swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Extension of therapeutic indication

Scemblix

International non-proprietary name:	asciminib as asciminib hydrochloride
Pharmaceutical form:	film-coated tablet
Dosage strength(s):	20 mg, 40 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Novartis Pharma Schweiz AG
Marketing authorisation no.:	68441
Decision and decision date:	extension of therapeutic indication approved on 31 January 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed plasma/serum concentration of drug
CML	Chronic myeloid leukaemia
CP	Chronic phase
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MMR	Major Molecular Response
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
Ph+	Philadelphia chromosome positive
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)

RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TFR	Treatment-free remission
TKI	Tyrosine kinase inhibitors
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved indication in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 9 November 2021.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is coordinated by the FDA and provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Scemblix is indicated for the treatment of newly diagnosed or previously treated adult patients with chronic myeloid leukaemia in chronic phase (CML-CP).

2.2.2 Approved indication

Scemblix is indicated for the treatment of adult patients with newly diagnosed or c-Abl tyrosine kinase inhibitor-pretreated Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase (CP) (see "Clinical efficacy").

2.2.3 Requested dosage

No change to the dosage recommendation was requested as part of the application for extension of indication.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	28 June 2024
Formal control completed	2 July 2024
Preliminary decision	9 December 2024
Response to preliminary decision	17 December 2024

Final decision	31 January 2025
Decision	approval

3 Medical context

Chronic myeloid leukaemia (CML) is associated with the Philadelphia chromosome (Ph), which refers to the t(9;22)(q34;q11) chromosomal translocation. This rearrangement creates a *BCR::ABL1* gene fusion, which encodes the constitutively active tyrosine kinase, BCR::ABL1. The incidence of CML ranges between 10 and 15 cases/10^6/year without any major geographic or ethnic differences. The median age at diagnosis ranges between 60 and 65 years in Europe, but is considerably lower in countries with a younger population. The prevalence of CML is steadily rising due to the substantial prolongation of survival that has been achieved with targeted therapy [1]. The most common clinical presentation of CML is chronic phase (CP; 90-95% at diagnosis), which is manifest as leukocytosis, hypercellular bone marrow with marked granulocytic proliferation and few blasts, with or without splenomegaly [2].

BCR::ABL1 tyrosine kinase inhibitors (TKIs) are the mainstay of CML therapy. The selection of a TKI depends on multiple factors, including disease phase (i.e., CML-CP versus advanced disease), CML risk score, side effect profile, and comorbid conditions [2]. First-generation (1G) TKI imatinib and second-generation (2G) TKIs bosutinib, dasatinib, and nilotinib are approved and recommended for the first-line (1L) treatment of Ph+ CP-CML. While 2G-TKIs lead to deeper and faster molecular responses than imatinib, they are associated with increased toxicities, whereas imatinib is associated with fewer cardiovascular and arterio-occlusive events compared to 2G TKIs [3,4].

In addition, despite higher rates of molecular responses, using 2G TKIs as initial therapy has not demonstrated improvements in overall survival (OS), progression-free survival (PFS), or treatment-free remission (TFR) compared with imatinib. And even for 3G TKIs there is currently no data confirming higher rates of cure. Importantly, failing a 2G TKI in the 1L setting was found to be adverse compared to failing it in the second-line (2L) setting. Consequently, there is debate over the best strategy for initial therapy, ranging from starting with a 2G TKI for a quicker and more profound response to switching to a 2G TKI after an inadequate response to imatinib [3].

Patients with disease resistant to primary treatment with imatinib should be treated with a 2G TKI in the 2L setting. Patients with disease resistant to primary treatment with a 2G TKI can be treated with an alternative TKI (other than imatinib), taking into consideration identifiable *BCR::ABL1* mutations that confer resistance to TKI therapy [3,5]. 3G TKIs such as ponatinib and asciminib can be used in the presence of resistance or intolerance to at least 2 prior TKIs. However, ponatinib should be avoided in patients with significant cardiovascular disease [5].

3.1 References

1. Hochhaus A et al. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2017;28 (Supplement 4): iv41–iv51.
2. Schiffer CA and Atallah E. Overview of the treatment of chronic myeloid leukemia. UpToDate. Literature review current through: Sep 2024. Topic last updated: 02 Dec 2022.
3. George B et al. Therapeutic options for chronic myeloid leukemia following the failure of second-generation tyrosine kinase inhibitor therapy. Front Oncol 2024;14:1446517.
4. Walia A and Prasad V. Is it time to reconsider molecular response milestones in chronic myeloid leukemia? Am J Hematol 2023;98:562–563.
5. NCCN Guidelines Chronic Myeloid Leukemia Version 1.2025 – 8 August 2024

4 Nonclinical aspects

4.1 Nonclinical conclusions

The applicant did not submit new nonclinical studies to support the requested extension of the indication for Scemblix. This was considered acceptable since there are no changes with regard to posology and method of administration.
Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.
From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

5 Clinical aspects

5.1 Clinical pharmacology

New PK information obtained in the Phase 3 study J12301 was in good agreement with results of a previously conducted popPK analysis. The combined updated popPK analysis adequately described the PK of asciminib, and the updated model parameters were consistent with those of the previously developed popPK model. The final model was a 2-compartment model with first order absorption, lag time for absorption (T_{lag}), clearance from central compartment, and total daily dose as a structural covariate on clearance. The final covariate model included race on T_{lag}, formulation on (K_a), total daily dose, baseline age, sex, baseline weight, and baseline absolute glomerular filtration rate (aGFR) on CL, and formulation, sex, and baseline weight on volume of distribution (V1). These covariates, which were retained in the final model, while statistically significant, were not found to have a clinically relevant impact on the PK of asciminib.

Updated exposure-response analyses regarding efficacy, augmented by external data validation, and safety supported the adequacy of the proposed dosing regimens and the extrapolation to 2L treatment modalities for asciminib.

5.2 Dose finding and dose recommendation

The applicant proposed using the same monotherapy dosages as approved in the 3L+ setting CML.

5.3 Efficacy

At the time of submission, Scemblix was approved for pre-treated Ph+ CML-CP after at least 2 prior TKI, i.e., for the 3L+ setting, based on the results of the randomised, controlled Phase 3 study A2301 (ASCEMBL). The proposed new indication aimed to extend the approval in two ways. The main purpose of the present application was the inclusion of newly diagnosed (first-line, 1L) Ph+ CML-CP. The inclusion of 2L Ph+ CML-CP was an additional objective, and – along with the current 3L+ approval – was intended to allow use in patients with pre-treated Ph+ CML-CP regardless of prior lines of therapy.

5.3.1. Newly diagnosed (first-line, 1L) Ph+ CML-CP

To support the proposed extension of indication to patients with newly diagnosed Ph+ CML-CP, the applicant submitted efficacy and safety data from **pivotal study J12301** (CABL001J12301, ASC4FIRST; NCT04971226), which was ongoing at the time of submission. Study J12301 is a Phase 3, multicentre, open-label study in adult participants with newly diagnosed Ph+ CML-CP, randomised 1:1 to oral asciminib 80 mg once daily versus investigator-selected (IS)-TKI (imatinib, nilotinib, dasatinib, or bosutinib). The study initiated in October 2021, and the applicant presented the results of the primary efficacy and safety analysis, as of data cut-off (DCO) 28-Nov-2023 (30-Oct-2023 for PK results) and database lock 19-Dec-2023, when all randomised patients had been on study treatment for at least 48 weeks or discontinued earlier (primary analysis of the study; no formal interim analysis was planned in the study).

Overall, 405 patients were randomised and included in the full analysis set (FAS): 201 to asciminib (101 in the imatinib stratum and 100 in the 2G TKI stratum) and 204 to IS-TKIs (102 with imatinib and 102 with 2G TKIs). 401 patients received treatment, and were included in the safety set: 200 (99.5%) in the asciminib arm and 201 (98.5%) in the IS-TKI arm (99 imatinib, 49 nilotinib, 42 dasatinib, and 11 bosutinib).

For details regarding the relevant baseline characteristics of patients and disease, see Information for healthcare professionals.

