

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Scemblix 20 mg film-coated tablets
Scemblix 40 mg film-coated tablets
Scemblix 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Scemblix 20 mg film-coated tablets

Each film-coated tablet contains 21.62 mg asciminib hydrochloride, equivalent to 20 mg asciminib.

Excipient with known effect

Each film-coated tablet contains 43 mg lactose monohydrate.

Scemblix 40 mg film-coated tablets

Each film-coated tablet contains 43.24 mg asciminib hydrochloride, equivalent to 40 mg asciminib.

Excipient with known effect

Each film-coated tablet contains 86 mg lactose monohydrate.

Scemblix 100 mg film-coated tablets

Each film-coated tablet contains 108.10 mg asciminib hydrochloride, equivalent to 100 mg asciminib.

Excipient with known effect

Each film-coated tablet contains 216 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Scemblix 20 mg film-coated tablets

Pale yellow, round, biconvex film-coated tablets with bevelled edges of approximately 6 mm diameter, debossed with company logo on one side and “20” on the other side.

Scemblix 40 mg film-coated tablets

Violet white, round, biconvex film-coated tablets with bevelled edges of approximately 8 mm diameter, debossed with company logo on one side and “40” on the other side.

Scemblix 100 mg film-coated tablets

Light red, round, biconvex film-coated tablets with bevelled edges of approximately 11 mm diameter, debossed with company logo on one side and “100” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Scemblix is indicated for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) (see section 5.1).

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

4.2 Posology and method of administration

Treatment should be initiated by a physician experienced in the diagnosis and treatment of patients with leukaemia.

Posology

Ph+ CML-CP

The recommended total daily dose of asciminib is 80 mg. Asciminib 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 (see section 4.4).

Patients switching from 40 mg twice daily to 80 mg once daily should start taking asciminib once daily approximately 12 hours after the last twice-daily dose, and then continue at 80 mg once daily.

Patients switching from 80 mg once daily to 40 mg twice daily should start taking asciminib twice daily approximately 24 hours after the last once-daily dose, and then continue at 40 mg twice daily at approximately 12-hour intervals.

The decision on the appropriate dosage regimen should be taken at the prescriber's discretion as necessary for the benefit of the patient.

Ph+ CML-CP with the T315I mutation in patients resistant to, intolerant to or ineligible for ponatinib

The recommended dose is 200 mg twice daily at approximately 12-hour intervals.

Use of the 100 mg film-coated tablets is restricted to patients with Ph+ CML-CP with the T315I mutation.

Missed dose

Once-daily dosage regimen:

If a dose is missed by less than 12 hours, it should be taken and the next dose should be taken as scheduled.

If a dose is missed by more than approximately 12 hours, it should be skipped and the next dose should be taken as scheduled.

Twice-daily dosage regimen:

If a dose is missed by less than 6 hours, it should be taken and the next dose should be taken as scheduled.

If a dose is missed by more than approximately 6 hours, it should be skipped and the next dose should be taken as scheduled.

Treatment duration

Treatment with asciminib should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

Dose adjustments for adverse reactions

Ph+ CML-CP

The starting dose is 80 mg once daily or 40 mg twice daily, while the reduced dose is 40 mg once daily or 20 mg twice daily, respectively. The dose can be modified based on individual safety and tolerability as shown in Table 1. Asciminib should be permanently discontinued in patients unable to tolerate a dose of 40 mg once daily or 20 mg twice daily.

Ph+ CML-CP with the T315I mutation in patients resistant to, intolerant to or ineligible for ponatinib

The starting dose is 200 mg twice daily, while the reduced dose is 160 mg twice daily. The dose can be modified based on individual safety and tolerability as shown in Table 1. Asciminib should be permanently discontinued in patients unable to tolerate a dose of 160 mg twice daily.

Table 1 Asciminib dose modification schedule for the management of adverse reactions

Adverse reaction	Dose modification
Thrombocytopenia and/or neutropenia	
ANC $<1.0 \times 10^9/l$ and/or PLT $<50 \times 10^9/l$	Withhold asciminib until resolved to ANC $\geq 1 \times 10^9/l$ and/or PLT $\geq 50 \times 10^9/l$. If resolved: • Within 2 weeks: resume at starting dose. • After more than 2 weeks: resume at reduced dose. For recurrent severe thrombocytopenia and/or neutropenia, withhold asciminib until resolved to ANC $\geq 1 \times 10^9/l$ and PLT $\geq 50 \times 10^9/l$, then resume at reduced dose.
Asymptomatic amylase and/or lipase elevation	
Elevation $>2.0 \times \text{ULN}$	Withhold asciminib until resolved to $<1.5 \times \text{ULN}$. • If resolved: resume at reduced dose. If events reoccur at reduced dose, permanently discontinue. • If not resolved: permanently discontinue. Perform diagnostic tests to exclude pancreatitis.
Non-haematological adverse reactions	
Grade 3 or higher ¹ adverse reactions	Withhold asciminib until resolved to grade 1 or lower. • If resolved: resume at a reduced dose. • If not resolved: permanently discontinue.

ANC: absolute neutrophil count; PLT: platelets; ULN: upper limit of normal
¹Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 4.03.

Special populations

Elderly

No dose adjustment is required in patients aged 65 years or above.

Renal impairment

No starting dose adjustment is required in patients with mild or moderate renal impairment at all recommended doses and in patients with severe renal impairment at the 80 mg total daily dose. No clinical data are available in patients with severe renal impairment at the 200 mg asciminib twice daily dose. Therefore, no recommendations for dose adjustment can be given. Caution should be exercised in patients with severe renal impairment receiving the 200 mg twice daily dose (see sections 4.4 and 5.2).

Hepatic impairment

No starting dose adjustment is required in patients with mild or moderate hepatic impairment at all recommended doses and in patients with severe hepatic impairment at the 80 mg total daily dose. No clinical data are available in patients with severe hepatic impairment at the 200 mg asciminib twice daily dose. Therefore, no recommendations for dose adjustment can be given. Caution should be exercised in patients with severe hepatic impairment receiving the 200 mg twice daily dose (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Scemblix in paediatric patients aged below 18 years have not been established. No data are available.

Method of administration

Scemblix is for oral use. The film-coated tablets should be swallowed whole with a glass of water and should not be broken, crushed or chewed.

