 3), reversible, resolving without dose interruption and modification, and that none of the patients discontinued the treatment due to fluid-retention relevant events, the existing evidence currently does not warrant the inclusion of fluid retention as a relevant warning in Section 4.4 of the proposed SmPC.

Treatment-related AEs were noted in 6 patients (5 patients with photosensitivity and 1 retinal phototoxicity) in asciminib All Patients Safety Pool. The applicant considers no specific precautions or

warnings in section 4.4 of the proposed SmPC regarding the risk of photosensitivity are needed based on available non-clinical and clinical data. The assessor is, however, of the opinion that data, obtained so far from the study X2101 where patients are exposed to the asciminib considerably longer than in the pivotal study, has showed asciminib potential to induce photosensitivity reactions in relevant number of patient. It is acknowledged that no events related to phototoxicity were reported in the pivotal Study A2301, however, this only reflects a limited number of patients enrolled. Of note, in the bosutinib arm of the pivotal study no photosensitivity reactions were reported although bosutinib is known to cause photosensitivity reactions with common frequency. It is also not clear whether the patients in the pivotal study were advised to avoid direct sunlight or ultraviolet (UV) radiation as this is precaution advised in order to minimise the risk of photosensitivity associated with bosutinib treatment. No mention of this could be found in the protocol of the study. The applicant presented updated data with responses to the Day 180 List of outstanding Issues regarding photosensitivity reactions. No new photosensitivity/phototoxicity findings were reported in the Week 96 cut-off data from Study A2301. The photosensitivity-/phototoxicity-related events will be monitored in the context of the periodic safety update report (PSUR) and SmPC is to be revised accordingly should there be an increased signal detected.

Haemorrhage events occurred with relatively similar incidence (+2.3%) in patients in the asciminib and the bosutinib treatment groups, despite the fact that thrombocytopenia was much more frequently observed in asciminib treatment group. No pattern for a specific site of bleeding has been identified.

With regard to other laboratory findings, worsened post-baseline clinical chemistry laboratory abnormalities occurred in similar proportions of patients in the two treatment groups, with only few notable differences. Most of these abnormalities were mild-to-moderate (grade 1 or 2) in both treatment group. Triglycerides increase was more pronounced in the asciminib arm (Asci: 70.5% vs. Bosu: 53.9% in the asciminib and bosutinib treatment group respectively).

Hyperglycaemia was more frequently reported as AEs in patients on asciminib. However, after treatment initiation, worsening of glycated haemoglobin was observed with similar frequency in patients on bosutinib (5.8%) vs. asciminib (4.9%). The majority of glucose concentration increases were grade 1/2 and did not result in HbA1c increase. This suggest that the higher frequency of increases in glucose in the asciminib arm were not sustained over time. This is acknowledged. Still, almost all patients experienced an incidental glucose increase, and it is considered valuable information for the treating physician that this might occur with asciminib treatment, therefore "Hyperglycaemia" as ARD is included in the section 4.8 of the SmPC, as requested.

The number of patients ≥65 years of age in the pivotal Study A2301 (n=29) and the number of patients ≥75 years of age in the All patients Safety Pool (n=21) were low. . The incidence of majority of AEs in both the age subgroups in the asciminib arm were consistent. Overall, no concerns are raised with regard to any differences in terms of age, gender or race. However, subgroup conclusions from such small population are in general less informative.

There is a limited safety data in patients with renal impairment, in fact, no patient with severe renal impairment was included in the asciminib studies. From the safety data of the pivotal (A2301) and supportive study (X2101) a worse safety profile for patients with moderate renal impairment compared to patients with normal renal function or mild renal impairment may be suggested although these results should be interpreted with caution due to a small sample size. The effect of renal impairment on the PK of asciminib is extensively discussed in PK section of this report, in particularly the comparability of asciminib 80 mg q.d. vs 40 mg b.i.d dose. Overall, it can be agreed with the applicant that no dose adjustment is needed for subjects with renal impairment, including severe renal impairment.