The study had two primary objectives, i.e., primary endpoint major molecular response (MMR) at week 48 (asciminib vs. IS-TKI) was to be analysed in the FAS as well as in the imatinib stratum of both treatment arms (FAS-IMA). The FAS-IMA comprised the patients for whom imatinib had been the TKI of choice. While the study was to be declared positive if it met either of the two primary objectives, ultimately both were met.

The **MMR rate at week 48 in the FAS** was 67.66% in the asciminib arm compared to 49.02% in the IS-TKI arm, treatment difference 18.88% (95%CI 9.59, 28.17; one-sided adjusted p-value: <0.001).

The **MMR rate at week 48 in the FAS-IMA**, i.e., within the imatinib stratum, was 69.31% in the asciminib arm compared to 40.20% in the IS-TKI arm, treatment difference 29.55% (95%CI 16.91, 42.18; one-sided adjusted p-value: <0.001).

The study had two multiplicity-controlled key secondary objectives, i.e., key secondary endpoint MMR at week 96 (asciminib vs. IS-TKI) in the FAS as well as in the imatinib stratum of both treatment arms (FAS-IMA). Analyses of MMR at week 96 were to be conducted in hierarchical order and when all randomised patients had been treated for at least 96 weeks or discontinued from study treatment prior to week 96. This 96-week analysis time point had not yet been achieved as of the time of submission.

The **MMR rate at week 48 in the FAS-2G TKI**, i.e., within the stratum comprising the patients for whom a 2G TKI had been the TKI of choice, was a secondary endpoint, and was 66.00% in the asciminib arm compared to 57.84% in the IS-TKI arm, treatment difference 8.17% (95%CI -5.14, 21.47) per the CMH one-sided test, stratified by ELTS risk score.

5.3.2. Previously treated (2L) Ph+ CML-CP

To support the proposed extension of indication to patients with previously treated Ph+ CML-CP regardless of prior lines of therapy, the applicant submitted key efficacy and safety data from a 6-month interim analysis (IA2) as of DCO 28-Jun-2024 for patients with pre-treated Ph+ CML-CP, who received asciminib in the 2L setting in study AUS08 (2L cohort).

Study AUS08 (CABL001AUS08, ASC2ESCALATE) was a Phase 2, US multicentre, open-label, single-arm, dose escalation study in patients with Ph+ CML-CP receiving asciminib monotherapy as 2L or 1L treatment, and was ongoing at the time of submission. The primary endpoint was MMR rate at 12 months with key efficacy assessments of molecular responses at various timepoints.

At IA2, 71 patients, all of whom had received prior TKI therapy, had been enrolled in the 2L cohort, and 28 patients were evaluable for efficacy at 6 months, having completed the efficacy assessment or discontinued prior to the timepoint.

After a median duration of exposure to study treatment in the 2L cohort of approximately 19 weeks, the MMR rate at 6 months was 42.9% (95% CI: 24.5, 62.8) in the 28 evaluable patients of the 2L cohort, which is intermediate to the MMR rates observed in the 1L setting in study J12301 (MMR at week 24: 58%) and the 3L+ setting in study A2301 (MMR at week 24: 25%), as would be expected.

In addition to clinical data from Study AUS08, PK-PD modelling was used to support extrapolation to the 2L setting based on asciminib 1L and 3L+ data from 430 patients with CML-CP enrolled in studies J12301, A2301 and X2101. The PK-PD model was found to adequately predict MMR rates, including the 2L setting.

The following uncertainties regarding efficacy were noted.

Duration of exposure and follow-up were short in pivotal study J12301 and supportive study AUS08, and the latter had a low number of evaluable patients as of DCO (28 patients). Multiplicity-controlled key secondary efficacy endpoint MMR at week 96 in pivotal study J12301 was not yet available as the 96-week analysis time point had not yet been achieved as of DCO 28-Nov-2023, and time-to-event endpoints were immature. The submission of the week 96 results of study J12301 in April 2025, and 5-year results in June 2028 were requested as a post-approval requirement.

Treatment differences in molecular response rates were not clinically meaningful when compared within the 2G TKI stratum, i.e., rates of molecular responses comparing asciminib and IS-TKI in the

FAS were driven by treatment effects in the imatinib stratum. In addition, it is debatable whether the distribution of 50% imatinib and 50% 2G TKIs as selected in study J12301 represents the proportion of use in routine medical practice in the 1L setting, and this is expected to vary considerably by country and other factors.

No convincing evidence for improved quality of life (QoL) on asciminib therapy was provided, and no association with increased overall survival (OS) had been demonstrated for the primary and key secondary efficacy endpoint MMR. For instance, despite higher MMR rates, 2G and 3G TKIs have not demonstrated improvements in OS compared to imatinib [4,5]. When used in 1L, 2G TKIs did not even demonstrate improvements in PFS or TFR compared with imatinib [3].

Supportive 1L data from studies AUS08 and ASC4START, which is an ongoing open-label, randomised, Phase 3 study (NCT05456191) of asciminib vs nilotinib in 1L Ph+ CML-CP, are lacking, but the submission of relevant results from both studies was requested as a post-approval requirement.

5.4 Safety

The most common adverse events (AEs) on asciminib therapy were infections, mainly due to COVID-19 and upper respiratory tract infections, with cough among the most common AEs by preferred term (PT); gastrointestinal disorders, mainly due to diarrhoea, nausea, vomiting, abdominal pain, and constipation; and AEs related to investigations, mainly due to increased lipase and amylase, increased liver function tests, and decreased count of platelets and neutrophils, with cytopenias, i.e., thrombocytopenia, neutropenia, and anaemia among the most common AEs by PT.

The safety profile in the asciminib arm compared favourably with the IS-TKI arm overall, and especially when compared with 2G TKI. In addition, the safety profile in the asciminib arm was consistent with the known safety profile of asciminib.

For details regarding the safety profile of asciminib, see Information for healthcare professionals.

The following uncertainties regarding safety were present.

As has been noted for efficacy, the duration of exposure and follow-up in pivotal study J12301 was short. For instance, multiplicity-controlled secondary safety endpoint treatment due to adverse event (TTDAE) at week 96 was not available, but submission of the week 96 results of Study J12301 was requested as a post-approval requirement (see above).

The open-label approach was a significant weakness of the pivotal study design (see above). Safety assessments requiring investigator evaluation might have been affected by unblinded assessments. The potential impact on safety was of particular relevance, as TTDAE was a multiplicity-controlled secondary endpoint, and given the importance of the safety profile in determining the benefit-risk balance and the selection of TKIs during CML therapy.

5.5 Final clinical benefit risk assessment

The goals of care for patients with CML are to achieve clinical, cytogenetic, and molecular remission; maintain long-term disease control; and avoid progression to advanced disease, while optimising quality of life by limiting treatment-related toxicity. Many patients and clinicians also consider achieving TFR an important goal [2].

Despite the uncertainties presented above, the benefit-risk is considered positive for the **1L setting** as the pivotal study J12301 met its two primary objectives, and showed a favourable comparative safety profile for asciminib, in particular when compared with 2G TKI, which are approved and broadly used for the treatment of newly diagnosed (1L) Ph+ CML-CP.

Regarding the **2L setting**, the totality of evidence, consisting of clinical efficacy results from the 2L cohort of study AUS08 and from the 1L and 3L+ settings, as investigated in the pivotal randomised, controlled Phase 3 studies J12301 and A2301, and further supported by PK-PD data, is considered sufficient to support the proposed extension of the CML-CP indication to the 2L setting.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Scemblix was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This allows quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse effects. See “Adverse effects” for information on reporting adverse effects.

Scemblix®

Composition

Active substances

Asciminib (as asciminib hydrochloride).

