NOVARTIS

1 Tradename

Scemblix® 20 mg and 40 mg film-coated tablets.

2 Description and composition

Pharmaceutical form

- 20 mg film-coated tablets: pale yellow, round, biconvex, film-coated tablets with beveled edges, approximately 6.2 mm diameter, unscored, debossed with “Novartis” logo on one side and “20” on the other side.
- 40 mg film-coated tablets: violet white, round, biconvex, film-coated tablets with beveled edges, approximately 8.2 mm diameter, unscored, debossed with “Novartis” logo on one side and “40” on the other side.

Active substance(s)

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

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

Excipients

- 20 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, iron oxide (E172, yellow and red), lecithin (E322), xanthan gum (E415).
- 40 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, iron oxide (E172, black and red), lecithin (E322), xanthan gum (E415).

Information might differ in some countries.

3 Indications

Scemblix® is indicated for the treatment of adult patients with:

- Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) previously treated with two or more tyrosine kinase inhibitors (see section 12 Clinical studies).
- Ph+ CML in CP harboring the T315I mutation.

4 Dosage regimen and administration

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

Dosage regimen

General target population

Ph+ CML-CP

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 Scemblix 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 Scemblix twice daily approximately 24 hours after the last once-daily dose and then continue at 40 mg twice daily at approximately 12-hour intervals.

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

Ph+ CML-CP harboring the T315I mutation

The recommended dose of Scemblix is 200 mg taken orally twice daily at approximately 12 hour intervals.

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

Missed dose

Once-daily dosage regimen: If a Scemblix 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 regimens: If a Scemblix dose is missed by more than approximately 6 hours, it should be skipped, and the next dose should be taken as scheduled.

Dose modifications

Ph+ CML-CP

For the management of adverse drug reactions, Scemblix dose can be reduced based on individual safety and tolerability, as described in Table 4-1. If adverse drug reactions are effectively managed, Scemblix may be resumed as described in Table 4-1.

Scemblix should be permanently discontinued in patients unable to tolerate a total daily dose of 40 mg.

PH+ CML-CP harboring the T315I mutation

For the management of adverse drug reactions, Scemblix dose can be reduced based on individual safety and tolerability, as described in Table 4-1. If adverse drug reactions are effectively managed, Scemblix may be resumed as described in Table 4-1.

Scemblix should be permanently discontinued in patients unable to tolerate a dose of 160 mg twice daily.

Table 4-1 Scemblix dosage 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
200 mg twice daily	160 mg twice daily	200 mg twice daily

The recommended dosage modification for the management of selected adverse drug reactions is shown in Table 4-2.

Table 4-2 Scemblix dosage modification for the management of selected adverse drug reactions

Adverse drug reaction	Dosage modification
Thrombocytopenia and/or neutropenia	
ANC[1] <1 x 10^9/L and/or PLT[2] <50 x 10^9/L	Withhold Scemblix until resolved to ANC ≥1 x 10^9/L and/or PLT ≥50 x 10^9/L. If resolved: • Within 2 weeks: resume Scemblix at starting dose. • After more than 2 weeks: resume Scemblix at reduced dose. For recurrent severe thrombocytopenia and/or neutropenia, withhold Scemblix 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 x ULN[3]	Withhold Scemblix until resolved to <1.5 x ULN. • If resolved: resume Scemblix at reduced dose. If reactions reoccur at reduced dose, permanently discontinue Scemblix. • If not resolved: permanently discontinue Scemblix. Perform diagnostic tests to exclude pancreatitis.
Non-hematologic adverse drug reactions	
Grade 3 or higher[4] adverse drug reactions	Withhold Scemblix until resolved to grade 1 or lower. • If resolved: resume Scemblix at a reduced dose. • If not resolved: permanently discontinue Scemblix.

[1]ANC: absolute neutrophil count; [2]PLT: platelets; [3]ULN: upper limit of normal,

[4]Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 4.03.

Special populations

Renal impairment

No dose adjustment is required in patients with mild, moderate, or severe renal impairment not requiring dialysis (absolute Glomerular Filtration Rate (aGFR) ≥15 mL/min) receiving Scemblix. Caution should be exercised in patients with severe renal impairment receiving Scemblix 200 mg twice daily dose. (see section 11 Clinical pharmacology).

