SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Scemblix 40® mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Scemblix 40 mg film-coated tablets

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

Excipients with known effect
Each film-coated tablet contains 86 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Scemblix 40 mg film-coated tablets

Violet white, round, biconvex film-coated tablets with bevelled edges of approximately 8 mm diameter, unscored, debossed with company logo on one side and “40” 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 (Ph + CML) in chronic phase (CP) ,

previously treated with two or more tyrosine kinase inhibitors, and without a known T315I mutation.

4.2 Posology and method of administration

Treatment with Scemblix should be initiated by a physician knowledgeable in the diagnosis and treatment of patients with chronic myeloid leukaemia.

Posology

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 changing 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 changing 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.

Any change in the dosage regimen is at the prescriber's discretion, as necessary for the management of the patient.

Missed dose

Once-daily dosage regimen: 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 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

For the management of adverse reactions, the dose can be reduced based on individual safety and tolerability, as described in Table 1.

If adverse reactions are effectively managed, asciminib may be resumed as described in Table 1. It should be permanently discontinued in patients unable to tolerate a total daily dose of 40 mg.

Table 1 Asciminib 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 dosage modification for the management of selected adverse reactions is shown in Table 2.

Table 2 Asciminib dose modification schedule for the management of adverse reactions

Adverse reaction	Dosage modification
Thrombocytopenia and/or neutropenia	
ANC <1.0 x 10^9/l and/or PLT <50 x 10^9/l	Withhold asciminib until resolved to ANC ≥1 x 10^9/l and/or PLT ≥50 x 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 ≥1 x 10^9/l and PLT ≥50 x 10^9/l, then resume at reduced dose.
Asymptomatic amylase and/or lipase elevation	
Elevation >2.0 x ULN	Withhold asciminib until resolved to <1.5 x 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 adverse reactions[1]	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

[1]Based 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 dose adjustment is required in patients with mild, moderate or severe renal impairment (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild, moderate or severe hepatic impairment (see section 5.2). Since there are no data available in patients with moderate or severe hepatic impairment, caution should be exercised in these patients (see section 4.8 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 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 sections 4.5 and 5.2).

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

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

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 (see section 4.2).

Pancreatic toxicity

Pancreatitis and asymptomatic elevation 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 elevation 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 elevation, the dose should be temporarily withheld, reduced or permanently discontinued (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 concomitantly with medicinal products with a known risk of torsades de pointes, or in patients who have a history of or predisposition for QTc prolongation or uncontrolled or significant cardiac disease including bradycardia (see sections 4.5 and 5.1).

Hypertension

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

Hypertension should be monitored and managed using standard antihypertensive therapy during treatment with asciminib 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 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.

Lactose

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

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 that may decrease asciminib plasma concentrations

Strong CYP3A4 inducers

Co-administration of a strong CYP3A4 inducer in healthy subjects decreased asciminib AUC_{inf} by 14.9% 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

Physiologically-based pharmacokinetic (PBPK) models predict that co-administration of asciminib at 80 mg once daily with rifampicin would decrease asciminib AUC_{tau} and C_{max} by 52% and 23%.

Caution should be exercised during concomitant administration of asciminib with strong CYP3A inducers, including, but not limited to, carbamazepine, phenobarbital, phenytoin or St. John's wort (*Hypericum perforatum*). Dose adjustment of asciminib is not required.

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. PBPK models predict that co-administration of asciminib at 80 mg once daily would increase midazolam AUC_{inf} and C_{max} by 24% and 17%, respectively.

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

CYP2C9 substrates
Co-administration of asciminib with a CYP2C9 substrate (warfarin) increased S-warfarin AUC_{inf} and C_{max} by 41% and 8%, respectively, in healthy subjects receiving asciminib 40 mg twice daily. PBPK models predict that co-administration of asciminib at 80 mg once daily would increase S-warfarin AUC_{inf} and C_{max} by 52% and 4%, respectively.

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

Substrates of OATP1B or BCRP
Co-administration of asciminib at 80 mg once daily with an OATP1B, CYP3A4 and P-gp substrate (atorvastatin) increased atorvastatin AUC_{inf} and C_{max} by 14% and 24%, respectively, in healthy subjects. Clinically relevant interactions between Scemblix and OATP1B substrates are unlikely to occur.