Excipients

20 mg film-coated tablets: 43 mg lactose monohydrate, microcrystalline cellulose (E460i), hydroxypropylcellulose (E463), croscarmellose sodium (E468), polyvinyl alcohol (E1203), titanium dioxide (E171), magnesium stearate (E470b), talc (E553b), colloidal anhydrous silica, iron oxide (E172, yellow and red), lecithin (E322), xanthan gum (E415).
One 20 mg film-coated tablet contains max. 0.47 mg sodium.
40 mg film-coated tablets: 86 mg lactose monohydrate, microcrystalline cellulose (E460i), hydroxypropylcellulose (E463), croscarmellose sodium (E468), polyvinyl alcohol (E1203), titanium dioxide (E171), magnesium stearate (E470b), talc (E553b), colloidal anhydrous silica, iron oxide (E172, black and red), lecithin (E322), xanthan gum (E415).
One 40 mg film-coated tablet contains max. 0.93 mg sodium.

Pharmaceutical form and quantity of active substance per unit

Scemblix 20 mg film-coated tablets:
The tablets are pale yellow, round and biconvex with bevelled edges and a diameter of approx. 6 mm, unscored, and imprinted with the Novartis logo on one side and “20” on the other side.
Each 20 mg film-coated tablet contains 21.62 mg asciminib hydrochloride equivalent to 20 mg asciminib.

Scemblix 40 mg film-coated tablets:
The tablets are violet-white, round and biconvex with bevelled edges and a diameter of approx. 8 mm, unscored, and imprinted with the Novartis logo on one side and “40” on the other side.
Each 40 mg film-coated tablet contains 43.24 mg asciminib hydrochloride equivalent to 40 mg asciminib.

Indications/Potential uses

Scemblix is indicated for the treatment of adult patients with newly diagnosed or c-Abl tyrosine kinase inhibitor-pretreated Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase (CP) (see “Clinical efficacy”).

Dosage/Administration

Treatment with Scemblix should be initiated by a physician experienced in the use of anticancer therapies.

Usual dosage

The recommended total daily dose of Scemblix is 80 mg. Scemblix can be taken orally either as 80 mg once daily at approximately the same time each day or as 40 mg twice daily at approximately 12-hour intervals.
Patients who are switched from 40 mg twice daily to 80 mg once daily should start taking Scemblix once daily approximately 12 hours after the last twice-daily dose and then continue at 80 mg once daily.
Patients who are switched from 80 mg once daily to 40 mg twice daily should start taking Scemblix twice daily approximately 24 hours after the last once-daily dose and then continue at 40 mg twice daily at approximately 12-hour intervals (see “Clinical efficacy”).

Treatment duration

Scemblix treatment should be continued as long as a clinical benefit is observed or until unacceptable toxicity occurs.

Dose modification due to adverse effects/interactions

For the management of adverse drug reactions of Scemblix the dose can be reduced based on individual safety and tolerability as described in Table 1. If adverse drug reactions are effectively managed, treatment with Scemblix may be resumed as described in Table 1.
Scemblix should be permanently discontinued in patients unable to tolerate a total daily dose of 40 mg.

Table 1 Scemblix dose modification

Starting dose	Reduced dose	Resumed dose
80 mg once daily	40 mg once daily	80 mg once daily
40 mg twice daily	20 mg twice daily	40 mg twice daily

The recommended dose modification for the management of selected adverse drug reactions is shown in Table 2.

Table 2 Scemblix dose modification for the management of selected adverse drug reactions

Adverse drug reaction	Dose modification
Thrombocytopenia and/or neutropenia	
ANC[1] <1 x 10^9/l and/or PLT[2] <50 x 10^9/l	Withhold Scemblix until ANC ≥1 x 10^9/l and/or PLT ≥50 x 10^9/l.

Adverse drug reaction	Dose modification
	If resolved: • Within 2 weeks: Resume treatment at the original Scemblix starting dose. • After more than 2 weeks: Resume treatment at a reduced Scemblix dose. For recurrent severe thrombocytopenia and/or neutropenia withhold Scemblix treatment until ANC ≥1 x 10^9/l and PLT ≥50 x 10^9/l, then resume at reduced dose.
Asymptomatic amylase and/or lipase elevation	
Elevation >2 x ULN[3]	Withhold Scemblix until value has decreased to <1.5 x ULN. • If resolved: Resume treatment at a reduced Scemblix dose. If adverse drug reactions reoccur at reduced dose, permanently discontinue Scemblix. • If not resolved: Permanently discontinue Scemblix. Perform diagnostic tests to exclude pancreatitis.
Non-haematological adverse drug reactions	
Grade 3 or higher adverse drug reactions [4]	Withhold Scemblix until resolved or improvement to grade 1 or lower. • If resolved: Resume treatment at a reduced Scemblix dose. • If not resolved: Permanently discontinue Scemblix.
[1]ANC: absolute neutrophil count; [2]PLT: platelets; [3]ULN: upper limit of normal; [4]Based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.03	

Patients with hepatic impairment

No dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment receiving Scemblix (see “Pharmacokinetics”).

Patients with renal impairment

No dose adjustment is necessary in patients with mild, moderate or severe renal impairment receiving Scemblix (see “Pharmacokinetics”).

Elderly patients

No dose adjustment is required in patients 65 years of age and over.

Children and adolescents

Safety and efficacy in patients under 18 years of age have not been established.

Late administration

Once-daily dosage regimen: If a dose of Scemblix is more than approx. 12 hours late, it should be skipped and the next one taken as scheduled.
Twice-daily dosage regimen: If a dose of Scemblix is more than approx. 6 hours late, it should be skipped and the next one taken as scheduled.

Method of administration

Scemblix should be taken orally without food. Food should be avoided for at least 2 hours before and 1 hour after taking Scemblix (see “Interactions” and “Pharmacokinetics”).
Scemblix film-coated tablets must be swallowed whole with a glass of water and should not be broken, crushed or chewed.

Contraindications

Hypersensitivity to the active substance or any of the excipients listed under “Composition”.

Warnings and precautions

Myelosuppression
Thrombocytopenia, neutropenia and anaemia have occurred in patients receiving Scemblix. Severe (NCI CTCAE grade 3 or 4) thrombocytopenia and neutropenia have been reported during treatment with Scemblix (see “Adverse effects”). Myelosuppression was generally reversible and managed by temporarily withholding Scemblix. A complete blood count should be performed every 2 weeks in the first 3 months of treatment and then monthly thereafter or as clinically indicated. Patients should be monitored for signs and symptoms of myelosuppression.
Based on the severity of thrombocytopenia and/or neutropenia, the Scemblix dose should be reduced, temporarily withheld or permanently discontinued as described in Table 2 (see “Dosage/Administration”).

Pancreatic toxicity
Pancreatitis occurred in 11 of 556 (2%) patients receiving Scemblix, with grade 3 adverse drug reactions occurring in 6 (1.1%) patients. Scemblix was permanently discontinued in 3 (0.5%) patients, while it was temporarily withheld in 5 (1.1%) patients due to pancreatitis. Asymptomatic elevation of serum lipase and amylase occurred in 107 of 556 (19.2%) patients receiving Scemblix treatment, with grade 3 and 4 adverse drug reactions occurring in 41 (7.4%) and 11 (2%) patients, respectively.

Scemblix was permanently discontinued in 11 (2%) patients due to asymptomatic elevation of serum lipase and amylase..
Serum lipase and amylase levels should be assessed monthly during treatment with Scemblix or as clinically indicated. Patients should be monitored for signs and symptoms of pancreatic toxicity. More frequent monitoring should be performed in patients with a history of pancreatitis. If serum lipase and amylase elevation is accompanied by abdominal symptoms, treatment should be temporarily withheld and appropriate diagnostic tests should be considered to exclude pancreatitis (see "Dosage/Administration").
Based on the severity of serum lipase and amylase elevation, the Scemblix dose should be reduced, temporarily withheld or permanently discontinued as described in Table 2 (see "Dosage/Administration").

QT prolongation
Electrocardiogram QT prolongation occurred in 5 of 556 (0.9%) patients receiving Scemblix treatment (see "Adverse effects"). In the ASCEMBL clinical study one patient had a prolonged QTcF greater than 500 ms together with a more than 60 ms QTcF increase from baseline and one patient had a prolonged QTcF with a more than 60 ms QTcF increase from baseline.
It is recommended that an electrocardiogram is performed prior to the start of treatment with Scemblix and that ECG monitoring is carried out during treatment as clinically indicated. Hypokalaemia and hypomagnesaemia should be corrected prior to Scemblix administration and monitored during treatment as clinically indicated.
Caution is required when co-administering Scemblix with medicinal products known to increase the risk of torsade de pointes (see "Interactions" and "Pharmacokinetics").