Hepatic impairment

No dose adjustment is required in patients with mild, moderate, or severe hepatic impairment receiving Scemblix. Caution should be exercised in patients with severe hepatic impairment receiving Scemblix 200 mg twice daily dose. (see section 11 Clinical pharmacology).

Pediatric patients (below 18 years)

The safety and efficacy of Scemblix in pediatric patients (below 18 years) has not been established.

Geriatric patients (65 years of age or above)

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

Method of administration

Scemblix should be taken orally without food. Food consumption should be avoided for at least 2 hours before and 1 hour after taking Scemblix (see section 8 Interactions and 11 Clinical pharmacology).

Scemblix film-coated tablets should be swallowed whole and should not be broken, crushed, or chewed.

5 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 2 Description and composition.

6 Warnings and precautions

Myelosuppression

Thrombocytopenia, neutropenia, and anemia occurred in patients receiving Scemblix. Severe (NCI CTCAE grade 3 or 4) thrombocytopenia and neutropenia were reported during treatment with Scemblix (see section 7 Adverse drug reactions). Myelosuppression was generally reversible and managed by temporarily withholding Scemblix. Complete blood counts should be performed every two weeks for the first 3 months of treatment and monthly thereafter, or as clinically indicated. Patients should be monitored for signs and symptoms of myelosuppression.

Based on the severity of thrombocytopenia and/or neutropenia, the Scemblix dose should be reduced, temporarily withheld, or permanently discontinued as described in Table 4-2 (see section 4 Dosage regimen and administration).

Pancreatic toxicity

Pancreatitis occurred in 9 of 356 (2.5%) patients receiving Scemblix, with grade 3 reactions occurring in 4 (1.1%) patients. All these reactions occurred in the phase I study (X2101). Of the 9 patients with pancreatitis, 2 (0.6%) permanently discontinued Scemblix, while Scemblix was temporarily withheld in 4 (1.1%) patients due to the adverse drug reaction. Asymptomatic elevation of serum lipase and amylase occurred in 76 of 356 (21.3%) patients receiving Scemblix, with grade 3 and 4 reactions occurring in 36 (10.1%) and 8 (2.2%) of patients, respectively. Of the 76 patients with pancreatic enzymes elevation, Scemblix was permanently discontinued in 8 (2.2%) patients due to the adverse drug reaction.

Serum lipase and amylase levels should be assessed monthly during treatment with Scemblix, or as clinically indicated. Patients should be monitored for signs and symptoms of pancreatic toxicity. More frequent monitoring should be performed in patients with a history of pancreatitis. If serum lipase and amylase elevation are accompanied by abdominal symptoms, treatment should be temporarily withheld, and appropriate diagnostic tests should be considered to exclude pancreatitis (see section 4 Dosage regimen and administration).

Based on the severity of serum lipase and amylase elevation, the Scemblix dose should be reduced, temporarily withheld, or permanently discontinued as described in Table 4-2 (see section 4 Dosage regimen and administration).

QT prolongation

Electrocardiogram QT prolongation occurred in 3 of 356 (0.8%) patients receiving Scemblix (see section 7 Adverse drug reactions). 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 one patient had prolonged QTcF with more than 60 ms QTcF increase from baseline.

It is recommended that an electrocardiogram is performed prior to the start of treatment with Scemblix and monitored during treatment as clinically indicated. Hypokalemia and hypomagnesemia should be corrected prior to Scemblix administration and monitored during treatment as clinically indicated.

Caution should be exercised when administering Scemblix concomitantly with medicinal products known to cause torsades de pointes. (see section 8 Interactions and section 11 Clinical pharmacology).

Hypertension

Hypertension occurred in 66 of 356 (18.5%) patients receiving Scemblix, with grade 3 and 4 reactions reported in 30 (8.4%) and 1 (0.3%) patients, respectively. Among the patients with hypertension ≥grade 3, the median time to first occurrence of reactions was 14 weeks (range: 0.1 to 156 weeks). Of the 66 patients with hypertension, Scemblix was temporarily withheld in 3 (0.8%) patients due to the adverse drug reaction.

Hypertension should be monitored and managed using standard antihypertensive therapy during treatment with Scemblix as clinically indicated. Based on the severity of hypertension, the Scemblix dose should be temporarily withheld, reduced or permanently discontinued (see section 4 Dosage regimen and administration).