The tablets should be taken orally without food. Food consumption should be avoided for at least 2 hours before and 1 hour after taking asciminib (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Ph+ CML-CP with the T315I mutation in patients resistant to, intolerant to or ineligible for ponatinib

In patients with Ph+ CML-CP with the T315I mutation treated with the 200 mg twice-daily dose, close monitoring should be considered since there are uncertainties regarding a potential increase of safety risks compared to the 80 mg total daily dose due to the small dataset of 48 patients, of whom 34 had a treatment intensity of >90%.

Myelosuppression

Thrombocytopenia, neutropenia and anaemia occurred in patients receiving asciminib. Severe (NCI CTCAE grade 3 or 4) thrombocytopenia and neutropenia were reported during treatment with asciminib (see section 4.8). Myelosuppression was generally reversible and managed by temporarily withholding treatment. Complete blood counts should be performed every two weeks for the first 3 months of treatment and then monthly thereafter, or as clinically indicated. Patients should be monitored for signs and symptoms of myelosuppression.

Based on the severity of thrombocytopenia and/or neutropenia, the dose should be temporarily withheld, reduced or permanently discontinued as described in Table 1 (see section 4.2).

Pancreatic toxicity

Pancreatitis and asymptomatic elevations of serum lipase and amylase, including severe reactions, occurred in patients receiving asciminib (see section 4.8).

Serum lipase and amylase levels should be assessed monthly during treatment with asciminib, or as clinically indicated. Patients should be monitored for signs and symptoms of pancreatic toxicity. More frequent monitoring should be performed in patients with a history of pancreatitis. If serum lipase and amylase elevations are accompanied by abdominal symptoms, treatment should be temporarily withheld and appropriate diagnostic tests should be considered to exclude pancreatitis (see section 4.2).

Based on the severity of serum lipase and amylase elevations, the dose should be temporarily withheld, reduced or permanently discontinued as described in Table 1 (see section 4.2).

QT prolongation

QT prolongation occurred in patients receiving asciminib (see section 4.8).

It is recommended that an electrocardiogram is performed prior to the start of treatment with asciminib, and monitored during treatment as clinically indicated. Hypokalaemia and hypomagnesaemia should be corrected prior to asciminib administration and monitored during treatment as clinically indicated.

Caution should be exercised when administering asciminib at a total daily dose of 80 mg concomitantly with medicinal products with known risk of *torsades de pointes*.

Concomitant administration of asciminib at 200 mg twice daily with medicinal products with a known risk of *torsades de pointes* should be avoided (see sections 4.5 and 5.1).

Hypertension

Hypertension, including severe hypertension, occurred in patients receiving asciminib (see section 4.8).

Hypertension and other cardiovascular risk factors should be monitored regularly and managed using the standard therapies during treatment with asciminib.

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 asciminib. HBV carriers who require treatment with asciminib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Special populations

Renal impairment

In the absence of clinical data, caution should be exercised when administering asciminib at 200 mg twice daily in patients with severe renal impairment (see sections 4.2 and 5.2).

Hepatic impairment

In the absence of clinical data, caution should be exercised when administering asciminib at 200 mg twice daily in patients with severe hepatic impairment (see sections 4.2 and 5.2).

Potential for lower efficacy with the 80 mg once-daily regimen compared with the 40 mg twice-daily regimen

Equivalent efficacy of the different posologies has not been formally demonstrated in clinical studies. Clinical, pharmacokinetic and exposure-response modelling data in patients with Ph+ CML-CP previously treated with two or more TKIs suggest that the 40 mg twice-daily dose regimen might be more effective than the 80 mg once-daily dose regimen (see sections 5.1 and 5.2).

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products with known risk of *torsades de pointes*

Caution should be exercised during concomitant administration of asciminib at a total daily dose of 80 mg and medicinal products with known risk of *torsades de pointes*, including, but not limited to, bepridil, chloroquine, clarithromycin, halofantrine, haloperidol, methadone, moxifloxacin or pimozone.

Concomitant administration of asciminib 200 mg twice daily with medicinal products with a known risk of *torsades de pointes* should be avoided (see section 5.1).

Medicinal products that may increase asciminib plasma concentrations

Strong CYP3A4 inhibitors

Caution should be exercised during concomitant administration of asciminib at 200 mg twice daily with strong CYP3A4 inhibitors, including, but not limited to, clarithromycin, telithromycin, troleandomycin, itraconazole, ketoconazole, voriconazole, ritonavir, indinavir, nelfinavir or saquinavir. Dose adjustment of asciminib is not required.

Medicinal products that may decrease asciminib plasma concentrations

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 asciminib dose of 40 mg. Co-administration of a strong CYP3A4 inducer (phenytoin) decreased asciminib AUC_{inf} and C_{max} by 34% and 22%, respectively, in healthy subjects receiving a single asciminib dose of 200 mg.

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

Medicinal products that may have their plasma concentrations altered by asciminib

CYP3A4 substrates with narrow therapeutic index

Co-administration of asciminib with a CYP3A4 substrate (midazolam) increased midazolam AUC_{inf} and C_{max} by 28% and 11%, respectively, in healthy subjects receiving asciminib 40 mg twice daily.

Caution should be exercised during concomitant administration of asciminib at all recommended doses with CYP3A4 substrates known to have a narrow therapeutic index, including, but not limited to, the CYP3A4 substrates fentanyl, alfentanil, dihydroergotamine or ergotamine (see section 5.2). Dose adjustment of asciminib is not required.

CYP2C9 substrates

Co-administration of asciminib with a CYP2C9 substrate (warfarin) increased S-warfarin AUC_{inf} and C_{max} by 41% and 8%, respectively, in healthy subjects receiving asciminib 40 mg twice daily.

Caution should be exercised during concomitant administration of asciminib at a total daily dose of 80 mg with CYP2C9 substrates known to have a narrow therapeutic index, including, but not limited to, phenytoin or warfarin (see section 5.2). Dose adjustment of asciminib is not required.

Concomitant administration of asciminib at 200 mg twice daily with CYP2C9-sensitive substrates and CYP2C9 substrates known to have a narrow therapeutic index should be avoided and alternative medicines should be considered (see section 5.2). If co-administration cannot be avoided, the CYP2C9 substrate dose should be reduced. If co-administration with warfarin cannot be avoided, the frequency of international normalised ratio (INR) monitoring should be increased as the anticoagulant effect of warfarin may be enhanced.