Furthermore, considering the results of the dedicated hepatic impairment study where no relevant impact of mild or moderate hepatic impairment on the PK of asciminib was shown, the applicant recommended

no dose adjustment in patents with hepatic impairment. In the development program of asciminib, only patients with mild hepatic impairment were included and the data showed that the safety in these patients was comparable to patients with normal hepatic function. When analysing AESIs, although most of the safety topics of interest were well balanced between the subgroups in both 40 mg b.i.d. Safety Pool and All patients Safety Pool, myelosuppression and pancreatic toxicity-laboratory events were reported with >10% higher incidence in the mild hepatic impairment group compared to the group of patients with normal hepatic function. The relevance of this finding is hard to assess, considering the low number of patients with mild hepatic impairment at baseline. Reassuring is that no increase of hepatic toxicity clinical events was detected in patients with mild hepatic impairment, the events were with low frequency and were well balanced between the subgroups. It is agreed with the applicant that no warning in patients with hepatic impairment towards the possible risk of developing fatal hepatic failure during asciminib therapy, nor dose adjustment in patents with hepatic impairment is currently warranted.

The proposed indication allows for treatment of patients harbouring the T315I mutation, however, the applicant did not intend to allow for treatment of Ph+ CML-CP patients harboring a T315I mutation who have received two or more TKIs. In total 48 patients harbouring the T315I mutation have been treated in supportive Study X2101 with asciminib 200 mg b.i.d., the recommended dose for this population. Grade ≥3 AEs (56.3%) and SAEs (20.8%) were reported in higher frequencies compared to the asciminib arm in the pivotal trial (50.6% and 13.5%, respectively). However, the number of T315I mutated patients is relatively limited and median exposure was substantially longer (69.8 weeks) compared to the pivotal trial (43.4). No new safety signals have emerged and study discontinuation due to AEs was in line with the pivotal trial (6.3%). Although hampered by indirect comparison, the safety profile seems favourable compared to the registered alternative in this setting, ponatinib.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

## 2.6.11. Conclusions on the clinical safety

From the safety outcome in the limited database available for the treatment with asciminib, it may be presumed that the safety risks associated with asciminib treatment are tolerable and indicate a manageable safety profile similar to that of other approved TKIs.

In addition, the updated safety data as provided with the response to Day 180 questions, suggests no new safety signals compared to the primary data cut-off. Furthermore, no association of AOEs with dose intensity, cumulative dose or duration of exposure of asciminib based on the currently available data has been shown.

The CHMP considers a number of category 3 PASS necessary to address issues related to long term safety. The studies are listed in the Pharmacovigilance plan.

## *2.7. Risk Management Plan*

## 2.7.1. Safety concerns

**Table 33        Part II SVIII.1: Summary of safety concerns**

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

## 2.7.2.  Pharmacovigilance plan

**Table 34        Part III.1: Ongoing and planned additional pharmacovigilance activities**

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization** | | | | |
| None | | | | |
| **Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances** | | | | |
| None | | | | |
| **Category 3 - Required additional pharmacovigilance activities** | | | | |
| **CABL001X2101**<br><br>A Phase I, multicenter, open-label study of oral ABL001 in patients with chronic myelogenous leukemia or Philadelphia Chromosome-positive acute lymphoblastic leukemia<br><br>Ongoing | To characterize a safe and tolerated dose of ABL001 in patients with Ph+ CML and Ph+ ALL patients who are relapsed or refractory to or intolerant of TKIs | Long-term safety, acute pancreatitis (including isolated pancreatic enzyme elevations), myelosuppression, QTc prolongation, hepatotoxicity | Final report submission | 30-Sep-2024 |
| **CABL001A2301**<br><br>A Phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with Chronic | To compare the efficacy of asciminib with that of bosutinib in the treatment of patients with CML-CP having previously been treated with a minimum of 2 prior ATP-binding site | Long-term safety, acute pancreatitis (including isolated pancreatic enzyme elevations), myelosuppression, QTc prolongation, hepatotoxicity | Final report submission | 31-Jul-2025 |