Hypersensitivity

Hypersensitivity events occurred in 111 of 356 (31.2%) patients receiving Scemblix, with ≥grade 3 events reported in 6 (1.7%) patients. Patients should be monitored for signs and symptoms of hypersensitivity and appropriate treatment should be initiated as clinically indicated.

Hepatitis B reactivation

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

Embryo-fetal toxicity

Based on findings from animal studies, Scemblix can cause fetal harm when administered to a pregnant woman. Pregnant women and females of reproductive potential should be advised of the potential risk to a fetus if Scemblix is used during pregnancy or if the patient becomes pregnant while taking Scemblix. The pregnancy status of females of reproductive potential should be verified prior to starting treatment with Scemblix. Sexually active females of reproductive potential should use effective contraception during treatment with Scemblix and for at least 3 days after the last dose (see section 9 Pregnancy, lactation, females and males of reproductive potential).

Cardiovascular toxicity

Cardiovascular events (including ischemic cardiac and CNS conditions, arterial thrombotic and embolic conditions) and cardiac failure occurred in 28 (8%) and in 10 (2.8%) of 356 patients receiving Scemblix, respectively. Grade 3 cardiovascular events were reported in 11 (3.1%) patients, while grade 3 cardiac failure was observed in 7 (2.0%) patients. Grade 4 cardiovascular events occurred in 1 (0.3%) patient, with fatalities occurring in 2 (0.6%) patients.

Permanent discontinuation of Scemblix occurred in 2 (0.6%) due to cardiovascular events and in 1 (0.3%) patient due to cardiac failure. Cardiovascular events occurred in patients with pre-existing cardiovascular conditions or risk factors, and/or prior exposure to multiple TKIs.

Monitor patients with history of cardiovascular risk factors for cardiovascular signs and symptoms. Initiate appropriate treatment as clinically indicated; for Grade 3 or higher cardiovascular events, temporarily withhold, reduce dose, or permanently discontinue Scemblix depending on persistence of cardiovascular events.

7 Adverse drug reactions

Summary of the safety profile

The overall safety profile of Scemblix has been evaluated in 356 patients with Ph+ CML in chronic (CP) and accelerated (AP) phases receiving Scemblix as monotherapy. It is based on the safety pool of the pivotal phase III study A2301 (ASCEMBL) (N=156 Ph+ CML-CP patients) and the phase I study X2101, including patients with:

- Ph+ CML-CP (N=115),
- Ph+ CML-CP harboring the T315I mutation (N=70),
- Ph+ CML-AP (N=15).

The safety pool (N=356) includes patients receiving Scemblix at doses ranging from 10 to 200 mg twice daily and 80 to 200 mg once daily. In the pooled dataset, the median duration of exposure to Scemblix was 116 weeks (range: 0.1 to 342 weeks).

The most common adverse drug reactions of any grade (incidence ≥20%) in patients receiving Scemblix were musculoskeletal pain (37.1%), upper respiratory tract infections (28.1%), thrombocytopenia (27.5%), fatigue (27.2%), headache (24.2%), arthralgia (21.6%) increased pancreatic enzymes (21.3%), abdominal pain (21.3%), diarrhoea (20.5%) and nausea (20.2%). The most common adverse drug reactions of ≥grade 3 (incidence ≥5%) in patients receiving Scemblix were thrombocytopenia (18.5%), neutropenia (15.7%), increased pancreatic enzymes (12.4%), hypertension (8.7%) and anaemia (5.3%).

Serious adverse drug reactions occurred in 12.4% of patients receiving Scemblix. The most frequent serious adverse drug reactions (incidence ≥1%) were pleural effusion (2.5%), lower respiratory tract infections (2.2%), thrombocytopenia (1.7%), pyrexia (1.4%), pancreatitis (1.1%), non-cardiac chest pain (1.1%) and vomiting (1.1%).