Based on physiologically-based pharmacokinetic (PBPK) modelling, caution should be exercised during concomitant administration of asciminib with BCRP substrates, including, but not limited to, sulfasalazine, methotrexate and rosuvastatin. Refer to BCRP substrates' product information.

P5-gp substrates of narrow therapeutic index
Based on physiologically-based pharmacokinetic (PBPK) modelling, caution should be exercised during concomitant administration of asciminib with P-gp substrates known to have a narrow therapeutic index, including but not limited to digoxin, dabigatran and colchicine (see section 5.2). Dose adjustment of asciminib is not required.

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

(see sections 4.4, 4.8 and 5.1).

Drug-food interactions
The bioavailability of asciminib decreases on consumption of food (see sections 4.2 and 5.2).

Hydroxypropyl-β-cyclodextrin as an excipient (e.g., itraconazole oral solution)
Caution should be exercised during concomitant administration of asciminib with hydroxypropyl-β-cyclodextrin containing oral products (see section 5.2).

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.

Women of childbearing potential should be advised to use effective contraception during treatment with asciminib and for at least 3 days after stopping treatment and to avoid becoming pregnant while receiving asciminib.

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 for use during pregnancy, or 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 is 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 is not recommended 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 (see section 5.3).

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 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 (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of asciminib has been evaluated in 356 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. In ASCEMBL, patients received asciminib as monotherapy at a dose of 40 mg twice daily. In X2101, patients received asciminib as monotherapy at doses ranging from 10 to 200 mg twice daily and 80 to 200 mg once daily.

The safety pool (N=356) includes patients receiving asciminib at doses ranging from 10 to 200 mg twice daily and 80 to 200 mg once daily, with 156 patients receiving asciminib at 40 mg twice daily in the pivotal study, and 35 patients receiving 40 mg twice daily and 18 patients receiving 80 mg once daily from study X2101 as a starting dose. In the pooled dataset, the median duration of exposure to asciminib was 167 weeks (range: 0.1 to 349 weeks).

The most common adverse reactions of any grade (incidence ≥20%) in patients receiving asciminib were musculoskeletal pain (38.8%), upper respiratory tract infections (29.5%), fatigue (28.9%), thrombocytopenia (28.1%), headache (26.4%), arthralgia (24.4%), increased pancreatic enzymes (23%), diarrhoea (22.5%), abdominal pain (22.2%), rash (21.6%), hypertension (20.8%) and nausea (20.8%).

The most common adverse reactions of ≥ grade 3 (incidence ≥5%) in patients receiving asciminib were thrombocytopenia (18.5%), neutropenia (15.7%), increased pancreatic enzymes (12.94%), hypertension (11.2%) and anaemia (5.3%).

Serious adverse reactions occurred in 13.2% of patients receiving asciminib. The most frequent serious adverse reactions (incidence ≥1%) were pleural effusion (2.5%), lower respiratory tract infections (2.2%), thrombocytopenia (1.7%), pyrexia (1.4%), pancreatitis (1.1%), abdominal pain (1.1%), non-cardiac chest pain (1.1%) and vomiting (1.1%). The predicted safety profile of asciminib at the 80 mg once-daily dose is similar to the 40 mg twice-daily dose, based on exposure-safety analysis.

Tabulated list of adverse reactions

Adverse reactions from clinical studies (Table 3) 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 are defined as: 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 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
Metabolism and nutrition disorders	Very common	Dyslipidaemia[6]
	Common	Decreased appetite
Nervous system disorders	Very common	Headache, dizziness
Eye disorders	Common	Dry eye, vision blurred
Cardiac disorders	Common	Palpitations
Vascular disorders	Very common	Hypertension[7]
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea, cough
	Common	Pleural effusion, non-cardiac chest pain
Gastrointestinal disorders	Very common	Pancreatic enzymes increased[8], vomiting, diarrhoea, nausea, abdominal pain[9], constipation
	Common	Pancreatitis[10]
Hepatobiliary disorders	Very common	Hepatic enzyme increased[11]
	Common	Blood bilirubin increased[12]
Skin and subcutaneous tissue disorders	Very common	Rash[13], pruritis
	Common	Urticaria
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[14], arthralgia
General disorders and administration site conditions	Very common	Fatigue[15], oedema[16], pyrexia[17]
Investigations	Common	Electrocardiogram QT prolonged, blood creatine phosphokinase increased