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

## 2.7.3. Risk minimisation measures

**Table 35    Summary of pharmacovigilance activities and risk minimization activities by safety concerns**

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| **Important identified risks** | | |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| Acute pancreatitis (including isolated pancreatic enzyme elevations) | **Routine risk minimization measures**<br><br>SmPC Section 4.2 where posology and method of administration are described.<br><br>SmPC Section 4.4 where description of the risk along with monitoring and treatment guidance are added.<br><br>SmPC Section 4.8 where the adverse reactions related to acute pancreatitis (including isolated pancreatic enzyme elevations) are listed.<br><br>PL Section 2 where precautions, monitoring and treatment are described.<br><br>PL Section 4 where possible side effects of asciminib are described.<br><br>Legal status: Medical prescription only product<br><br>**Additional risk minimization measures**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**<br><br>None<br><br>**Additional pharmacovigilance activities**<br><br>Evaluation of data from studies CABL001X2101 (Final report submission: 30-Sep-2024),<br><br>CABL001A2301 (Final report submission: 31-Jul-2025),<br><br>CABL001A2302 (Final report submission: 11-Mar-2027), and CABL001A2001B (Final report submission: 31-Dec-2028) |
| Myelosuppression | **Routine risk minimization measures**<br><br>SmPC Section 4.2 where posology and method of administration are described.<br><br>SmPC Section 4.4 where description of the risk along with monitoring and treatment guidance are added.<br><br>SmPC Section 4.8 where the adverse reactions related to myelosuppression are listed.<br><br>PL Section 2 where precautions, monitoring and treatment are described.<br><br>PL Section 4 where possible side effects of asciminib are described.<br><br>Legal status: Medical prescription only product<br><br>**Additional risk minimization measures** | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**<br><br>None<br><br>**Additional pharmacovigilance activities**<br><br>Evaluation of data from studies CABL001X2101 (Final report submission: 30-Sep-2024),<br><br>CABL001A2301 (Final report submission: 31-Jul-2025),<br><br>CABL001A2302 (Final report submission: 11-Mar-2027), and<br><br>CABL001A2001B (Final report submission: 31-Dec-2028) |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | None | |
| QTc prolongation | **Routine risk minimization measures**<br><br>SmPC Section 4.2 where posology and method of administration are described.<br><br>SmPC Section 4.4 where description of the risk along with monitoring and treatment guidance are added.<br><br>SmPC Section 4.5 where precaution while administrating asciminib with medicinal products with known risk of torsades de pointes is added.<br><br>SmPC Section 4.8 where adverse reactions related to QTc prolongation are listed.<br><br>SmPC Section 5.1 where effect of asciminib in cardiac electrophysiology is described.<br><br>PL Section 2 where precautions, monitoring and treatment are described.<br><br>PL Section 4 where possible side effects of asciminib are described.<br><br>Legal status: Medical prescription only product<br><br>**Additional risk minimization measures**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**<br><br>None<br><br>**Additional pharmacovigilance activities**<br><br>Evaluation of data from studies CABL001X2101 (Final report submission: 30-Sep-2024),<br><br>CABL001A2301 (Final report submission: 31-Jul-2025),<br><br>CABL001A2302 (Final report submission: 11-Mar-2027), and<br><br>CABL001A2001B (Final report submission: 31-Dec-2028) |
| **Important potential risks** | | |
| Hepatotoxicity | **Routine risk minimization measures**<br><br>SmPC Section 4.2 where posology and method of administration are described.<br><br>SmPC Section 4.8 where the adverse reactions related to hepatotoxicity are listed.<br><br>SmPC Section 5.2 where PK of asciminib in patients with hepatic impairment is described. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**<br><br>None<br><br>**Additional pharmacovigilance activities**<br><br>Evaluation of data from studies CABL001X2101 (Final report submission: 30-Sep-2024),<br><br>CABL001A2301 (Final report submission: 31-Jul-2025), |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | PL Section 4 where possible side effects of asciminib are described.<br><br>Legal status: Medical prescription only product<br><br>**Additional risk minimization measures**<br>None | CABL001A2302 (Final report submission: 11-Mar-2027), and<br><br>CABL001A2001B (Final report submission: 31-Dec-2028) |
| Hepatitis B virus infection reactivation | **Routine risk minimization measures**<br>SmPC Section 4.4 where description of the risk along with monitoring and treatment guidance are added.<br><br>PL Section 2 where precautions, monitoring and treatment are described.<br><br>Legal status: Medical prescription only product<br><br>**Additional risk minimization measures**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**<br>None<br><br>**Additional pharmacovigilance activities**<br>Evaluation of data from studies<br>CABL001A2302 (Final report submission: 11-Mar-2027), and<br><br>CABL001A2001B (Final report submission: 31-Dec-2028) |
| Reproductive toxicity | **Routine risk minimization measures**<br>SmPC Section 4.6 where effects of asciminib in fertility, pregnancy and lactation are described.<br><br>PL Section 2 where precautions, monitoring and treatment are described.<br><br>Legal status: Medical prescription only product<br><br>**Additional risk minimization measures**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**<br>Follow-up using a targeted checklist.<br><br>**Additional pharmacovigilance activities**<br>None |
| **Missing information** | | |
| Long-term safety | **Routine risk minimization measures**<br>SmPC: None<br><br>PL: None<br><br>**Additional risk minimization measures** | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**<br><br>None |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | None | **Additional pharmacovigilance activities**<br><br>Evaluation of data from studies CABL001X2101 (Final report submission: 30-Sep-2024),<br><br>CABL001A2301 (Final report submission: 31-Jul-2025),<br><br>CABL001A2302 (Final report submission: 11-Mar-2027), and<br><br>CABL001A2001B (Final report submission: 31-Dec-2028 |
| Use in patients with renal impairment | **Routine risk minimization measures**<br><br>SmPC Section 4.2 where posology and method of administration are described.<br><br>SmPC Section 5.2 where PK of asciminib in patients with renal impairment is described.<br><br>**Additional risk minimization measures**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**<br><br>None<br><br>**Additional pharmacovigilance activities**<br><br>Evaluation of data from study<br><br>CABL001A2302 (Final report submission: 11-Mar-2027) |
| Use in patients with hepatic impairment | **Routine risk minimization measures**<br><br>SmPC Section 4.2 where posology and method of administration are described.<br><br>SmPC Section 5.2 where PK of asciminib in patients with hepatic impairment is described.<br><br>**Additional risk minimization measures**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**<br><br>None<br><br>**Additional pharmacovigilance activities**<br><br>Evaluation of data from study<br><br>CABL001A2302 (Final report submission: 11-Mar-2027) |