Hypertension
Hypertension occurred in 88 of 556 (15.8%) patients receiving Scemblix treatment, with grade 3 and 4 adverse drug reactions reported in 47 (8.5%) and 1 (0.2%) patients, respectively. Among the patients with ≥ grade 3 hypertension, the median time to first occurrence of adverse drug reactions was 21.29 weeks (range: 0.14 to 365 weeks). Scemblix was temporarily withheld in 5 (0.9%) patients due to hypertension..
Hypertension should be monitored and managed with standard antihypertensive therapy during treatment with Scemblix as clinically indicated.

Hypersensitivity
Hypersensitivity events occurred in 169 of 556 (30.4%) patients receiving Scemblix, with ≥ grade 3 events reported in 8 (1.4%) patients. Patients should be monitored for signs and symptoms of hypersensitivity and appropriate treatment should be initiated as clinically indicated.

Hepatitis B reactivation
Reactivation of hepatitis B virus (HBV) has occurred in patients who are chronic carriers of this virus following administration of other BCR::ABL1 tyrosine kinase inhibitors (TKIs). Patients should be tested for HBV infection before the start of treatment with Scemblix. HBV carriers who require treatment with Scemblix should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Embryo-fetal toxicity
Based on findings from animal studies, Scemblix can cause fetal harm when administered to a pregnant woman. Pregnant women and women of child-bearing potential should be advised of the potential risk to the fetus if Scemblix is used during pregnancy or if the patient becomes pregnant while taking Scemblix. The pregnancy status of women of child-bearing potential should be verified prior to starting treatment with Scemblix. Sexually active women of childbearing potential should use effective contraception during treatment with Scemblix and for at least 3 days after the last dose (see “Pregnancy/Breast-feeding”).

Other components
The tablets contain lactose. Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.
This medicinal product contains less than 1 mmol (23 mg) of sodium per tablet, making it practically “sodium-free”.

Patients excluded from clinical studies
Patients with severe or uncontrolled disorders, including bleeding disorders, with a history of or risk factors for pancreatitis or with clinically significant cardiac impairment or cardiac repolarisation abnormalities were not enrolled in clinical studies on asciminib.

Interactions

Agents that may affect asciminib plasma concentrations:
Strong CYP3A4 inhibitors:
The AUC_{inf} and C_{max} of asciminib increased by 36% and 19%, respectively, after co-administration of a single dose of 40 mg Scemblix with a strong CYP3A4 inhibitor (clarithromycin). No clinically significant differences in the pharmacokinetics of asciminib were observed after co-administration with itraconazole, which is also a strong CYP3A4 inhibitor.
Strong CYP3A4 inducers

Co-administration of a strong CYP3A4 inducer (rifampicin) decreased asciminib AUC_{inf} by 15% and increased C_{max} by 9% in healthy subjects receiving a single Scemblix dose of 40 mg. Model calculations predict that co-administration of asciminib at 80 mg once daily with rifampicin decreases asciminib AUC_{tau} and C_{max} by 52% and 23%, respectively. Caution is required during co-administration of Scemblix with strong CYP3A4 inducers, including, but not limited to, carbamazepine, phenobarbital, phenytoin or St. John's wort (*Hypericum perforatum*). Scemblix dose adjustment is not required.

Imatinib

Asciminib AUC_{inf} and C_{max} increase by 108% and 59%, respectively, after co-administration of a single dose of 40 mg Scemblix with imatinib (an inhibitor of BCRP, CYP3A4, UGT2B17 and UGT1A3/4). The changes in exposure are not considered to be clinically significant.

Other agents

No clinically significant differences in the pharmacokinetics of asciminib were observed after co-administration with rabeprazole (acid-reducing agent) and quinidine (P-gp inhibitor).

Agents whose plasma concentrations may be altered by asciminib

CYP3A4 substrates with a narrow therapeutic index

Co-administration of asciminib with a CYP3A4 substrate (midazolam) increased midazolam AUC_{inf} and C_{max} by 28% and 11%, respectively, in healthy subjects receiving 40 mg Scemblix twice daily. Caution is required during co-administration of Scemblix with CYP3A4 substrates known to have a narrow therapeutic index, including, but not limited to, fentanyl, alfentanil, dihydroergotamine or ergotamine (see "Pharmacokinetics"). Scemblix dose adjustment is not required.

CYP2C8 substrates

The AUC_{inf} and C_{max} of repaglinide (substrate of CYP2C8, CYP3A4 and OATP1B) increased by 8% and 14%, respectively, after co-administration of repaglinide with 40 mg Scemblix twice daily. The AUC_{inf} and C_{max} of repaglinide increased by 12% and 8%, respectively, after co-administration with 80 mg Scemblix once daily. The AUC_{inf} and C_{max} of rosiglitazone (substrate of CYP2C8 and CYP2C9) increased by 20% and 3%, respectively, after co-administration of rosiglitazone with 40 mg Scemblix twice daily. The AUC_{inf} and C_{max} of rosiglitazone increased by 24% and 2%, respectively, after co-administration with 80 mg Scemblix once daily. The changes in exposure are not considered to be clinically significant.

CYP2C9 substrates

Co-administration of asciminib with a CYP2C9 substrate (warfarin) increased S-warfarin AUC_{inf} and C_{max} by 41% and 8%, respectively, in healthy subjects receiving 40 mg Scemblix twice daily. Co-administration of asciminib at 80 mg once daily would be expected to increase S-warfarin AUC_{inf} and C_{max} by 52% and 4%, respectively.
Caution is required during co-administration of Scemblix with CYP2C9 substrates known to have a narrow therapeutic index, including, but not limited to, phenytoin or warfarin (see “Pharmacokinetics”). Scemblix dose adjustment is not required.

Substrates of OATP1B, BCRP or both transporter proteins

Using PBPK models it is predicted that co-administration of asciminib at a dosage of 40 mg twice daily or 80 mg once daily with an OATP1B substrate (pravastatin) would increase pravastatin C_{max} by 43% and 63% and AUC_{inf} by 37% and 51%, respectively.
Using PBPK models it is predicted that co-administration of asciminib at a dosage of 40 mg twice daily or 80 mg once daily with a substrate of OATP1B, CYP3A4 and P-gp (atorvastatin) would increase atorvastatin C_{max} by 97% and 143% and AUC_{inf} by 81% and 122%, respectively.
Using PBPK models it is predicted that co-administration of asciminib at a dosage of 40 mg twice daily or 80 mg once daily with a BCRP substrate (sulfasalazine) would increase sulfasalazine C_{max} by 334% and 342% and AUC_{inf} by 333% and 340%, respectively.
Using PBPK models it is predicted that co-administration of asciminib at a dosage of 40 mg twice daily or 80 mg once daily with a substrate of BCRP and OATP1B (rosuvastatin) would increase rosuvastatin C_{max} by 453% and 530% and AUC_{inf} by 190% and 202% respectively.
Caution is required if Scemblix is co-administered with substrates of OATP1B, BCRP or both transporter proteins, including, but not limited to, sulfasalazine, methotrexate, pravastatin, atorvastatin, pitavastatin, rosuvastatin and simvastatin. Refer to the dose reductions for OATP1B and BCRP substrates recommended in their prescribing information.
Co-administration of Scemblix with rosuvastatin should be avoided and other statins should instead be considered. If co-administration cannot be avoided, the rosuvastatin dose should be reduced as per the recommendations in its prescribing information.

P-gp substrates with a narrow therapeutic index

PBPK models predict that co-administration of asciminib at 40 mg twice daily and 80 mg once daily with a P-gp substrate such as digoxin would increase the maximum plasma concentration (C_{max}) of digoxin by 30% and 38% and the area under the concentration-time curve (AUC_{inf}) by 20% and 22%, respectively. Caution is required during co-administration of Scemblix with P-gp substrates known to have a narrow therapeutic index such as digoxin, dabigatran and colchicine.