The predicted safety profile of Scemblix at the 80 mg once-daily dose is similar to the 40 mg twice-daily dose, based on exposure-safety analysis.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical studies (Table 7-1 and Table 7-2) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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 7-1 Adverse drug reactions observed with Scemblix in clinical studies

Adverse drug reactions	Scemblix 40 mg BID[1] N=156 n (%) All grades	Bosutinib 500 mg QD[2] N=76 n (%) All grades	Scemblix 40 mg BID[1] N=156 n (%) Grade ≥3	Bosutinib 500 mg QD[2] N=76 n (%) Grade ≥3	Scemblix safety pool[3] N=356 (%) All grades	Frequency category[3] N=356 All grades
Infections and infestations						
Upper respiratory tract infection[4]	38 (24.4)	7 (9.2)	1 (0.6)	0	100 (28.1)	Very common
Lower respiratory tract infection[5]	6 (3.8)	2 (2.6)	1 (0.6)	0	26 (7.3)	Common
Influenza	5 (3.2)	2 (2.6)	0	0	15 (4.2)	Common
Blood and lymphatic system disorders						
Thrombocytopenia[6]	46 (29.5)	15 (19.7)	35 (22.4)	7 (9.2)	98 (27.5)	Very common
Neutropenia[7]	36 (23.1)	16 (21.1)	29 (18.6)	11 (14.5)	69 (19.4)	Very common
Anaemia[8]	16 (10.3)	7 (9.2)	2 (1.3)	3 (3.9)	46 (12.9)	Very common
Febrile neutropenia	1 (0.6)	0	1 (0.6)	0	3 (0.8)	Uncommon
Immune system disorders						
Hypersensitivity	0	1 (0.3)	0	0	1 (0.3)	Uncommon
Metabolism and nutrition disorders						
Dyslipidaemia[9]	9 (5.8)	2 (2.6)	4 (2.6)	0	37 (10.4)	Very common
Decreased appetite	8 (5.1)	6 (7.9)	0	0	25 (7)	Common
Nervous system disorders						
Headache	31 (19.9)	12 (15.8)	3 (1.9)	0	86 (24.2)	Very common
Dizziness	11 (7.1)	2 (2.6)	0	0	40 (11.2)	Very common
Eye disorders						
Vision blurred	4 (2.6)	0	0	0	17 (4.8)	Common
Dry eye	3 (1.9)	2 (2.6)	0	0	19 (5.3)	Common
Cardiac disorders						
Palpitations	4 (2.6)	0	0	0	15 (4.2)	Common
Vascular disorders						

Adverse drug reactions	Scemblix 40 mg BID[1] N=156 n (%) All grades	Bosutinib 500 mg QD[2] N=76 n (%) All grades	Scemblix 40 mg BID[1] N=156 n (%) Grade ≥3	Bosutinib 500 mg QD[2] N=76 n (%) Grade ≥3	Scemblix safety pool[3] N=356 (%) All grades	Frequency category[3] N=356 All grades
Hypertension[10]	21 (13.5)	4 (5.3)	10 (6.4)	3 (3.9)	66 (18.5)	Very common
Respiratory, thoracic and mediastinal disorders						
Cough	13 (8.3)	5 (6.6)	0	0	45 (12.6)	Very common
Pleural effusion	2 (1.3)	3 (3.9)	0	2 (2.6)	16 (4.5)	Common
Dyspnoea	8 (5.1)	4 (5.3)	0	0	33 (9.3)	Common
Non-cardiac chest pain	8 (5.1)	1 (1.3)	2 (1.3)	0	26 (7.3)	Common
Gastrointestinal disorders						
Pancreatic enzymes increased[11]	13 (8.3)	7 (9.2)	6 (3.8)	4 (5.3)	76 (21.3)	Very common
Vomiting	12 (7.7)	20 (26.3)	2 (1.3)	0	56 (15.7)	Very common
Diarrhoea	20 (12.8)	55 (72.4)	0	8 (10.5)	73 (20.5)	Very common
Nausea	18 (11.5)	35 (46.1)	1 (0.6)	0	72 (20.2)	Very common
Abdominal pain[12]	20 (12.8)	17 (22.4)	0	2 (2.6)	76 (21.3)	Very common
Pancreatitis[13]	0	0	0	0	9 (2.5)	Common
Hepatobiliary disorders						
Hepatic enzyme increased[14]	11 (7.1)	25 (32.9)	3 (1.9)	13 (17.1)	52 (14.6)	Very common
Blood bilirubin increased[15]	4 (2.6)	1 (1.3)	0	0	14 (3.9)	Common
Skin and subcutaneous tissue disorders						
Rash[16]	22(14.1)	19 (25)	0	4 (5.3)	70 (19.7)	Very common
Urticaria	2 (1.3)	2 (2.6)	0	0	12 (3.4)	Common
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain[17]	32 (20.5)	12 (15.8)	2 (1.3)	1 (1.3)	132 (37.1)	Very common
Arthralgia	20 (12.8)	3 (3.9)	1 (0.6)	0	77 (21.6)	Very common