Substrates of BCRP or OATP1B

Co-administration of asciminib with a BCRP and OATP1B substrate (rosuvastatin) increased rosuvastatin AUC_{inf} 2.18-fold and C_{max} 2.82-fold in healthy subjects receiving 80 mg once daily.

Co-administration of asciminib at 80 mg once daily with an OATP1B, CYP3A4 and P-gp substrate (atorvastatin) increased atorvastatin AUC_{inf} 1.14-fold and C_{max} 1.24-fold in healthy subjects. Clinically relevant interactions between asciminib and OATP1B substrates are unlikely to occur.

Caution should be exercised during concomitant administration of asciminib at all recommended doses with BCRP substrates, including, but not limited to, sulfasalazine, methotrexate and rosuvastatin. The summary of product characteristics (SmPC) of the relevant medicinal products should be consulted for dose reduction recommendations.

P-gp substrates with narrow therapeutic index

Co-administration of asciminib with a P-gp substrate (digoxin) increased digoxin C_{max} 1.30-fold and AUC_{inf} 1.18-fold in healthy subjects receiving 80 mg once daily.

Caution should be exercised during concomitant administration of asciminib at 200 mg twice daily with P-gp substrates known to have a narrow therapeutic index, including but not limited to digoxin, dabigatran, and colchicine. Dose adjustment of asciminib is not required. The summary of product characteristics (SmPC) of the relevant medicinal products should be consulted for dose reduction recommendations.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

The pregnancy status of women of childbearing potential should be verified prior to starting treatment with asciminib.

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

Pregnancy

There are no or limited amount of data from the use of asciminib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Asciminib is not recommended during pregnancy and in women of childbearing potential not using contraception. The patient should be advised of a potential risk to the foetus if asciminib is used during pregnancy or if the patient becomes pregnant while taking asciminib.

Breast-feeding

It is unknown whether asciminib/metabolites are excreted in human milk. There are no data on the effects of asciminib on the breast-fed newborn/infant or on milk production. Because of the potential for 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.

Fertility

There are no data on the effect of asciminib on human fertility. In rat fertility studies, asciminib did not affect reproductive function in male and female rats. However, adverse effects on sperm motility and count were observed in rats at doses of 200 mg/kg/day (see section 5.3). The relevance for humans is not known.

4.7 Effects on ability to drive and use machines

Asciminib has no or negligible influence on the ability to drive and use machines. However, it is recommended that patients experiencing dizziness, fatigue or other undesirable effects (see section 4.8) with a potential impact on the ability to drive or use machines safely should refrain from these activities as long as the undesirable effects persist.

4.8 Undesirable effects

Summary of the safety profile

Ph+ CML (ASCEMBL, X2101, ASC4FIRST studies)

The most common adverse reactions of any grade (incidence $\geq 20\%$) in patients receiving asciminib were musculoskeletal pain (34.4%), thrombocytopenia (28.1%), fatigue (25.4%), upper respiratory tract infections (24.8%), headache (22.8%), neutropenia (21.8%), arthralgia (20.7%) and diarrhoea (20.7%).

The most common adverse reactions of $\geq$ grade 3 (incidence $\geq 5\%$) in patients receiving asciminib were thrombocytopenia (16.5%), neutropenia (13.8%), increased pancreatic enzymes (9.4%) and hypertension (9.2%).

Serious adverse reactions occurred in 9.9% of patients receiving asciminib. The most frequent serious adverse reactions (incidence $\geq 1\%$) were pleural effusion (1.6%), lower respiratory tract infections (1.6%), thrombocytopenia (1.3%), pancreatitis (1.1%) and pyrexia (1.1%).

Ph+ CML-CP with the T315I mutation in patients resistant to, intolerant to or ineligible for ponatinib (X2101 study)

The safety dataset for the 200 mg twice-daily dose is limited to 48 patients, of whom 34 had a treatment intensity of $>90\%$.

The most common adverse reactions of any grade (incidence $\geq 20\%$) in patients receiving asciminib were musculoskeletal pain (41.7%), fatigue (35.4%), increased pancreatic enzymes (31.3%), diarrhoea (27.1%), nausea (27.1%), increased hepatic enzymes (25.0%), arthralgia (25.0%), cough (22.9%), thrombocytopenia (20.8%), vomiting (20.8%) and headache (20.8%).

The most common adverse reactions of $\geq$ grade 3 (incidence $\geq 5\%$) in patients receiving asciminib were increased pancreatic enzymes (22.9%), thrombocytopenia (16.7%), neutropenia (12.5%), increased hepatic enzymes (10.4%), hypertension (8.3%), anaemia (6.3%), vomiting (6.3%) and abdominal pain (6.3%).

Serious adverse reactions occurred in 12.5% of patients receiving asciminib. The most frequent serious adverse reactions (incidence $\geq 1\%$) were abdominal pain (4.2%), vomiting (4.2%), lower respiratory tract infections (4.2%), constipation (2.1%), headache (2.1%), non-cardiac chest pain (2.1%) and pleural effusion (2.1%).

Tabulated list of adverse reactions

The overall safety profile of asciminib has been evaluated in 556 patients with Ph+ CML in chronic (CP) and accelerated (AP) phases in the pivotal phase III study A2301 (ASCEMBL) and the phase I study X2101, and with newly diagnosed Ph+ CML-CP in the pivotal phase III study J12301 (ASC4FIRST). In ASCEMBL (N=156), patients received asciminib as monotherapy at a dose of 40 mg twice daily. In X2101 (N=200), patients received asciminib as monotherapy at doses ranging from 10 to 200 mg twice daily and 80 to 200 mg once daily. Of these patients, 48 with the T315I mutation received asciminib 200 mg twice daily. In ASC4FIRST (N=200), patients received asciminib as monotherapy at a dose of 80 mg once daily. In the pooled dataset, the median duration of exposure to asciminib was 123.29 weeks (range: 0.1 to 439 weeks).

Adverse reactions from clinical studies (Table 2) are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is based on the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\,000$ to $< 1/100$); rare ($\geq 1/10\,000$ to $< 1/1\,000$); very rare ($< 1/10\,000$).