QT-prolonging agents

Caution is required during co-administration of Scemblix and medicinal products known to increase the risk of torsade de pointes, including, but not limited to, chloroquine, clarithromycin, haloperidol, methadone or moxifloxacin (see “Pharmacokinetics”).

Interactions with food

The bioavailability of asciminib decreases on consumption of food (see “Dosage/Administration” and “Pharmacokinetics”).

In vitro evaluation of drug interaction potential

CYP450 and UGT enzymes

In vitro, asciminib reversibly inhibits CYP3A4/5, CYP2C9 and UGT1A1 at plasma concentrations reached at a total daily dose of 80 mg.

Transporters

Asciminib is a substrate of BCRP and P-gp. Asciminib inhibits BCRP, P-gp, OATP1B1, OATP1B3 and OCT1 with Ki values of 24.3, 21.7, 2.46, 1.92 and 3.41 micromolar, respectively. Based on information from PBPK models, asciminib increases exposure to substrates of OATP1B and BCRP (see “Interactions”). Co-administration of Scemblix with a medicinal product that is a P-gp substrate may lead to a clinically relevant increase in plasma concentrations of P-gp substrates, with minimal concentration changes possibly leading to severe toxicities.

Multiple metabolic pathways

Asciminib is metabolised by several pathways, including the CYP3A4, UGT2B7 and UGT2B17 enzymes and biliary secretion by the transporter BCRP.

Medicinal products inhibiting or inducing multiple metabolic pathways may alter Scemblix exposure.

Asciminib inhibits several metabolic pathways, including CYP3A4, CYP2C9, OATP1B, P-gp and BCRP. Therefore, Scemblix may increase exposure to medicinal products that are substrates of these metabolic pathways (see “Interactions”).

Pregnancy/Breast-feeding

Treatment of women of childbearing potential/contraception

The pregnancy status of women of child-bearing potential should be verified prior to starting treatment with Scemblix.

Sexually active women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with Scemblix and for at least 3 days after the last dose.

Pregnancy

There are no studies in pregnant women to inform a medicinal product-associated risk.
Animal reproduction studies in pregnant rats and rabbits demonstrated that oral administration of asciminib during organogenesis induced embryotoxicity, fetotoxicity and malformations (see “Preclinical data”). Asciminib is not recommended during pregnancy and in women of childbearing potential not using contraceptives. If Scemblix is used during pregnancy or if the patient becomes pregnant during treatment with Scemblix, the patient must be informed of the potential risk to the fetus (see “Warnings and precautions”).

Breast-feeding

It is unknown whether asciminib or its metabolites are excreted in human milk following administration of Scemblix. There are no data on the effects of asciminib on the breast-fed infant or milk production. Because of the potential for serious adverse effects in the breast-fed infant, breast-feeding is not recommended during treatment with Scemblix and for at least 3 days after the last dose.

Fertility

There are no data on the effects of Scemblix on human fertility.
In the rat fertility study asciminib did not affect reproductive function in male and female rats (see “Preclinical data/Fertility”).

Effects on ability to drive and use machines

No relevant studies have been performed. Patients experiencing dizziness, fatigue, nausea, visual impairment or other adverse effects with a potential impact on the ability to drive or use machines should refrain from these activities as long as the adverse effects persist (see “Adverse effects”).

Adverse effects

Summary of the safety profile

The overall safety profile of asciminib was investigated in 556 patients with Ph+ CML. In the pooled data set of the phase III pivotal study J12301 (ASC4FIRST) (N=200 newly diagnosed Ph+ CML-CP patients) (80 mg once-daily dosage), the phase III pivotal study A2301 (ASCEMBL) (N=156 Ph CML-CP patients previously treated with two or more TKIs) (40 mg twice-daily dosage) and the phase I study X2101, the median duration of exposure to asciminib was 83.2 weeks (range: 0.1 to 439 weeks), with 79.3% of patients having been exposed for at least 48 weeks and 42.4% of patients having been exposed for at least 96 weeks.

The most common adverse drug reactions of any grade (incidence ≥20%) in patients receiving Scemblix were musculoskeletal pain (32.9%), thrombocytopenia (28.1%), fatigue (25%), upper respiratory tract infections (23.7%), headache (21.8%), neutropenia (21.6%) and diarrhoea (20%).
The most common adverse drug reactions of ≥ grade 3 (incidence ≥5%) in patients receiving Scemblix were thrombocytopenia (16.5%), neutropenia (13.7%), increased pancreatic enzymes (9.4%) and hypertension (8.6%).
Serious adverse drug reactions occurred in 9.5% of patients receiving Scemblix.
The most frequent serious adverse drug reactions (incidence ≥1%) were pleural effusion (1.6%), lower respiratory tract infections (1.4%), thrombocytopenia (1.3%), pancreatitis (1.1%) and pyrexia (1.1%).

List of adverse drug reactions

Adverse drug reactions are ordered by MedDRA system organ class and frequency according to the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 3 Adverse drug reactions observed with Scemblix in clinical studies

Adverse drug reactions	Frequency category[1] (N=556) (all grades)
Infections and infestations	
Upper respiratory tract infection[2]	Very common (23.7%)
COVID-19	Very common (17.1%)
Lower respiratory tract infection[3]	Common
Influenza	Common
Blood and lymphatic system disorders	
Thrombocytopenia[4]	Very common (28.1%)
Neutropenia[5]	Very common (21.6%)
Anaemia[6]	Very common (12.6%)
Febrile neutropenia	Uncommon
Immune system disorders	
Hypersensitivity	Uncommon
Endocrine disorders	
Hypothyroidism[7]	Common
Metabolism and nutrition disorders	
Dyslipidaemia[8]	Very common (12.4%)
Decreased appetite	Common
Nervous system disorders	
Headache	Very common (21.8%)
Dizziness	Very common (11%)
Eye disorders	
Blurred vision	Common

Adverse drug reactions	Frequency category[1] (N=556) (all grades)
Dry eye	Common
Cardiac disorders	
Palpitations	Common
Atrial fibrillation	Common
Vascular disorders	
Hypertension[9]	Very common (15.8%)
Respiratory, thoracic and mediastinal disorders	
Cough	Very common (12.1%)
Pleural effusion	Common
Dyspnoea	Common
Non-cardiac chest pain	Common
Gastrointestinal disorders	
Increased pancreatic enzymes[10]	Very common (19.2%)
Vomiting	Very common (13.5%)
Diarrhoea	Very common (20%)
Nausea	Very common (16.5%)
Abdominal pain[11]	Very common (18.7%)
Constipation	Very common (11.2%)
Pancreatitis[12]	Common
Large intestine perforation	Uncommon
Hepatobiliary disorders	
Increased hepatic enzymes[13]	Very common (14.2%)
Increased blood bilirubin[14]	Common
Cholecystitis[15]	Uncommon
Skin and subcutaneous tissue disorders	
Rash[16]	Very common (19.2%)
Pruritus	Very common (10.4%)
Urticaria	Common
Musculoskeletal and connective tissue disorders	
Musculoskeletal pain[17]	Very common (32.9%)
Arthralgia	Very common (19.4%)
General disorders and administration site conditions	
Fatigue[18]	Very common (25%)
Oedema[19]	Common
Pyrexia[20]	Common
Investigations	
Prolonged electrocardiogram QT	Uncommon
Increased blood creatine phosphokinase	Common

[1]Frequency based on the safety pool (J12301, A2301 and X2101) for all grades of adverse drug reactions with Scemblix (N=556).