## 2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable.

## 2.8. Pharmacovigilance

### 2.8.1. Pharmacovigilance system

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

## 2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 29.10.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

## *2.9. Product information*

## 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

# 3. Benefit-Risk Balance

## 3.1. Therapeutic Context

### 3.1.1. Disease or condition

Scemblix is indicated 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 (see section 5.1)

### 3.1.2. Available therapies and unmet medical need

Since the approval of imatinib in 2001, the 10 year survival rates for patients with CML have improved from approximately 20% to around 80-90%, and targeted therapy with TKIs has become the gold standard of treatment (Jabbour and Kantarjian 2018). There are four TKIs approved for the treatment of newly diagnosed CML (imatinib, nilotinib, dasatinib, bosutinib), with imatinib being the most commonly used in clinical practice in CML-CP patients (Apperley 2015, Banegas et al 2019, and Hochhaus et al 2020).

For patients with CML-CP who experience treatment failure (intolerance or resistance) to previous TKI therapy, the therapeutic options are limited. Treatment selection is further complicated by consideration of the patients' comorbidities, age, emergence of mutations, and the safety profile of each particular TKI (Hochhaus et al 2017, Hochhaus et al 2020, NCCN 2020).

After treatment failure on a 2G-TKI, ponatinib, a 3G-TKI, is an option. However, clinical guidelines do not recommend its use in patients with existing cardiovascular risk factors because cardiovascular toxicity can occur in about 30% of patients (Cortes et al 2018, Hochhaus et al 2020, NCCN 2020).

Despite available therapies for CML have greatly broadened treatment choices and improved patient outcomes, there remain challenges in the management of CML. The choice and sequencing of TKIs remains controversial with the complexity of safety and tolerability considerations in the context of a long-term therapy (Mauro et al 2013, Cortes and Kantarjian 2016). Especially patients treated in the third and further lines of therapy represent a population with a high unmet need requiring therapies with potent anti-leukemic activity to control the disease and with a well-tolerated safety profile.

The current European Treatment guidelines (Hochhaus et al, 2020) summarises the current situation and concludes for the treatment beyond the second line:

*"The definition of an acceptable response to third, fourth or fifth line treatment cannot be formalised, but a BCR-ABL1 transcript level >1% or a cytogenetic response less than complete (Ph+ >0%) are insufficient for optimal survival. There are no comparative studies and the choice of TKI should be guided by the sensitivity profile of specific BCR-ABL1 KD-mutations if possible, and, in particular T315I where only ponatinib is efficacious. Suboptimal responses to two or more TKIs should lead to prompt consideration of an allogeneic stem cell transplantation (allo-SCT)."*

Insofar, an efficacious inhibitor that targets the myristoyl pocket of BCR-ABL1, in contrast to the currently available TKIs that target the BCR-ABL1 ATP binding site and does not interact with the ATP-binding site may be beneficial. It offers the chance for activity against cells expressing clinically observed ATP-binding TKI resistant mutations. However, whether inhibition of the new binding site is also associated with an improved safety and tolerability when administered as monotherapy compared to TKIs binding to the

ATP-binding site of BCR-ABL1 remains open, since inhibition of a new binding site may also lead to different toxicities in humans.

Asciminib in principle may thereby fulfil a medical need in the treatment of CML, particularly in the situation of post 2G-TKI treatment failure as currently applied.