Table 2 Adverse reactions observed with asciminib in clinical studies

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

¹ Upper respiratory tract infection includes: upper respiratory tract infection, nasopharyngitis, pharyngitis and rhinitis.

² Lower respiratory tract infections include: pneumonia, bronchitis and tracheobronchitis.

³ Thrombocytopenia includes: thrombocytopenia and platelet count decreased.

⁴ Neutropenia includes: neutropenia and neutrophil count decreased.

⁵ Anaemia includes: anaemia, haemoglobin decreased and normocytic anaemia.

⁶ Hypothyroidism includes hypothyroidism, autoimmune thyroiditis, blood thyroid stimulating hormone increased, autoimmune hypothyroidism and primary hypothyroidism.

⁷ Dyslipidaemia includes: hypertriglyceridaemia, blood cholesterol increased, hypercholesterolaemia, blood triglycerides increased, hyperlipidaemia and dyslipidaemia.

⁸ Hypertension includes: hypertension and blood pressure increased.

⁹ Pancreatic enzymes increased includes: lipase increased, amylase increased and hyperlipasaemia.

¹⁰ Abdominal pain includes: abdominal pain and abdominal pain upper.

¹¹ Pancreatitis includes: pancreatitis and pancreatitis acute.

¹² Hepatic enzymes increased includes: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, transaminases increased and hypertransaminasaemia.

¹³ Blood bilirubin increased includes: blood bilirubin increased, bilirubin conjugated increased and hyperbilirubinaemia.

¹⁴ Rash includes: rash, rash maculopapular and rash pruritic.

¹⁵ Musculoskeletal pain includes: pain in extremity, back pain, myalgia, bone pain, musculoskeletal pain, neck pain, musculoskeletal chest pain and musculoskeletal discomfort.

¹⁶ Fatigue includes: fatigue and asthenia.

¹⁷ Oedema includes: oedema and oedema peripheral.

¹⁸ Pyrexia includes: pyrexia and body temperature increased.

Description of selected adverse reactions

Myelosuppression

Thrombocytopenia occurred in 28.1% of patients receiving asciminib, with grade 3 and 4 reactions reported in 7% and 9.5% of patients, respectively. Among the patients with thrombocytopenia $\geq$ grade 3, the median time to first occurrence of reactions was 6 weeks (range: 0.14 to 64.14 weeks), with median duration of any occurring reaction of 1.57 weeks (95% CI, range: 1.14 to 2 weeks). 2% of patients receiving asciminib permanently discontinued due to thrombocytopenia, while asciminib was temporarily withheld in 12.6% of patients due to the adverse reaction.

Thrombocytopenia occurred in 20.8% of patients with the T315I mutation receiving asciminib, with grade 3 and 4 reactions reported in 16.7% of patients. Among the patients with thrombocytopenia $\geq$ grade 3, the median time to first occurrence of reactions was 8.36 weeks (range: 1.43 to 38.43 weeks), with median duration of any occurring reaction of 4.29 weeks (95% CI, range: 1.71 to 5.71 weeks). 2.1% of patients with the T315I mutation receiving asciminib permanently discontinued due to thrombocytopenia, while asciminib was temporarily withheld in 6.3% of patients due to the adverse reaction.

Neutropenia occurred in 21.8% of patients receiving asciminib, with grade 3 and 4 reactions reported in 7.6% and 6.3% of patients, respectively. Among the patients with neutropenia $\geq$ grade 3, the median time to first occurrence of reactions was 7.14 weeks (range: 0.14 to 180.14 weeks), with median duration of any occurring reaction of 1.86 weeks (95% CI, range: 1.29 to 2 weeks). 1.3% of patients receiving asciminib permanently discontinued due to neutropenia, while asciminib was temporarily withheld in 9.4% of patients due to the adverse reaction.

Neutropenia occurred in 16.7% of patients with the T315I mutation receiving asciminib, with grade 3 and 4 reactions reported in 12.5% of patients. Among the patients with neutropenia $\geq$ grade 3, the median time to first occurrence of reactions was 4.14 weeks (range: 0.14 to 16.57 weeks), with median duration of any occurring reaction of 2.86 weeks (95% CI, range: 1.57 to 4.57 weeks). 2.1% of patients with the T315I mutation receiving asciminib permanently discontinued due to neutropenia, while asciminib was temporarily withheld in 2.1% of patients due to the adverse reaction.

Anaemia occurred in 12.9% of patients receiving asciminib, with grade 3 reactions occurring in 4.1% of patients. Among the patients with anaemia $\geq$ grade 3, the median time to first occurrence of reactions was 24.14 weeks (range: 0.14 to 207 weeks), with median duration of any occurring reaction of 0.86 weeks (95% CI, range: 0.29 to 1.71 weeks). Asciminib was temporarily withheld in 0.5% of patients due to the adverse reaction.

Anaemia occurred in 10.4% of patients with the T315I mutation receiving asciminib, with grade 3 and 4 reactions reported in 6.3% of patients. Among the patients with anaemia $\geq$ grade 3, the median time to first occurrence of reactions was 38.43 weeks (range: 24.14 to 131 weeks), with median duration of any occurring reaction of 0.86 weeks (95% CI, range: 0.14 to NE [not estimable] weeks).

Pancreatic toxicity

Pancreatitis occurred in 2% of patients receiving asciminib, with grade 3 reactions occurring in 1.1% of patients. 0.5% of patients receiving asciminib permanently discontinued due to pancreatitis, while asciminib was temporarily withheld in 1.1% of patients due to the adverse reaction. Asymptomatic elevations of serum lipase and amylase occurred in 19.8% of patients receiving asciminib, with grade 3 and 4 reactions occurring in 7.4% and 2% of patients, respectively. Of the patients with elevation of pancreatic enzymes, asciminib was permanently discontinued in 2% of patients due to the adverse reaction.

Pancreatitis occurred in 2.1% of patients with the T315I mutation receiving asciminib. Elevations of serum lipase and amylase occurred in 31.3% of patients with the T315I mutation receiving asciminib, with grade 3 and 4 reactions occurring in 22.9% of patients. 2.1% of patients with the T315I mutation receiving asciminib permanently discontinued due to elevation of pancreatic enzymes, while asciminib was temporarily withheld in 16.7% of patients due to the adverse reaction.