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

Description of selected adverse reactions

Myelosuppression
Thrombocytopenia occurred in 28.1% patients receiving asciminib, with grade 3 and 4 reactions reported in 6.7% and 11.8% of patients, respectively. Among the patients with thrombocytopenia ≥ grade 3, the median time to first occurrence of reactions was 6.14 weeks (range: 0.14 to 64.14 weeks) with median duration of any occurring reaction of 2 weeks (95% CI, range: 1.43 to 2 weeks). Of the patients with thrombocytopenia, 2.5% permanently discontinued asciminib, while asciminib was temporarily withheld in 12.4% patients due to the adverse reaction.

Neutropenia occurred in 19.7% patients receiving asciminib, with grade 3 and 4 reactions reported in 7.3% and 8.4% of patients, respectively. Among the patients with neutropenia ≥ grade 3, the median time to first occurrence of reactions was 6.14 weeks (range: 0.14 to 180.1 weeks) with median duration of any occurring reaction of 2 weeks (95% CI, range: 1.43 to 2.14 weeks). Of the patients with neutropenia, 1.7% patients permanently discontinued asciminib, while asciminib was temporarily withheld in 9.3% patients due to the adverse reaction.

Anaemia occurred in 13.2% patients receiving asciminib, with grade 3 reactions occurring in 5.3% of patients. Among the patients with anaemia ≥ grade 3, the median time to first occurrence of reactions was 30.43 weeks (range: 0.43 to 207 weeks) with median duration of any occurring reaction of 0.86 weeks (95% CI, range: 0.29 to 1.71 weeks). Of the patients with anaemia, asciminib was temporarily withheld in 0.6% of patients due to the adverse reaction (see section 4.4).

Pancreatic toxicity
Pancreatitis occurred in 2.5%m of patients receiving asciminib, with grade 3 reactions occurring in 1.1% of patients. All these reactions occurred in the phase I study (X2101). Of the patients with pancreatitis, 0.6% permanently discontinued asciminib, while asciminib was temporarily withheld in 1.4% of patients due to the adverse reaction. Asymptomatic elevations of serum lipase and amylase occurred in 23% of patients receiving asciminib, with

grade 3 and 4 reactions occurring in 10.4% and 2.5% patients, respectively. Of the patients with elevation of pancreatic enzymes, asciminib was permanently discontinued in 2.2% of patients due to the adverse drug reaction. (see section 4.4)

QT prolongation

Electrocardiogram QT prolongation occurred in 1.1% patients receiving asciminib. In the ASCEMBL clinical study, one patient had a prolonged QTcF greater than 500 ms together with more than 60 ms QTcF increase from baseline, and another patient had prolonged QTcF with more than 60 ms QTcF increase from baseline. (See sections 4.4, 4.5 and 5.1).

Hypertension

Hypertension occurred in 20.8% of patients receiving asciminib, with grade 3 and 4 reactions reported in 11% and 0.3% patients, respectively. Among the patients with hypertension ≥ grade 3, the median time to first occurrence of reactions was 29.21 weeks (range: 0.14 to 365 weeks). Of the patients with hypertension, asciminib was temporarily withheld in 0.8% of patients due to the adverse reaction (see section 4.4).

Laboratory abnormalities

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.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is limited experience of asciminib 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 an oral and potent inhibitor of ABL and BCR::ABL1 tyrosine kinases. Asciminib inhibits the ABL1 kinase activity of the BCR::ABL1 fusion protein, by specifically targeting the ABL myristoyl pocket.

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 (ΔQTcF) 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 ΔQTcF was 3.35 ms (upper bound of 90% CI:

4.43 ms) for the asciminib 40 mg twice-daily dose and 3.64 ms (upper bound of 90% CI: 4.68 ms) for the asciminib 80 mg once daily dose (see sections 4.4, 4.5 and 4.8).