Adverse drug reactions	Frequency category[1] (N=556) (all grades)
[2]Upper respiratory tract infections includes: upper respiratory tract infections, nasopharyngitis, pharyngitis and rhinitis; [3]Lower respiratory tract infections includes: pneumonia, bronchitis and tracheobronchitis; [4]Thrombocytopenia includes: thrombocytopenia and decreased platelet count; [5]Neutropenia includes: neutropenia and decreased neutrophil count; [6]Anaemia includes: anaemia, decreased haemoglobin and normocytic anaemia; [7]Hypothyroidism includes: hypothyroidism, autoimmune thyroiditis, increased blood thyroid-stimulating hormone, autoimmune hypothyroidism and primary hypothyroidism;[8]Dyslipidaemia includes: hypertriglyceridaemia, increased blood cholesterol, hypercholesterolaemia, increased blood triglycerides, hyperlipidaemia and dyslipidaemia; [9]Hypertension includes: hypertension and increased blood pressure; [10]Increased pancreatic enzymes includes: increased lipase, increased amylase and hyperlipasaemia; [11]Abdominal pain includes: abdominal pain and upper abdominal pain; [12]Pancreatitis includes: pancreatitis and acute pancreatitis; [13]Increased hepatic enzymes includes: increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyltransferase, increased transaminases and hypertransaminasaemia; [14]Increased blood bilirubin includes: increased blood bilirubin, increased conjugated bilirubin and hyperbilirubinaemia; [15]Cholecystitis includes: cholecystitis and acute cholecystitis; [16]Rash includes: rash, maculopapular rash and pruritic rash; [17]Musculoskeletal pain includes: pain in extremity, back pain, myalgia, bone pain, musculoskeletal pain, neck pain, musculoskeletal chest pain and musculoskeletal discomfort; [18]Fatigue includes: fatigue and asthenia; [19]Oedema includes: oedema and peripheral oedema; [20]Pyrexia includes: pyrexia and increased body temperature.	

In the ASCEMBL study a decrease in phosphate levels occurred as a laboratory abnormality in 17.9% (all grades) and 7.1% (grade 3/4) of 156 patients receiving Scemblix at 40 mg twice daily. In the ASC4FIRST study a decrease in phosphate levels based on the normal range occurred as a laboratory abnormality in 13% (all grades) of 200 patients receiving Scemblix at 80 mg once daily. An increase in potassium as a laboratory abnormality was observed on asciminib in 22.5% (all grades) and 1.3% (grade 3/4) of 556 participants in the asciminib safety pool.

Description of specific adverse effects and additional information

Myelosuppression

Thrombocytopenia occurred in 156 of 556 (28.1%) patients receiving Scemblix, with grade 3 and 4 adverse drug reactions reported in 39 (7%) and 53 (9.5%) patients, respectively. Among the patients with ≥ grade 3 thrombocytopenia the median time to first occurrence of adverse drug reactions was 6 weeks (range: 0.14 to 64.14 weeks) with a median duration of any occurring adverse drug reaction of 1.57 weeks (95% CI, range: 1.14 to 2 weeks). Scemblix was permanently discontinued in 11 (2%) patients, while it was temporarily withheld in 70 (12.6%) patients due to thrombocytopenia.
Neutropenia occurred in 120 of 556 (21.6%) patients receiving Scemblix treatment, with grade 3 and 4 adverse drug reactions reported in 41 (7.4%) and 35 (6.3%) patients, respectively. Among the patients with ≥ grade 3 neutropenia the median time to first occurrence of adverse drug reactions was 7.07 weeks (range: 0.14 to 180.14 weeks) with a median duration of any occurring adverse drug reaction of 1.86 weeks (95% CI, range: 1.29 to 2 weeks). Scemblix was permanently discontinued in 7 (1.3%) patients, while it was temporarily withheld in 52 (9.4%) patients due to neutropenia..
Anaemia occurred in 70 of 556 (12.6%) patients receiving Scemblix, with grade 3 adverse drug reactions occurring in 22 (4%) patients. Among the patients with grade ≥3 anaemia the median time to first occurrence of adverse drug reactions was 22.21 weeks (range: 0.14 to 207 weeks) with a median duration of any occurring adverse drug reaction of 0.79 weeks (95% CI, range: 0.29 to 1.71 weeks). Scemblix was temporarily withheld in 2 patients (0.4%) due to anaemia..

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal ElViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

There is only limited experience of overdose with Scemblix. In clinical studies Scemblix has been administered at doses up to 280 mg twice daily with no signs of increased toxicity. General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

Properties/Actions

ATC code

L01EA06

Mechanism of action

Asciminib is an oral and potent inhibitor of ABL/BCR::ABL1 tyrosine kinase. Asciminib inhibits the ABL1 kinase activity of the BCR::ABL1 fusion protein by specifically targeting the ABL myristoyl-binding pocket.

Pharmacodynamics

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 expressing the wild-type form of BCR::ABL1 asciminib inhibits cell growth with mean IC_{50} values of 0.61 ± 0.21 nanomolar.
In mouse xenograft models of CML asciminib dose-dependently inhibited the growth of tumours harbouring the wild-type form of BCR::ABL1, with tumour regression being observed at doses above 7.5 mg/kg twice daily.

Cardiac electrophysiology

Scemblix treatment has been associated with an exposure-related prolongation of the QT interval. The correlation between asciminib concentration and the estimated maximum mean change from baseline of the QT interval with Fridericia's correction (ΔQTcF) was evaluated in 239 patients with Ph+ CML or Ph+ acute lymphoblastic leukaemia (ALL) receiving Scemblix at doses ranging from 10 to 280 mg twice daily and 80 to 200 mg once daily. The estimated mean ΔQTcF was 3.35 ms (upper bound of 90% CI: 4.43 ms) for the Scemblix 40 mg twice-daily dose and 3.64 ms (upper bound of 90% CI: 4.68 ms) for the 80 mg once-daily dose.

Clinical efficacy

Newly diagnosed Ph+ CML-CP

The clinical efficacy and safety of Scemblix in the treatment of patients with newly diagnosed Philadelphia chromosome-positive myeloid leukaemia in chronic phase (Ph+ CML-CP) were demonstrated in the multicentre, randomised, active-controlled and open-label phase III study ASC4FIRST.

In this study a total of 405 patients were randomised in a 1:1 ratio to receive either Scemblix or investigator-selected tyrosine kinase inhibitors (IS TKIs). Prior to randomisation the investigator selected the TKI (imatinib or second-generation [2G] TKI) to be used in the event of randomisation in the comparator arm based on patient characteristics and comorbidities. Patients were stratified by EUTOS long-term survival (ELTS) risk group (low, intermediate, high) and pre-randomisation selection of TKI (imatinib or 2G TKI stratum). Patients received either Scemblix or IS TKIs and continued to receive treatment until unacceptable toxicity or treatment failure occurred.

Patients were 36.8% female and 63.2% male with a median age of 51 years (range: 18 to 86 years). Of the 405 patients, 23.5% were aged 65 years or older, while 6.2% were aged 75 years or older. Patients were white (53.8%), Asian (44.4%) and black (1%) and 0.7% were of unknown ethnicity.

Demographic characteristics within the imatinib (N=203) and 2G TKI strata (N=202) were as follows:

- median age: 55 years and 43 years, respectively;
- ELTS high-risk group: 8.4% and 13.9%, respectively;
- Framingham group with high risk for cardiovascular disorders: 35.5% and 17.8%, respectively.

Demographic characteristics were balanced between Scemblix and IS TKIs and between both arms within the imatinib and 2G TKI strata.

Of the 405 patients, 200 received Scemblix and 201 received IS TKIs. Of the 201 patients who received IS TKIs, 99 were treated with imatinib, 49 with nilotinib, 42 with dasatinib and 11 with bosutinib. 4 patients did not receive any treatment.

The median duration of treatment was 69.8 weeks (range: 0.7 to 107.7 weeks) in patients receiving Scemblix and 64.3 weeks (range: 1.3 to 103.1 weeks) in patients receiving IS TKIs. Within 48 weeks 90% of patients on Scemblix and 80.6% of patients on IS TKIs were still receiving treatment.

The study had 2 primary objectives for the assessment of major molecular response (MMR) at 48 weeks. One primary objective evaluated Scemblix compared to IS TKIs. The other primary objective evaluated Scemblix compared to IS TKIs within the imatinib stratum. A secondary objective evaluated MMR at 48 weeks, with Scemblix having been evaluated compared to IS TKIs within the 2G TKI stratum.