QT prolongation

Electrocardiogram QT prolongation occurred in 0.9% of patients receiving asciminib. In the ASCEMBL clinical study, one patient had a prolonged QTcF greater than 500 milliseconds (ms) together with more than 60 ms QTcF increase from baseline, and one patient had prolonged QTcF with more than 60 ms QTcF increase from baseline.

Hypertension

Hypertension occurred in 17.1% of patients receiving asciminib, with grade 3 and 4 reactions reported in 9% and 0.2% of patients, respectively. Among the patients with hypertension $\geq$ grade 3, the median time to first occurrence of reactions was 40.14 weeks (range: 0.14 to 365 weeks). Asciminib was temporarily withheld in 0.9% of patients due to the adverse reaction.

Hypertension occurred in 14.6% of patients with the T315I mutation receiving asciminib, with grade 3 and 4 reactions reported in 8.3% of patients. Among the patients with hypertension $\geq$ grade 3, the median time to first occurrence of reactions was 32.64 weeks (range: 11.14 to 277.3 weeks), with median duration of any occurring reaction of 7.57 weeks (95% CI, range: 2.14 to NE weeks).

Laboratory abnormalities

In the ASCEMBL study, decrease in phosphate levels occurred as a laboratory abnormality in 17.9% (all grades) and 7.1% (grade 3/4) of 156 patients receiving asciminib at 40 mg twice daily. In the ASC4FIRST study, decrease in phosphate levels based on normal ranges occurred as a laboratory abnormality in 20.5% (all grades) of 200 patients receiving asciminib at 80 mg once daily.

In the X2101 study, decrease in phosphate levels occurred as a laboratory abnormality in 47.9% (all grades) and 8.3% (grade 3/4) of 48 patients receiving asciminib at 200 mg twice daily.

Increases in ALT, AST and bilirubin levels occurred as laboratory abnormalities in 50%, 37.5% and 25% (all grades) of 48 patients receiving asciminib at 200 mg twice daily, respectively. Among these patients, increased ALT $\geq$ grade 3 events and increased AST $\geq$ grade 3 events were reported in 8.3% and 2.1% of patients, respectively.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

In clinical studies, asciminib has been administered at doses up to 280 mg twice daily with no evidence of increased toxicity.

General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EA06

Mechanism of action

Asciminib is a 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 pocket.

Pharmacodynamic effects

In vitro, asciminib inhibits the tyrosine kinase activity of ABL1 at mean IC₅₀ values below 3 nanomolar. In patient-derived cancer cells, asciminib specifically inhibits the proliferation of cells harbouring BCR::ABL1 with IC₅₀ 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 IC₅₀ 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.

Cardiac electrophysiology

Asciminib treatment is associated with an exposure-related prolongation of the QT interval.

The correlation between asciminib concentration and the estimated mean change from baseline of the QT interval with Fridericia's correction (Δ QTcF) was evaluated in 239 patients with Ph+ CML or Ph+ acute lymphoblastic leukaemia (ALL) receiving asciminib at doses ranging from 10 to 280 mg twice daily and 80 to 200 mg once daily. The estimated mean Δ QTcF was 3.35 ms (upper bound of 90% CI: 4.43 ms) for the asciminib 40 mg twice-daily dose, 3.64 ms (upper bound of 90% CI: 4.68 ms) for the 80 mg once daily dose and 5.37 ms (upper bound of 90% CI: 6.77 ms) for the 200 mg twice-daily dose (see section 4.4).

Clinical efficacy and safety

Newly diagnosed Ph+ CML-CP

The clinical efficacy and safety of asciminib in the treatment of patients with newly diagnosed Philadelphia chromosome-positive myeloid leukaemia in chronic phase (Ph+ CML-CP) were evaluated 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 asciminib 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 according to European Treatment and Outcome Study (EUTOS) long-term survival (ELTS) risk group (low, intermediate, high) and pre-randomisation selection of TKI (imatinib or 2G TKI stratum). Patients continued 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 Caucasian (53.8%), Asian (44.4%), Black (1%) and 0.7% unknown. The 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.

The demographic characteristics were balanced across asciminib and IS TKIs, as well as across the two arms within the imatinib and 2G TKI strata.

Of the 405 patients, 200 received asciminib, while 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. Four patients did not receive any treatment.

The median duration of the randomised treatment was 26.6 months (range: 0.16 to 35.58 months) for patients receiving asciminib and 25 months (range: 0.3 to 34.53 months) for patients receiving IS TKIs. By 96 weeks, 81.6% of patients on asciminib and 60.3% of patients on IS TKIs were still receiving treatment.

Results

The study had multiple primary objectives assessing major molecular response (MMR) at 48 weeks. One primary objective evaluated asciminib compared to IS TKIs. The other primary objective evaluated asciminib compared to IS TKIs within the imatinib stratum. The key secondary objective evaluated MMR at 96 weeks for asciminib compared both to IS-TKIs and to IS-TKIs within the imatinib stratum. Secondary objectives evaluated MMR at 48 and 96 weeks for asciminib compared to IS TKIs within the 2G TKI stratum.

The main efficacy outcomes from the ASC4FIRST study are summarised in Table 3.

Table 3 Efficacy results in newly diagnosed Ph+ CML-CP patients (ASC4FIRST)

Asciminib 80 mg once daily		IS TKIs ¹			Difference (95% CI) ²	p-value
		100-400 mg once or twice daily				
		All patients (N=204)	Imatinib stratum (N=102)	2G TKIs 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 TKIs stratum (N=100)	66 (55.85, 75.18)			57.84 (47.66, 67.56)	8.17 (-5.14, 21.47)	Not formally tested
MMR rate, % (95% CI) at 96 weeks						
All patients (N=201)	74.13 (67.50, 80.03)	51.96 (44.87, 58.99)			22.42 (13.55, 31.29)	<0.001 ³
Imatinib stratum (N=101)	76.24 (66.74, 84.14)		47.06 (37.10, 57.20)		29.68 (17.57, 41.79)	<0.001 ⁴
2G TKIs stratum (N=100)	72 (62.13, 80.52)			56.86 (46.68, 66.63)	15.14 (2.32, 27.95)	Not formally tested

Abbreviations: MMR, major molecular response (BCR::ABL1IS ≤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 common risk difference stratified by PRS TKI and baseline ELTS risk groups.