Patients with T315I mutated BCR-ABL1 are a separate, multi-drug resistant population for which up to now only ponatinib has shown efficacy and is specifically and separately approved.

### 3.1.3. Main clinical studies

Efficacy claim for the applied indication "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" is based on the results of the primary analysis of the pivotal Phase III study Study A2301 (data cut-off date of 25-May-2020/06-Oct 2021). This trial is an ongoing, randomized, open-label, active-controlled (bosutinib), multi-center Phase III study to compare the efficacy and safety of asciminib with that of bosutinib in patients with CML-CP, previously treated with at least 2 prior TKIs. A total of 233 patients were randomized in a 2:1 ratio to receive either asciminib 40 mg b.i.d. (n=157) or bosutinib 500 mg q.d. (n=76), stratified by the patient's cytogenetic response status at baseline.

Supportive evidence from Phase I Study X2101 is available. Cut-off date is 02-Apr-2020. This trial is an ongoing Phase I, first-in-patients, multicenter, open-label, dose escalation study intended to define the maximum tolerated dose and/or recommended dose for further clinical evaluation (MTD/RDEs-approach). Primary objective in this trial was to characterize safety and tolerability and to assess the pharmacokinetic (PK) profile as well as dose-finding for the pivotal trial by analysing the preliminary evidence of efficacy. Asciminib was studied given as single agent or in combination with either nilotinib or imatinib or dasatinib in patients with CML or Ph+ acute lymphoblastic leukemia (ALL)[ 5 arm-trial].

### *3.2. Favourable effects*

In the pivotal Study A2301, superiority with regard to the primary endpoint "MMR rate at week 24" against the comparator bosutinib was shown (25.5% versus 13.2%, respectively; treatment difference: 12.2%; 95% CI: 2.2, 22.3; p = 0.029) (Cochran-Mantel-Haenszel chi-square test, stratified by MCyR status at baseline, two-sided). At the new cut-off (6-Oct 2021), clinical superiority versus bosutinib increased compared to the primary analysis, as reflected by a more than 2-fold improvement in MMR rate compared to bosutinib at Week 96; 37.6.% (95% CI: 29.99, 45.65) in the asciminib arm compared to 15.8 % (95% CI: 8.43, 25.96) in the bosutinib arm, corresponding to a common treatment difference of 21.7%; 95% CI: 10.5, 33.0; p = 0.001 (after adjusting for baseline MCyR status).

The Kaplan-Meier (KM) estimated proportion of patients maintaining MMR for at least 72 weeks was 96.7% (95% CI: 87.4, 99.2) in the asciminib arm and 92.9% (95% CI: 59.1, 99.0) in the bosutinib arm.

The CCyR rate (based on patients who were not in CCyR at baseline) by Week 24 was 40.8% in the asciminib arm compared to 24.2% in the bosutinib arm. The CCyR rate by Week 48 was 45.6% in the asci arm compared to 35.5% in the bosutinib arm and 39.8% in the asciminib arm and 16.1% in the bosutinib arm at Week 96.

In ASCEMBL, 12.7% of patients treated with asciminib and 13.2% of patients receiving bosutinib had one or more BCR::ABL1 mutations detected at baseline. MMR at 24 weeks was observed in 35.3% and 24.8% of patients receiving asciminib with or without any BCR::ABL1 mutation at baseline, respectively. MMR at 24 weeks was observed in 25% and 11.1% of patients receiving bosutinib with or without any mutation at baseline, respectively. The MMR rate at 24 weeks in patients in whom the randomised

treatment represented the third, fourth, or fifth or more line of TKI was 29.3%, 25%, and 16.1% in patients treated with asciminib and 20%, 13.8%, and 0% in patients receiving bosutinib, respectively.

## 3.3. Uncertainties and limitations about favourable effects

The clinical relevance of a more rapid or even deeper molecular response remains uncertain as it is not sufficiently linked to better overall survival. Considering the known slower velocity of response for bosutinib at the time the trial was planned, the early comparison of MMR at week 24 (PEP) favours significantly asciminib. Therefore MMR rate at 96 weeks and CCyR rate at 24 and 96 weeks are also considered supportive and included in the effects table and the SmPC.

Uncertainty remains also regarding the characterisation of impact of mutations on asciminib response and clonal evolution during treatment therefore the submission of biomarker results of study A2301, included in final biomarker report of final CSR is recommended.