Clinical efficacy and safety

Ph+ CML-CP

The clinical efficacy and safety of asciminib in the treatment of patients with Philadelphia chromosome-positive myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors were demonstrated in the multicentre, randomised, active-controlled and open-label phase III study ASCEMBL.

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 continued treatment until unacceptable toxicity or treatment failure occurred. Patients with known presence T315I and/or V299L mutations at any time prior to study entry were not included in ASCEMBL.

Patients with Ph+ CML-CP 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. Last TKI was discontinued due to lack of efficacy in 63.9% of patients and to lack of tolerability in 34.8%.

The median duration of 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 major molecular response rate (MMR) at 24 weeks and the key secondary endpoint was MMR rate at 96 weeks. MMR is defined as BCR::ABL1 IS ratio ≤0.1%. Other secondary endpoints were complete 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 4Efficacy results in patients treated with two or more tyrosine kinase inhibitors (ASCEMBL)

Efficacy results in patients treated with two or more tyrosine kinase inhibitors (ASCEMBL)	**40 mg Scemblix twice daily**	**500 mg bosutinib once daily**	**Difference (95% CI)[1]**	**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 (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 (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

Major molecular response (MMR) is defined as a BCR::ABL1 ratio ≤0.1% on the International Scale.

Complete cytogenetic response (CCyR) is defined as no Philadelphia chromosome metaphases in bone marrow with a minimum of 20 metaphases examined.

[1] *Adjusted 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 predicted MMR rate at 24 weeks for the asciminib 80 mg once-daily dose is comparable to the MMR rate at 24 weeks observed in ASCEMBL with the asciminib 40 mg twice-daily dose, based on exposure response analysis.

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 rates by mutation status are presented in Table 5.

Table 5. MMR rate at Week 24 according to BCR::ABL1 mutation status at baseline and line of therapy of randomized treatment

	40 mg Scemblix twice daily n/N (%)	**500 mg bosutinib once daily** n/N (%)
BCR::ABL1 mutation status at baseline[1]		
No mutation identified	31/125 (24.8)	7/63 (11.1)
Mutation identified	6/17 (35.3)	2/8 (25.0)
Line of therapy of randomized treatment		
3	24/82 (29.3)	6/30 (20.0)
4	11/44 (25.0)	4/29 (13.8)
≥5	5/31 (16.1)	0/17 (0.0)

n = Number of patients in MMR.

N = Number of patients in the subgroup and treatment group with response variable defined.

[1]Mutation assessment was based on Sanger sequencing. Patients with BCR::ABL1 T315I or V299L mutations or non-evaluable mutation assessment were excluded from the subgroup analysis.

The MMR rate at 48 weeks was 29.3% (95% CI: 22.32, 37.08) in patients receiving asciminib and 13.2% (95% CI: 6.49, 22.87) in patients receiving bosutinib. 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).

Elderly patients

No overall differences in the safety or efficacy of Scemblix were observed between patients of

65 years of age or above and younger patients. There is an insufficient number of patients of 75 years of age or above to assess whether there are differences in safety or efficacy.

Paediatric population

The licensing authority has waived the obligation to submit the results of studies with Scemblix in paediatric patients aged less than 3 years in CML. The licensing authority has deferred the obligation to submit the results of studies with Scemblix in paediatric patients aged from 3 years to less than 18 years 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} at steady state is 1781 ng/ml (23%) and 793 ng/ml (49%) following administration of asciminib at 80 mg once-daily and 40 mg twice-daily doses, respectively. The geometric mean (geoCV%) of AUC_{tau} is 5262 ng*h/ml (48%) following administration of asciminib at the 40 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, independent of the dose (see sections 4.2 and 4.5).

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. Asciminib is 97.3% bound to human plasma proteins, independent of the dose.

Biotransformation

Asciminib is primarily metabolised via CYP3A4-mediated oxidation (36%), UGT2B7-mediated glucuronidation and UGT2B17-mediated glucuronidation (13.3% and 7.8%, respectively). PBPK models predict that asciminib biliary secretion via BCRP accounts for 31.1% of its total systemic clearance. 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.