The key efficacy outcomes of ASC4FIRST are summarised in Table 4.

Table 4 Efficacy outcomes in newly diagnosed Ph+ CML-CP patients (ASC4FIRST)

80 mg Scemblix once daily		IS TKIs[1] 100-400 mg once or twice daily			Difference (95% CI)[2]	p-value
		All patients (N=204)	Imatinib stratum (N=102)	2G TKI stratum (N=102)		
MMR rate, % (95% CI) at 48 weeks						
All patients (N=201)	67.66 (60.72, 74.07)	49.02 (41.97, 56.10)			18.88 (9.59, 28.17)	<0.001[3]
Imatinib stratum (N=101)	69.31 (59.34, 78.10)		40.2 (30.61, 50.37)		29.55 (16.91, 42.18)	<0.001[4]
2G TKI stratum (N=100)	66 (55.85, 75.18)			57.84 (47.66, 67.56)	8.17 (-5.14, 21.47)	

Abbreviations: MMR, major molecular response (BCR::ABL1^{IS} ≤0.1%); IS TKIs, investigator-selected tyrosine kinase inhibitors; 2G TKIs, second-generation tyrosine kinase inhibitors; PRS TKI, pre-randomisation selection of TKI.

[1] IS TKIs include imatinib (400 mg once daily) and 2G TKIs, i.e. nilotinib (300 mg twice daily), dasatinib (100 mg once daily) or bosutinib (400 mg once daily).

[2] Estimated using a general risk difference stratified by baseline PRS TKI and ELTS risk groups.

[3] Adjusted p-value using one-sided Cochran-Mantel-Haenszel test, stratified by baseline PRS TKI and ELTS risk groups.

[4] Adjusted p-value using one-sided Cochran-Mantel-Haenszel test, stratified according to baseline ELTS risk groups.

The median time to MMR in patients who received Scemblix, IS TKIs, IS TKIs within the imatinib stratum and IS TKIs within the 2G TKI stratum was: 24.3 weeks (95% CI: 24.1 to 24.6 weeks), 36.4 weeks (95% CI: 36.1 to 48.6 weeks), 48.6 weeks (95% CI: 36.1 to 59.6 weeks) and 36.1 weeks (95% CI: 24.4 to 48.1 weeks).

BCR::ABL1 mutations were observed in 4% of patients treated with Scemblix and in 2% of patients treated with IS TKIs.

Pretreated Ph+ CML-CP

The clinical efficacy and safety of Scemblix in the treatment of patients with Ph+ CML-CP with treatment failure or intolerance to two or more tyrosine kinase inhibitors were investigated in the multicentre, randomised, active-controlled and open-label phase III study ASCEMBL.

Resistance to the last TKI was defined as:

- Lack of haematological or cytogenetic response at 3 months
- BCR::ABL1 on the International Scale [IS] >10% at 6 months or thereafter
- >65% Philadelphia-positive (Ph+) metaphases at 6 months or >35% at 12 months or thereafter
- Loss of complete haematological response (CHR), of partial cytogenetic response (PCyR), of complete cytogenetic response (CCyR) or of major molecular response (MMR) at any time
- New BCR::ABL1 mutations which potentially cause resistance to the study medicinal product or clonal evolution in Ph+ metaphases at any time.

Intolerance to the last TKI was defined as non-haematological toxicities unresponsive to optimal management or as haematological toxicities recurring after dose reduction to the lowest recommended dose.

In this study a total of 233 patients were randomised in a 2:1 ratio and stratified according to major cytogenetic response (MCyR) status at baseline for treatment with either 40 mg Scemblix twice daily (N=157) or 500 mg bosutinib once daily (N=76). There are only limited clinical data on the 80 mg once-daily dosage. Pharmacological analyses indicate that both dosages have a comparable clinical profile. Patients continued treatment until unacceptable toxicity or treatment failure occurred. Patients with a known T315I and/or V299L mutation at any time prior to study entry were not included in ASCEMBL.

Patients with Ph+ CML-CP previously treated with two or more TKIs were 51.5% female and 48.5% male with a median age of 52 years (range: 19 to 83 years). Of the 233 patients, 18.9% were 65 years or older, while 2.6% were 75 years or older. Patients were white (74.7%), Asian (14.2%) and black (4.3%). Of the 233 patients, 80.7% and 18% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, respectively. The proportion of patients who had previously received 2, 3, 4, 5 or more prior lines of TKIs were 48.1%, 31.3%, 14.6% and 6%, respectively. The median duration of treatment was 156 weeks (range: 0.1 to 256.3 weeks) for patients receiving Scemblix and 30.5 weeks (range: 1 to 239.3 weeks) for patients receiving bosutinib.

The primary endpoint of the study was MMR rate at 24 weeks and MMR rate at 96 weeks was the key secondary endpoint. MMR rate is defined as a BCR::ABL1 ratio ≤0.1% on the International Scale [IS]. Other secondary endpoints were complete cytogenetic response rate (CCyR) at 24 and 96 weeks, defined as no Philadelphia-positive metaphases in bone marrow with a minimum of 20 metaphases examined.

The most important efficacy results from the ASCEMBL study are summarised in Table 5.

Table 5 Efficacy results in Ph+ CML-CP patients previously treated with two or more tyrosine kinase inhibitors (ASCEMBL)

	40 mg Scemblix twice daily	**500 mg bosutinib once daily**	**Difference (95% CI)**	**p-value**
MMR rate, % (95% CI) at 24 weeks	**N=157** 25.48 (18.87, 33.04)	**N=76** 13.16 (6.49, 22.87)	12.24[1] (2.19, 22.30)	0.029[2]
MMR rate, % (95% CI) at 96 weeks	**N=157** 37.58 (29.99, 45.65)	**N=76** 15.79 (8.43, 25.96)	21.74[1] (10.53, 32.95)	0.001[2]
CCyR rate, % (95% CI) at 24 weeks	**N=103**[3] 40.78 (31.20, 50.9)	**N=62**[3] 24.19 (14.22, 36.74)	17.3 (3.62, 30.99)	Not formally tested

CCyR rate, % (95% CI) at 96 weeks	**N=103**[3] 39.81 (30.29, 49.92)	**N=62**[3] 16.13 (8.02, 27.67)	23.87 (10.30, 37.43)	Not formally tested

[1]On adjustment for the baseline major cytogenetic response status

[2]Cochran-Mantel-Haenszel two-sided test stratified by baseline major cytogenetic response status

[3]CCyR analysis based on patients who were not in CCyR at baseline

In the ASCEMBL study 12.7% of patients treated with Scemblix 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 Scemblix with or without any BCR::ABL1 mutation at baseline, respectively.

The clinical efficacy and safety of Scemblix in the treatment of patients with Ph+ CML-CP in whom treatment with a tyrosine kinase inhibitor failed or who did not tolerate such treatment were investigated in a cohort of the ongoing multicentre, single-arm, open-label, phase II dose escalation study ASC2ESCALATE.
The primary endpoint of the study is the MMR rate at 12 months in the second-line cohort (2L).
At the time of the interim analysis, 71 patients had been enrolled in the 2L cohort, with a median duration of Scemblix treatment of 19 weeks (range: 6.1 to 29.6 weeks). The MMR at 24 weeks was achieved in 42.9% of evaluable patients (N=28) in the 2L cohort (95% CI: 24.5% to 62.8%).

Elderly patients

Of the 556 patients treated with Scemblix in the ASC4FIRST, ASCEMBL and X2101 studies, 130 (23.4%) were aged 65 years or older and 31 (5.6%) were aged 75 years or older. No clear overall differences in the efficacy of Scemblix were observed between patients aged 65 years or older and younger patients.

Paediatric population

No studies on safety and efficacy have been performed in children and adolescents aged under 18 years.