³ Adjusted p-value using a Cochran-Mantel-Haenszel 1-sided test stratified by PRS TKI and baseline ELTS risk groups.

⁴ Adjusted p-value using a Cochran-Mantel-Haenszel 1-sided test stratified by baseline ELTS risk groups.

The median time to MMR in patients who received asciminib, 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 to 60.0 weeks) and 36.1 weeks (95% CI: 24.4 to 48.1 weeks), respectively.

MMR rates at 96 weeks by ELTS risk group in patients receiving asciminib, IS TKIs, IS TKIs within the imatinib stratum, and IS TKIs within the 2G TKIs stratum were: 80.3%, 64.8%, 62.5% and 67.2% for low risk, respectively; 66.1%, 35.1%, 23.3% and 48.2% for intermediate risk, respectively; 60.9%, 22.7%, 12.5% and 28.6% for high risk, respectively.

By 96 weeks, MR4.0 achieved by patients receiving asciminib, IS TKIs, IS TKIs within the imatinib stratum, and IS TKIs within the 2G TKIs stratum was: 52.7%, 34.3%, 28.4% and 40.2%, respectively. By 96 weeks, MR4.5 achieved by patients receiving asciminib, IS TKIs, IS TKIs within the imatinib stratum and IS TKIs within 2G TKIs stratum was: 36.3%, 21.6%, 15.7% and 27.5%, respectively.

The hazard ratio of time to discontinuation of study treatment due to adverse events (TTDAE) for patients receiving asciminib versus 2G TKIs and asciminib versus imatinib is 0.46 (95% CI: 0.215, 0.997) and 0.38 (95% CI: 0.178, 0.818), respectively. The probability of discontinuation due to AEs during the first 24 months of treatment was 5.5% (95% CI: 2.9, 9.3), 13.1% (95% CI: 7.4, 20.6) and 12.7% (95% CI: 7.1, 20) for patients receiving asciminib, imatinib and 2G TKIs, respectively.

Ph+ CML-CP previously treated with two or more TKIs

ASCEMBL

The clinical efficacy and safety of asciminib in the treatment of patients with Ph+ CML-CP with treatment failure or intolerance to two or more tyrosine kinase inhibitors were evaluated in the multicentre, randomised, active-controlled and open-label phase III study ASCEMBL. Resistance to last TKI was defined as any of the following: failure to achieve either haematological or cytogenetic response at 3 months; BCR::ABL1 (on the International Scale, IS) >10% at 6 months or thereafter; >65% Ph+ metaphases at 6 months or >35% at 12 months or thereafter; loss of complete haematological response (CHR), partial cytogenetic response (PCyR), complete cytogenetic response (CCyR) or major molecular response (MMR) at any time; new BCR::ABL1 mutations which potentially cause resistance to study medicinal product or clonal evolution in Ph+ metaphases at any time. Intolerance to 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 to receive either asciminib 40 mg twice daily (N=157) or bosutinib 500 mg once daily (N=76). Patients with known presence of T315I and/or V299L mutations at any time prior to study entry were not included in ASCEMBL. Patients continued treatment until unacceptable toxicity or treatment failure occurred.

Patients with Ph+ CML-CP previously treated with two or more TKIs were 51.5% female and 48.5% male, with median age 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 Caucasian (74.7%), Asian (14.2%) and Black (4.3%). Of the 233 patients, 80.7% and 18% had Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, respectively. 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 the randomised treatment was 156 weeks (range: 0.1 to 256.3 weeks) for patients receiving asciminib and 30.5 weeks (range: 1 to 239.3 weeks) for patients receiving bosutinib.

Results

The primary endpoint of the study was MMR rate at 24 weeks and the key secondary endpoint was MMR rate at 96 weeks. MMR is defined as BCR::ABL1 IS ratio $\leq 0.1\%$. Other secondary endpoints were CCyR rate at 24 and 96 weeks, defined as no Philadelphia-positive metaphases in bone marrow with a minimum of 20 metaphases examined.

The main efficacy outcomes from the ASCEMBL study are summarised in Table 4.

Table 4 Efficacy results in Ph+ CML-CP patients previously treated with two or more tyrosine kinase inhibitors (ASCEMBL)

	Asciminib 40 mg twice daily	Bosutinib 500 mg once daily	Difference (95% CI)¹	p-value
	N=157	N=76		
MMR rate, % (95% CI) at 24 weeks	25.48 (18.87, 33.04)	13.16 (6.49, 22.87)	12.24 (2.19, 22.30)	0.029 ²
MMR rate, % (95% CI) at 96 weeks	37.58 (29.99, 45.65)	15.79 (8.43, 25.96)	21.74 (10.53, 32.95)	0.001 ²
	N=103³	N=62³		
CCyR rate, % (95% CI) at 24 weeks	40.78 (31.20, 50.90)	24.19 (14.22, 36.74)	17.30 (3.62, 30.99)	Not formally tested
CCyR rate, % (95% CI) at 96 weeks	39.81 (30.29, 49.92)	16.13 (8.02, 27.67)	23.87 (10.3, 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

The primary and key secondary endpoints were the only ones formally tested for statistical significance according to protocol.

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.

The Kaplan-Meier estimated proportion of patients receiving asciminib and maintaining MMR for at least 120 weeks was 97% (95% CI: 88.6, 99.2).

ASC4OPT

The clinical efficacy and safety of asciminib 40 mg twice daily and 80 mg once daily in patients with Ph+ CML-CP previously treated with two or more TKIs were evaluated in a multicentre, open-label phase III, treatment optimisation study A2302 (ASC4OPT). In this study 169 patients were randomised 1:1 to either 40 mg twice daily (n=85) or 80 mg once daily (n=84). The primary objective was to estimate overall MMR of asciminib at 48 weeks. Results are shown in Table 5.

Table 5 Efficacy results in Ph+ CML-CP patients previously treated with two or more tyrosine kinase inhibitors (ASC4OPT)

	Asciminib 40 mg twice daily and 80 mg once daily	Asciminib 40 mg twice daily	Asciminib 80 mg once daily	Difference (95%CI)²	p-value
	N=169	N=85	N=84		
MMR rate, % (95% CI) ¹ at 48 weeks	38.46 (31.09, 46.24)	42.35 (31.70, 53.55)	34.52 (24.48, 45.69)	-7.83 (-22.45, 6.79)	Not formally tested

¹ Clopper-Pearson 95% CI for response rates
² Unstratified Wald 95% CI

Ph+ CML-CP with the T315I mutation in patients resistant to, intolerant to or ineligible for ponatinib

The clinical efficacy and safety of asciminib in the treatment of patients with Ph+ CML-CP with the T315I mutation were assessed in the first-in-human, multicentre, open-label phase I study X2101.