## 3.4. Unfavourable effects

The safety profile of asciminib in treatment of adult patients with Ph+ CML in chronic phase previously treated with two or more tyrosine kinase inhibitors, is based mainly on short-term data from a comparative phase 3 study against the approved comparator bosutinib. Supportive Phase 1 safety data in a more heterogeneous study population is also available.

The incidence of AEs in all categories was lower in the asciminib treatment group compared to the bosutinib treatment group, with the exception of fatal SAEs, where no difference was apparent (crude frequencies: 1.3 % vs 1.3%, respectively, EAIR calculation was not provided).

Some AEs occurred more frequently in the asciminib treatment group (e.g., thrombocytopenia, arthralgia, hypertension, nasopharyngitis), others occurred more frequently in the bosutinib group (e.g. nausea, diarrhoea, vomiting, abdominal pain, rash, AST increase) and e.g. neutropenia and anaemia were reported equally in the both groups.

Thrombocytopenia (23.1%), neutropenia (19.2%), headache (18.6%), fatigue (13.5%). arthralgia (12.2%), hypertension (12.2%), diarrhoea (11.5%), nausea (11.5%), and nasopharyngitis (10.9%) were the AEs (all grades, regardless of study treatment relationship) that occurred most frequently ($\geq$ 10%) in the asciminib treatment group in the Study A2301. The frequency of thrombocytopenia was higher in patients in the asciminib group (23.1% vs 14.5% in bosutinib group) and three patients (out of in total 11) discontinued treatment with asciminib due to thrombocytopenia.

Overall mortality was increased in asciminib treated patients; 5 deaths occurred in the pivotal study A2301, 4 in asciminib and 1 in bosutinib treatment group. On-treatment deaths were reported for 3 patients with a similar frequency between treatment groups: 2 patients (1.3%) in the asciminib treatment group (embolism arterial and ischaemic stroke) and 1 (1.3%) in the bosutinib treatment group (septic shock). In Study X2101 asciminib 80 mg q.d. dose one on-treatment death has occurred due to cardiac arrest which is reported as not treatment related. However, in four out of 18 subjects exposed with this once daily 80 mg dose regime potential arterial occlusive events were reported.

Adverse events of special interest (AESIs) include myelosuppression, pancreatic toxicity, hypersensitivity, hepatotoxicity, hepatitis B virus reactivation, reproductive toxicity, GI toxicity, phototoxicity, QTc prolongation, cardiac failure, edema and fluid retention, ischemic heart disease and CNS conditions, and haemorrhage.

## 3.5. Uncertainties and limitations about unfavourable effects

Although the applicant in general presumed an improved safety profile and tolerability of Scemblix over bosutinib, the evidence for the correctness of this assumption is based on outcome after exposure in the small number of 356 patients with a limited follow up. Thus, the assessment of infrequent adverse events and interpretation of differences in the observed adverse event profiles remains uncertain as in other orphan drugs. Myelosuppression, pancreatic toxicity, QTc prolongation are identified as important identified risk and hepatotoxicity, hepatitis B virus reactivation, reproductive toxicity as important potential risk in the RMP. Long-term safety and use in in patients with renal and hepatic impairment are considered missing information. Several category 3 PASS studies are imposed to address long term safety and important identified risks.

Due to the new mode of action different class adverse events may occur beside those well known. For example, treatment with ponatinib, a drug also with a different target in BCR-ABL1, is associated with a risk for thromboembolic/ arterial occlusive events up to 30 %, which was detected first after approval. Current available safety data do not indicate an increased risk for arterial occlusive events (AOE) with asciminib treatment. The updated safety data suggests no new safety signals compared to the primary data cut-off. Furthermore, no association of AOEs with dose intensity, cumulative dose or duration of exposure of asciminib based on the currently available data has been shown. Nevertheless, AOE will be closely monitored and registered in upcoming PSURs.

Patient Related Outcome results suggest improvement in disease-related symptoms, health-related quality of life, work productivity and activity impairment with asciminib treatment. Although interpretation of PRO outcomes is hampered by the open-label design, the overall impact of the safety profile on quality of life seems limited.

CYP3A4 appeared to be the major contributor to Phase I metabolism (35.1% of total metabolic clearance). Moreover, according to the results of in vitro studies, asciminib has the potential to inhibit metabolic enzymes revealed Ki values in low micromolar range for CYP3A4/5, CYP2B6, CYP2C8, CYP2C9 and UGT1A1 as well BCRP, P-gp, MATE2-K, OAT3, and OCT1. In addition, it needs to be considered that a significant food effect was described, which demands that the drug has to be taken twice daily in fasting state. Although these consequences are adequately described in the product information, a lot of potential interactions and administration errors may occur and could affect the outcome in clinical practise. Therefore, submission of relevant studies is recommended.