Pharmacokinetics

Absorption

Asciminib is rapidly absorbed, with median maximum plasma levels (T_{max}) reached 2 to 3 hours after oral administration, independent of the dose. The geometric mean (geoCV%) of C_{max} at steady state is 1781 ng/ml (23%) and 793 ng/ml (49%) following administration of Scemblix at 80 mg once daily

and 40 mg twice daily, respectively. The geometric mean (geoCV%) of AUC_{tau} is 5262 ng*h/ml (48%) following administration of Scemblix at the 40 mg twice-daily dose. According to model calculations asciminib absorption is estimated at approximately 100%, while bioavailability is approximately 73%. Asciminib bioavailability may be reduced by co-administration of oral medicinal products containing hydroxypropyl-β-cyclodextrin as an excipient. Co-administration of multiple doses of itraconazole as oral solution containing hydroxypropyl-β-cyclodextrin at a total of 8 g per dose with a 40 mg dose of asciminib decreased asciminib AUC_{inf} by 40.2% in healthy subjects.

Food effect

Food consumption decreases asciminib bioavailability, with a high-fat meal having a higher impact on asciminib pharmacokinetics than a low-fat meal. Asciminib AUC and C_{max} are decreased by 62.3% and 68.2%, respectively, with a high-fat meal and by 30% and 34.8%, respectively, with a low-fat meal compared to the fasted state (see “Dosage/Administration” and “Interactions”).

Distribution

Asciminib apparent volume of distribution at steady state is 111 l based on a population pharmacokinetic analysis. Asciminib is mainly distributed to plasma, with a mean blood-to-plasma ratio of 0.58, independent of the dose. Asciminib is 97.3% bound to human plasma proteins, independent of the dose.

Metabolism

Asciminib is primarily metabolised via CYP3A4-mediated oxidation, UGT2B7-mediated glucuronidation and UGT2B17-mediated glucuronidation. Asciminib is the main circulating component in plasma (92.7% of the administered dose).

Elimination

Asciminib is mainly eliminated faecally, with only a minor proportion eliminated renally. 80% and 11% of the asciminib dose were recovered in the faeces and urine of healthy subjects, respectively, following oral administration of a single 80 mg dose of [^{14}C]-labelled asciminib. Faecal elimination of unchanged asciminib accounts for 56.7% of the administered dose. Asciminib is eliminated by biliary secretion via breast cancer resistant protein (BCRP).
The oral total clearance (CL/F) of asciminib is 6.31 l/hour based on a population pharmacokinetic analysis. The accumulation half-life of asciminib is 5.2 hours at dosages of 40 mg twice daily and 80 mg once daily.

Linearity/non-linearity

Asciminib exhibits a slight dose over-proportional increase in steady-state exposure (AUC and C_{max}) across the dose range of 10 to 200 mg administered once or twice daily.

The geometric mean accumulation ratio is approximately 2-fold, independent of the dose. Steady-state conditions are achieved within 3 days at the 40 mg twice-daily dose.

Pharmacokinetics in special populations

Asciminib systemic exposure is not affected by gender, age (20 to 88 years), ethnicity or body weight (42 to 184 kg) to any clinically relevant extent.

Hepatic impairment

A dedicated hepatic impairment study including 8 participants each with normal hepatic function, mild hepatic impairment (Child-Pugh A score 5 to 6), moderate hepatic impairment (Child -Pugh B score 7 to 9) or severe hepatic impairment (Child-Pugh C score 10 to 15) was conducted. Asciminib AUC_{inf} was increased by 22%, 3% and 66% in participants with mild, moderate and severe hepatic impairment, respectively, compared to participants with normal hepatic function following oral administration of a single 40 mg dose of Scemblix (see “Dosage/Administration”).

Renal impairment

A dedicated renal impairment study including 6 participants with normal renal function (absolute glomerular filtration rate [aGFR] ≥90 ml/min) and 8 participants with severe renal impairment not requiring dialysis (aGFR 15 to <30 ml/min) has been conducted. Asciminib AUC_{inf} and C_{max} are increased by 56% and 8%, respectively, in participants with severe renal impairment compared to participants with normal renal function following oral administration of a single 40 mg dose of Scemblix (see “Dosage/Administration”).
Population pharmacokinetic models show an increase in asciminib median steady-state AUC_{0-24h} by 11.5% in participants with mild to moderate renal impairment compared to participants with normal renal function.

Preclinical data

Asciminib was evaluated in safety pharmacology, repeated-dose toxicity, genotoxicity, reproductive toxicity and phototoxicity studies.

Safety pharmacology

Moderate cardiovascular effects (increased heart rate, decreased systolic pressure, decreased mean arterial pressure and decreased arterial pulse pressure) were observed in *in vivo* cardiac safety studies in dogs. No QTc prolongation was evident in dogs up to the highest asciminib free exposure of 6.3 micromolar.

Repeated-dose toxicity

Histopathological hepatic changes (centrilobular hepatocyte hypertrophy, slight bile duct hyperplasia, increased individual hepatocyte necrosis and diffuse hepatocellular hypertrophy) were seen in rats and monkeys. These changes occurred at AUC exposures either equivalent to (rats) or 8- to 18-fold

(dogs and monkeys) higher than those achieved in patients on 40 mg twice daily or 80 mg once daily. These changes were fully reversible.
Minimal mucosal hypertrophy/hyperplasia (increase in thickness of the mucosa with frequent elongation of villi) occurred in the duodenum of rats at AUC exposures 30-fold or 22-fold higher than those achieved in patients on 40 mg twice daily or 80 mg once daily, respectively. This change was fully reversible.
Minimal or slight hypertrophy of the adrenal gland and mild to moderate decreased vacuolation in the zona fasciculata occurred at AUC exposures either equivalent to (monkeys) or 19- to 13-fold (rats) higher than those achieved in patients on 40 mg twice daily or 80 mg once daily, respectively. These changes were fully reversible.

Carcinogenicity and mutagenicity

Asciminib did not show mutagenic, clastogenic or aneugenic potential *in vitro* or *in vivo*.
In a 2-year rat carcinogenicity study non-neoplastic proliferative changes in the form of ovarian Sertoli cell hyperplasia were observed in female animals at a dose of ≥30 mg/kg/day. Benign Sertoli cell tumours in the ovaries were observed in female rats at the highest tested dose of 66 mg/kg/day. AUC exposures to asciminib in female rats at a dosage of 66 mg/kg/day were generally 8-fold or 5-fold higher than in patients who received a dose of 40 mg twice daily or 80 mg once daily, respectively. However, no asciminib-related neoplastic or hyperplastic findings were observed in male rats at any dosage.
The clinical relevance of these findings is currently unknown.

Reproductive toxicity

In embryo-fetal development studies pregnant animals received oral doses of asciminib at 25, 150 and 600 mg/kg/day in rats and at 15, 50 and 300 mg/kg/day in rabbits during organogenesis. In embryo-fetal development studies a slight increase in fetal malformations (anasarca and cardiac malformations) and an increase in visceral and skeletal variants were observed in rats. An increased incidence of resorptions indicative of embryo-fetal mortality and a low incidence of cardiac malformations indicative of teratogenicity were observed in rabbits. In rats, at the fetal NOAEL of 25 mg/kg/day, the AUC exposures were equal to or less than those achieved in patients at the 40 mg twice-daily or 80 mg once-daily doses. In rabbits, at the fetal NOAEL of 15 mg/kg/day, the AUC exposures were equivalent to or below those achieved in patients at the 40 mg twice-daily or 80 mg once-daily doses.

Fertility

A slight effect on male sperm motility and sperm count was observed at doses of 200 mg/kg/day, likely at AUC exposures 19-fold or 13-fold higher than those achieved in patients at 40 mg twice daily and 80 mg once daily, respectively.

Phototoxicity

In mice asciminib showed dose-dependent phototoxic effects starting at 200 mg/kg/day. At the NOAEL of 60 mg/kg/day exposure based on C_{max} in plasma was 15-fold or 6-fold higher than the exposure in patients on 40 mg twice daily or 80 mg once daily, respectively.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

Do not store above 25°C.
Store in the original pack to protect the contents from moisture.
Keep out of the reach of children.

Swissmedic number

68441

Pack sizes

Pack of 60 film-coated tablets each containing 20 or 40 mg asciminib [A]

Marketing authorisation holder

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