This study included patients with Ph+ CML-CP with the T315I mutation who received asciminib at different doses. Patients (N=48) with Ph+ CML-CP with the T315I mutation received asciminib at a dose of 200 mg twice daily. Of these 48 patients, 29 were previously treated with ponatinib and 19 were ponatinib-naïve. Patients continued treatment until unacceptable toxicity or treatment failure occurred.

Patients with Ph+ CML-CP with the T315I mutation who received asciminib at a dose of 200 mg twice daily (N=48) were 77.1% male and 22.9% female, with median age 57 years (range: 26 to 86 years). Of these 48 patients, 33.3% were 65 years or older, while 8.3% were 75 years or older. Patients were Caucasian (47.9%), Asian (25%) and Black (2.1%). Seventy-five percent and 25% had ECOG performance status 0 or 1, respectively. Patients who had previously received 1, 2, 3, 4 and 5 or more prior lines of TKIs were 16.7%, 31.3%, 35.4%, 14.6% and 2.1%, respectively. The median duration of treatment was 181.7 weeks (range: 2 to 312 weeks).

Results

Major molecular response (MMR) is defined as BCR::ABL1 IS ratio $\leq 0.1\%$. The MMR rate of the evaluable patients (N=45) treated with asciminib by week 24 was 30.8% (90% CI: 16.3%, 48.7%) for the patients previously treated with ponatinib (N=26). MMR by 96 weeks was achieved in 34.6% of the patients previously treated with ponatinib.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Scemblix in one or more subsets of the paediatric population in CML (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Asciminib is rapidly absorbed, with median maximum plasma level (T_{max}) reached 2 to 3 hours after oral administration, independent of the dose. The geometric mean (geoCV%) of C_{max} , AUC_{tau} and C_{min} at steady state is 793 ng/ml (49%), 5 262 ng*h/ml (48%) and 263 ng/ml (68%), respectively, following administration of asciminib at the 40 mg twice-daily dose. The geometric mean (geoCV%) of C_{max} , AUC_{tau} and C_{min} at steady state is 1 781 ng/ml (23%), 15 112 ng*h/ml (28%) and 193 ng/ml (40%), respectively, following administration of asciminib at 80 mg once-daily dose. The geometric mean (geoCV%) of C_{max} , AUC_{tau} and C_{min} at steady state is 5 642 ng/ml (40%), 37 547 ng*h/ml (41%) and 2 715 ng/ml (58%), respectively, following administration of asciminib at the 200 mg twice-daily dose. PBPK models predict that asciminib absorption is 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 an itraconazole 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 is decreased by 62.3% with a high-fat meal and by 30% with a low-fat meal compared to the fasted state (see section 4.2).

Distribution

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

Biotransformation

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

Elimination

Asciminib is mainly eliminated via faecal excretion, with a minor contribution of the renal route. Eighty and 11% of the asciminib dose were recovered in the faeces and in the urine of healthy subjects, respectively, following oral administration of a single 80 mg dose of [¹⁴C]-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 7 l/hour after a total daily dose of 80 mg, based on population pharmacokinetic analysis. The elimination half-life of asciminib is between 7 and 15 hours at a total daily dose of 80 mg.

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. Steady-state conditions are achieved within 3 days at the 40 mg twice-daily dose.

Evaluation of the exposure-response relationship for 40 mg twice-daily and 80 mg once-daily regimens

Based on exposure-response modelling from study A2302 (ASC4OPT) in patients with Ph+ CML-CP previously treated with two or more TKIs, a 3% numerically higher MMR rate at week 48 was predicted for 40 mg twice daily (42.6% [95% CI: 38.4, 46]) than for 80 mg once daily (39.6% [95% CI: 35.4, 43]) (see sections 4.4 and 5.1).

In vitro evaluation of drug interaction potential

Asciminib is metabolised by several pathways, including the CYP3A4, UGT2B7 and UGT2B17 enzymes, and biliary secreted by the transporter BCRP. Medicinal products inhibiting or inducing the CYP3A4, UGT and/or BCRP pathways may alter asciminib exposure.

CYP450 and UGT enzymes

In vitro, asciminib reversibly inhibits CYP3A4/5, CYP2C9 and UGT1A1 at plasma concentrations reached at a 40 mg twice-daily dose. Asciminib may increase the exposure of medicinal products which are substrates of CYP3A4/5 and CYP2C9 (see section 4.5). In addition, asciminib reversibly inhibits CYP2C8 and CYP2C19 at plasma concentrations reached at a 200 mg twice-daily dose.

Transporters

Asciminib is a substrate of BCRP and P-gp.

Asciminib inhibits BCRP, P-gp, OATP1B and OCT1 with K_i values of 24, 22, 2 and 3 micromolar, respectively. The clinical relevance of the interaction with OCT1 is currently unknown at an asciminib 200 mg twice-daily dose.

Special populations

Gender, race, body weight

Asciminib systemic exposure is not affected by gender, race or body weight to any clinically relevant extent.

Renal impairment

A dedicated renal impairment study including 6 subjects with normal renal function (absolute glomerular filtration rate [aGFR] ≥ 90 ml/min) and 8 subjects with severe renal impairment not requiring dialysis (aGFR 15 to <30 ml/min) has been conducted. Asciminib AUC_{inf} and C_{max} were increased by 56% and 8%, respectively, in subjects with severe renal impairment compared to subjects with normal renal function, following oral administration of a single 40 mg dose of asciminib (see sections 4.2 and 4.4). Population pharmacokinetic models indicate an increase in asciminib median steady-state AUC_{0-24h} by 11.5% in subjects with mild to moderate renal impairment, compared to subjects with normal renal function.

Hepatic impairment

A dedicated hepatic impairment study including 8 subjects each with normal hepatic function, mild hepatic impairment (Child-Pugh A score 5-6), moderate hepatic impairment (Child-Pugh B score 7-9) or severe hepatic impairment (Child-Pugh C score 10-15) was conducted. Asciminib AUC_{inf} 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 (see sections 4.2 and 4.4).