Adverse drug reactions	Scemblix 40 mg BID[1] N=156 n (%) All grades	Bosutinib 500 mg QD[2] N=76 n (%) All grades	Scemblix 40 mg BID[1] N=156 n (%) Grade ≥3	Bosutinib 500 mg QD[2] N=76 n (%) Grade ≥3	Scemblix safety pool[3] N=356 (%) All grades	Frequency category[3] N=356 All grades
General disorders and administration site conditions						
Fatigue[18]	31 (19.9)	8 (10.5)	1 (0.6)	1 (1.3)	97 (27.2)	Very common
Pruritus	8 (5.1)	5 (6.6)	0	1 (1.3)	44 (12.4)	Very common
Pyrexia[19]	6 (3.8)	7 (9.2)	2 (1.3)	1 (1.3)	33 (9.3)	Common
Oedema[20]	12 (7.7)	2 (2.6)	0	0	35 (9.8)	Common
Investigations						
Blood creatine phosphokinase increased	4 (2.6)	3 (3.9)	3 (1.9)	1 (1.3)	13 (3.7)	Common
Electrocardiogram QT prolonged	2 (1.3)	0	1 (0.6)	0	3 (0.8)	Uncommon

[1]Scemblix median duration of exposure: 103 weeks (range: 0.1 to 201 weeks) with 53.5% of patients ongoing treatment .

[2]Bosutinib median duration of exposure: 31 weeks (range: 1 to 188 weeks) with 19.7.4% of patients ongoing treatment].

[3]Frequency based on the safety pool (A2301 and X2101) for Scemblix all grade reactions (N=356).

[4]Upper respiratory tract infection includes: upper respiratory tract infection, nasopharyngitis, pharyngitis and rhinitis; [5]Lower respiratory tract infections includes: pneumonia, bronchitis and tracheobronchitis; [6]Thrombocytopenia includes: thrombocytopenia and platelet count decreased; [7]Neutropenia includes: neutropenia and neutrophil count decreased; [8]Anaemia includes: anaemia, haemoglobin decreased, and normocytic anaemia;

[9]Dyslipidaemia includes: hypertriglyceridaemia, blood cholesterol increased, hypercholesterolaemia, blood triglycerides increased, hyperlipidaemia and dyslipidaemia ; [10]Hypertension includes: hypertension and blood pressure increased ; [11]Pancreatic enzymes increased includes: lipase increased, amylase increased and hyperlipasaemia; [12]Abdominal pain includes: abdominal pain and abdominal pain upper, [13]Pancreatitis includes: pancreatitis and pancreatitis acute;

[14]Hepatic enzymes increased includes: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased and transaminases increased; [15]Blood bilirubin increased includes: blood bilirubin increased, bilirubin conjugated increased and hyperbilirubinaemia ; [16]Rash includes: rash and rash maculopapular ; [17]Musculoskeletal pain includes: pain in extremity, back pain, myalgia, bone pain, musculoskeletal pain, neck pain, musculoskeletal chest pain, and musculoskeletal discomfort ; [18]Fatigue includes: fatigue and asthenia ;[19]Pyrexia includes: pyrexia and body temperature increased; [20]Oedema includes: oedema and oedema peripheral.

Decrease in phosphate levels occurred as a laboratory abnormality in 17.9% (all grades) and 6.4% (grade 3/4) of 156 patients receiving Scemblix at 40 mg twice daily.

Table 7-2 Adverse drug reactions observed with Scemblix in patients with Ph+ CML-CP harboring T315I mutation (study X2101)