## 3.6. Effects Table

**Table 36      Effects Table for Scemblix in the applied indication "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" (data cut-off: 6 Oct 2021).**

| Effect | Short Description | Unit | Asciminib | Bosutinib | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| Major molecular response (MMR) rate at 24 weeks | MMR rate at 24 weeks | % | 25.5 | 13.2 | Short time outcome, less discriminative regarding long term outcome, indicates velocity of response | (1) |

| Effect | Short Description | Unit | Asciminib | Bosutinib | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **MMR rate at 96 weeks** | **MMR rate at 96 weeks** | **%** | **N=59/157 (37.58%)** | **N=12/76 (15.79%)** | **Important to indicate sustainability of response and long term efficacy** | (1) |
| **Duration of MMR (at week 24)** | **% of pat. maint. MMR for at least 24** | **KM estimated** | **95.4% (95% CI: 82.8, 98.8)** | **100.0% (95% CI: NE, NE)** | Important to indicate sustainability of response and long term efficacy | (1) |
| **(at week 72)** | **% of pat. maint. MMR for at least 24** | **KM estimated** | **96.7% (95% CI: 87.4, 99.2)** | **92.9% (95% CI: 59.1, 99.0)** | Data more mature | D180 Response |
| Complete Cytogenetic Response-rate (at week 24) | CCyR-rate at week 24 | % | 40.8 (95% CI 31.20-50.90) | 24.2 (95% CI 14.22, 36,74) | Data not mature due to short follow-up, consequence of MMR inhibition, confirmatory | (1) |
| CCyR rate at Week 96 | CCyR rate at Week 96 | % | 39.8% | 16.1% | Data more mature | D180 Response |
| **Unfavourable Effects** | | | | | | |
| | | | All grades/ Grade ≥ 3 | All grades/ Grade ≥ 3 | | |
| Thrombocytopenia | Incidence of thrombocytopenia | % | 23.1/17.9 | 14.5/6.6 | | (1) |
| | | | 27.8/11.1 | | | (2) |
| | | | 27.5/18.5 | | | (4) |
| Neutropenia | Incidence of neutropenia | % | 19.2/15.4 | 17.1/11.8 | | (1) |
| | | | 22.2/11.1 | | | (2) |
| | | | 19.4/15.7 | | | (4) |
| Anaemia | Incidence of anaemia | % | 9.6/1.3 | 7.9/3.9 | | (1) |
| | | | 16.7/0 | | | (2) |
| | | | 12.9/5.3 | | | (4) |
| Hypertension | Incidence of hypertension | % | 12.2/5.8 | 5.3/3.9 | | (1) |
| | | | 33.3/22.2 | | | (2) |
| | | | 18.5/8.7 | | | (4) |
| Lipase increased | Incidence of lipase increased | % | 5.1/3.8 | 6.6/5.3 | | (1) |
| | | | 22.2/16.7 | | | (2) |
| | | | 21.3/12.3 | | | (4) |
| Pancreatitis/pancreatitis acute (SAE) | Incidence of pancreatitis | % | 1.1/0.6 | | | (4) |

Abbreviations:SAE serious adverse events
Notes: (1) Study A2301; (2) Study X2101 asciminib 80 mg q.d. ; (3) Safety pool Study A2301 and Study X2101 Asciminib 40 mg b.i.d; (4) Asciminib All patients safety pool (n=356)

## 3.7. Benefit-risk assessment and discussion

### 3.7.1. Importance of favourable and unfavourable effects

The efficacy of asciminib in patients with PH+ CML-CP treated with two or more TKIs has been shown in the pivotal study A2301 compared to an active control, bosutinib, and is supported with data from study X2101. The pivotal study met its primary objective with superiority demonstrated for asciminib 40 mg BID relative to bosutinib 500 mg QD (MMR rate at 24 weeks was 25.5% vs 13.2%; p-value: 0.029). The efficacy of asciminib is irrespective of the number of previous lines of TKIs (3rd, 4th, 5th line).

Efficacy data has been presented (MMR rate) up till week 96 showing an effect in favour of asciminib from week 12 and upward. Consistent to the primary analysis an increase in superiority of efficacy, as now reflected by a more than 2-fold improvement in MMR rate compared to bosutinib at Week 96; 37.6.% (95% CI: 29.99, 45.65) in the asciminib arm compared to 15.8 % (95% CI: 8.43, 25.96) in the bosutinib arm, corresponding to a common treatment difference (after adjusting for baseline MCyR status) can now be confirmed from the updated outcome.