5.3 Preclinical safety data

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, likely at AUC exposures 12-fold, 8-fold or 1.7-fold higher than those achieved in patients at the recommended dose (RD) of 40 mg twice daily, 80 mg once daily or 200 mg twice daily, respectively.

Repeat dose toxicity

Pancreatic effects (serum amylase and lipase increases, acinar cell lesions) occurred in dogs at AUC exposures below those achieved in patients at the RD of 40 mg twice daily, 80 mg once daily or 200 mg twice daily. A trend towards recovery was observed.

Elevations in liver enzymes and/or bilirubin were observed in rats, dogs and monkeys. Histopathological hepatic changes (centrilobular hepatocyte hypertrophy, slight bile duct hyperplasia, increased individual hepatocyte necrosis and diffuse hepatocellular hypertrophy) were seen in rats and monkeys. These changes occurred at AUC exposures either equivalent to (rats) or 8- to 18-fold (dogs and monkeys) higher than those achieved in patients at the RD of 40 mg twice daily or 80 mg once daily. AUC exposures were below (rats), equivalent to (dogs) or approximately 2-fold higher than (monkeys) those achieved in patients at the RD of 200 mg twice daily. These changes were fully reversible.

Effects on the haematopoietic system (reduction in red blood cell mass, increased splenic or bone marrow pigment and increased reticulocytes) were consistent with a mild and regenerative, extravascular, haemolytic anaemia in all species. These changes occurred at AUC exposures either equivalent to (rats) or 8- to 14-fold (dogs and monkeys) higher than those achieved in patients at the

RD of 40 mg twice daily or 80 mg once daily. AUC exposures were below (rats), equivalent to (dogs) or approximately 2-fold higher than (monkeys) those achieved in patients at the RD of 200 mg twice daily. These changes were fully reversible.

Minimal mucosal hypertrophy/hyperplasia (increase in thickness of the mucosa with frequent elongation of villi) was present in the duodenum of rats at AUC exposures 30- or 22-fold higher than those achieved in patients at the RD of 40 mg twice daily or 80 mg once daily, respectively. AUC exposures were 4-fold higher than those achieved in patients at the RD of 200 mg twice daily. 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-fold higher than (rats) those achieved in patients at the RD of 40 mg twice daily or at AUC exposures either equivalent to (monkeys) or 13-fold higher than (rats) those at the RD of 80 mg once daily. AUC exposures were below (monkeys) or 2-fold higher than (rats) those achieved in patients at the RD of 200 mg twice daily. These changes were fully reversible.

Carcinogenicity and mutagenicity

Asciminib did not have mutagenic, clastogenic or aneugenic potential either *in vitro* nor *in vivo*.

In a 2-year rat carcinogenicity study, non-neoplastic proliferative changes consisting of ovarian Sertoli cell hyperplasia were observed in female animals at doses equal to or above 30 mg/kg/day. Benign Sertoli cell tumours in the ovaries were observed in female rats at the highest dose of 66 mg/kg/day. AUC exposures to asciminib in female rats at 66 mg/kg/day were generally 8- or 5-fold higher than those achieved in patients at the RD of 40 mg twice daily, or 80 mg once daily, respectively, and equivalent to those achieved in patients at the RD of 200 mg twice daily.

The clinical relevance of these findings is currently unknown.

Reproductive toxicity

Animal reproduction studies in pregnant rats and rabbits demonstrated that oral administration of asciminib during organogenesis induced embryotoxicity, foetotoxicity and teratogenicity.

In embryo-foetal development studies, a slight increase in foetal malformations (anasarca and cardiac malformations) and increased visceral and skeletal variants were observed in rats. Increased incidence of resorptions indicative of embryo-foetal mortality and a low incidence of cardiac malformations indicative of teratogenicity were observed in rabbits. In rats, at the foetal no observed adverse effect level (NOAEL) of 25 mg/kg/day, the AUC exposures were equivalent to or below those achieved in patients at the RD of 40 mg twice daily or 80 mg once daily, respectively, and below those achieved in patients at the RD of 200 mg twice daily. In rabbits, at the foetal NOAEL of 15 mg/kg/day, the AUC exposures were equivalent to or below those achieved in patients at the RD of 40 mg twice daily or 80 mg once daily, respectively, and below those achieved in patients at the RD of 200 mg twice daily.

In the rat fertility study, asciminib did not affect reproductive function in male and female rats. A slight effect on male sperm motility and sperm count was observed at doses of 200 mg/kg/day, likely at AUC exposures 19-, 13- or 2-fold higher than those achieved in patients at the RD of 40 mg twice daily, 80 mg once daily or 200 mg twice daily, respectively.

A pre- and postnatal developmental toxicity study was not performed.

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-, 6- or 2-fold higher than the

exposure in patients at the RD of 40 mg twice daily, 80 mg once daily or 200 mg twice daily, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Scemblix 20 mg, 40 mg and 100 mg film-coated tablets

Lactose monohydrate
Microcrystalline cellulose (E460i)
Hydroxypropylcellulose (E463)
Croscarmellose sodium (E468)
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Magnesium stearate
Talc (E553b)
Colloidal silicon dioxide
Lecithin (E322)
Xanthan gum (E415)
Iron oxide red (E172)

Scemblix 20 mg film-coated tablets only

Iron oxide yellow (E172)

Scemblix 40 mg and 100 mg film-coated tablets only

Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Scemblix 20 mg and 40 mg film-coated tablets

3 years.

Scemblix 100 mg film-coated tablets

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Scemblix is supplied in PCTFE/PVC/alu (20 mg and 40 mg film-coated tablets) or PA/alu/PVC/alu (100 mg film-coated tablets) blisters containing 10 film-coated tablets.

The following pack sizes are available:

Scemblix 20 mg film-coated tablets

Packs containing 20 or 60 film-coated tablets.

Scemblix 40 mg film-coated tablets

Packs containing 20 or 60 film-coated tablets.

Multipacks containing 180 (3 packs of 60) film-coated tablets.

Scemblix 100 mg film-coated tablets

Packs containing 60 or 120 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1670/001-007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 August 2022

10. DATE OF REVISION OF THE TEXT

06/2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.