The oral total clearance (CL/F) of asciminib is 6.31 l/hour, based on population pharmacokinetic analysis. The accumulation half-life of asciminib is 5.2 hours at 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 average 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.

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 and P-gp with Ki values of 24.3 and 21.7 micromolar, respectively. Based on PBPK models, asciminib may increase the exposure of medicinal products which are substrates of BCRP and P-gp transporters.

Multiple pathways
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 multiple pathways may alter asciminib exposure.

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} are 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 section 4.2). Population pharmacokinetics 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} is 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 section 4.2).

5.3 Preclinical safety data

Asciminib was evaluated in safety pharmacology, repeated dose toxicity, genotoxicity,

reproductive toxicity and phototoxicity studies.

Safety pharmacology

In safety pharmacology studies, asciminib did not have any effect on the central nervous and respiratory systems in rats at doses up to 600 mg/kg/day.

In an *in vitro* study, asciminib inhibited the human ether-à-go-go-related gene (hERG) channels with an IC_{50} of 11.4 micromolar. This value translates into a clinical safety margin at least 200-fold or 100-fold higher when compared to asciminib free C_{max} in patients at the 40 mg twice-daily or 80 mg once-daily dose, respectively.

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.

Repeat dose toxicity

Repeat dose toxicity studies identified the pancreas, liver, haematopoietic system, adrenal gland and gastrointestinal tract as target organs of asciminib.
Pancreatic effects (serum amylase and lipase increases, acinar cell lesions) occurred in dogs at AUC exposures below those achieved in patients on 40 mg twice daily or 80 mg once 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 on 40 mg twice daily or 80 mg once 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 10- to 14-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) was present 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 13- to 19-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 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 cells hyperplasia no asciminib related neoplastic or hyperplastic findings were noted 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 the highest dose 66 mg/kg/day were generally 8 fold higher than those achieved in patients at the dose of 40 mg twice daily. No asciminib-related neoplastic or hyperplastic findings were noted in male rats at any dose level.

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, 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 the period of organogenesis.

In rats, asciminib was not tolerated in maternal animals at 600 mg/kg/day and resulted in the early termination of the dose group. There was no evidence of asciminib-related embryo-foetal death at doses below or equal to 150 mg/kg/day. A dose-related increase in foetal weights at 25 and 150 mg/kg/day was observed. Foetal variations in the urinary tract and skeleton (skull, vertebral column and ribs), indicative of changes in the rate of development, were observed primarily at 150 mg/kg/day. A slight increase in the malformation rate (anasarca and cardiac malformations) and some visceral variants indicative of adverse effects on embryo-foetal development were also observed at 150 mg/kg/day. The maternal no-observed-adverse-effect level (NOAEL) was 150 mg/kg/day and the foetal NOAEL was $\leq$ 25 mg/kg/day. At 25 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, respectively.

In rabbits, 300 mg/kg/day caused morbidity in the maternal animals and resulted in the early termination of the dose group. An increased incidence of resorptions, indicative of embryo-foetal mortality, and a low incidence of cardiac malformations, indicative of teratogenicity, were observed at 50 mg/kg/day. There was no effect on foetal growth. The NOAEL for maternal toxicity was 50 mg/kg/day and the foetal NOAEL was 15 mg/kg/day. At the foetal 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, respectively.

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-fold or 13-fold higher than those achieved in patients at the 40 mg twice-daily and 80 mg once-daily doses, 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate

Microcrystalline cellulose (fine and granular)

Hydroxypropylcellulose

Croscarmellose sodium

Magnesium stearate

Colloidal silicon dioxide

Tablet coating

Polyvinyl alcohol

Titanium dioxide (E171)

Talc

Lecithin (E322)

Xanthan gum (E415)

Iron oxide red (E172)

Scemblix 40 mg film-coated tablets only

Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

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

PCTFE/PVC/Alu blisters in packs containing 20 or 60 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

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W12 7FQ

United Kingdom

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10 DATE OF REVISION OF THE TEXT

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