This demonstrates a robust and mature efficacy for asciminib for the 'treatment of adult patients with Ph+ CML in chronic phase (CP) previously treated with two or more tyrosine kinase inhibitors'. However, it needs to be considered that only few participants remain in the bosutinib arm due to the low tolerability of the 500mg bosutinib dose.

Further, also the other secondary endpoints support the primary analysis as demonstrated in favour of asciminib with a shorter median time to MMR, a higher duration of MMR, deeper responses as reflected in the *BCR-ABL1* at week 24 IS ≤ 0.01% (MR4 or better), and a higher CCyR by Week 24.

The asciminib safety profile was in general favorable relative to that of the TKI bosutinib as indicated by lower incidences of AEs, AEs with lesser severity, fewer AEs requiring dose adjustments and treatment discontinuations with asciminib in pivotal study A2301. Compared to bosutinib, gastro-intestinal adverse events and hepatotoxicity events were reported with substantial lower frequencies. The safety profile of asciminib is dominated by haematological adverse events of which thrombocytopenia and neutropenia were most frequently reported. Infections and haemorrhage were reported with relatively high frequencies (39.7% and ~10%, respectively), but mostly of low grade (1-2). Although severe events have been reported, myelosuppression related events were generally reversible and managed by temporarily withholding treatment.

Overall, no new safety signals have emerged from the safety pool with all patients in pivotal study A2301 and supportive Study X2101 treated at 40 mg b.i.d., or updated safety data with an additional 9 month follow-up in the pivotal study.

### 3.7.2. Balance of benefits and risks

Efficacy of asciminib compared to bosutinib in patients with PH+ CML-CP treated with two or more TKIs has been established in the pivotal study A2301. The safety profile of asciminib was favorable relative to that of the TKI bosutinib and mainly concerns myelosuppression related adverse events. Although severe events have been reported in this heavily pre-treated CML population, the safety profile can be considered generally manageable with adequate monitoring and dose adjustment.

### 3.7.3. Additional considerations on the benefit-risk balance

N/A

## 3.8. Conclusions

The overall benefit/risk balance of Scemblix is positive, subject to the conditions stated in section 'Recommendations'.

# 4. Recommendations

***Similarity with authorised orphan medicinal products***

The CHMP by consensus is of the opinion that Scemblix is not similar to Iclusig within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Scemblix is favourable in the following indication(s):

Scemblix is indicated 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 (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

***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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

***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**

The MAH shall complete, within the stated timeframe, the below measures:

| Description | Due date |
|---|---|
| **CABL001X2101**:A phase I, multicenter, open-label study of oral ABL001 in patients with chronic myelogenous leukemia or Philadelphia Chromosome-positive acute lymphoblastic Leukemia (Category 3 PASS)<br><br>To address Important identified risks: Pancreatic toxicity, Myelosuppression, QTc information prolongation and Important potential risks: Hepatotoxicity and Missing Long-term safety. | 30-Sep-2024 |
| **CABL001A2301**: A phase 3, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CMLCP), previously treated with 2 or more tyrosine kinase inhibitors (Category 3 PASS)<br><br>To address Important identified risks: Pancreatic toxicity, Myelosuppression, QTc prolongation and Important potential risks: Hepatotoxicity and Missing information Long-term safety. | 31-Jul-2025 |
| **3. CABL001A2001B**: An open label, multi-center asciminib roll-over study to assess long-term safety in patients who have completed a Novartis sponsored asciminib study and are judged by the investigator to benefit from continued treatment (Category 3 PASS)<br><br>Myelosuppression, QTc prolongation and Important potential risks: Hepatotoxicity, Hepatitis B virus infection reactivation and Missing information Long-term safety. | 31-Dec-2028 |
| **4. CABL001A2302**: A phase 3b, multi-center, open-label, treatment optimization study of oral asciminib in patients with Chronic Myelogenous Leukemia in chronic phase (CMLCP) previously treated with 2 or more tyrosine kinase inhibitors (Category 3 PASS).<br><br>To address Important identified risks: Pancreatic toxicity, Myelosuppression, QTc prolongation and Important potential risks: Hepatotoxicity, Hepatitis B virus infection reactivation and Missing information Long-term safety. | 11-Mar-2027 |

*New Active Substance Status*

Based on the CHMP review of the available data, the CHMP considers that asciminib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union. Refer to Appendix on new active substance (NAS).