Adverse drug reactions	Scemblix 200 mg BID N= 48 n (%) All grades	Scemblix 200 mg BID N=48 n (%) Grade ≥3
Infections and infestations		
Upper respiratory tract infection[1]	6 (12.5)	0
Lower respiratory tract infection[2]	4 (8.3)	2 (4.2)
Blood and lymphatic system disorders		
Thrombocytopenia[3]	9 (18.8)	8 (16.7)
Neutropenia[4]	7 (14.6)	6 (12.5)
Anaemia[5]	5 (10.4)	3 (6.3)
Metabolism and nutrition disorders		
Dyslipidaemia[6]	2 (4.2)	1 (2.1)
Decreased appetite	2 (4.2)	0
Nervous system disorders		
Headache	8 (16.7)	1 (2.1)
Dizziness	3 (6.3)	0
Eye disorders		
Vision blurred	1 (2.1)	0
Dry eye	2 (4.2)	0
Cardiac disorders		
Palpitations	2 (4.2)	0
Vascular disorders		
Hypertension[7]	5 (10.4)	3 (6.3)
Respiratory, thoracic and mediastinal disorders		
Cough	7 (14.6)	0
Dyspnoea	3 (6.3)	0
Non-cardiac chest pain	3 (6.3)	1 (2.1)
Pleural effusion	1 (2.1)	1 (2.1)
Gastrointestinal disorders		

Adverse drug reactions	Scemblix 200 mg BID N= 48 n (%) All grades	Scemblix 200 mg BID N=48 n (%) Grade ≥3
Pancreatic enzymes increased[8]	15 (31.3)	11 (22.9)
Nausea	13 (27.1)	0
Diarrhoea	10 (20.8)	1 (2.1)
Vomiting	9 (18.8)	3 (6.3)
Abdominal pain[9]	7 (14.6)	3 (6.3)
Pancreatitis[10]	1 (2.1)	0
Hepatobiliary disorders		
Hepatic enzyme increased[11]	9 (18.8)	4 (8.3)
Blood bilirubin increased[12]	3 (6.3)	0
Skin and subcutaneous tissue disorders		
Rash[13]	7 (14.6)	0
Urticaria	1 (2.1)	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[14]	18 (37.5)	1 (2.1)
Arthralgia	8 (16.7)	0
General disorders and administration site conditions		
Fatigue[15]	15 (31.3)	1 (2.1)
Pruritus	6 (12.5)	0
Oedema[16]	5 (10.4)	2 (4.2)
Pyrexia[17]	4 (8.3)	0
Investigations		
Blood creatine phosphokinase increased	2 (4.2)	0

[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, 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 and transaminases increased; [12]Blood bilirubin increased includes: blood bilirubin increased, bilirubin conjugated increased and hyperbilirubinaemia ; [13]Rash includes: rash and rash maculopapular ; [14]Musculoskeletal pain includes: pain in extremity, back pain, myalgia, bone pain, musculoskeletal pain, neck pain, musculoskeletal chest pain, musculoskeletal discomfort ; [15]Fatigue includes: fatigue and asthenia ; [16]Oedema includes: oedema and oedema peripheral ; [17]Pyrexia includes: pyrexia and body temperature increased ;

Decrease in phosphate levels occurred as a laboratory abnormality in 45.8% (all grades) and 6.3% (grade 3/ 4) of 48 patients receiving Scemblix at 200 mg twice daily.

Description of selected adverse drug reactions

Myelosuppression

Thrombocytopenia occurred in 98 of 356 (27.5%) patients receiving Scemblix, with grade 3 and 4 reactions reported in 24 (6.7%) and 42 (11.8%) of patients, respectively. Among the patients with thrombocytopenia ≥grade 3, the median time to first occurrence of reactions was 6 weeks (range: 0.1 to 64 weeks) with median duration of any occurring reaction of 1.71 weeks (95% CI, range: 1.43 to 2 weeks). Of the 98 patients with thrombocytopenia, 7 (2%) permanently discontinued Scemblix, while Scemblix was temporarily withheld in 45 (12.6%) of patients due to the adverse drug reaction.

Neutropenia occurred in 69 of 356 (19.4%) patients receiving Scemblix, with grade 3 and 4 reactions reported in 26 (7.3%) and 30 (8.4%) patients, respectively. Among the patients with neutropenia ≥grade 3, the median time to first occurrence of reactions was 6 weeks (range: 0.14 to 180 weeks) with median duration of any occurring reaction of 1.79 weeks (95% CI, range: 1.29 to 2 weeks). Of the 69 patients with neutropenia, 4 (1.1%) permanently discontinued Scemblix, while Scemblix was temporarily withheld in 34 (9.6%) patients due to the adverse drug reaction.

Anaemia occurred in 46 of 356 (12.9%) patients receiving Scemblix, with grade 3 events occurring in 19 (5.3%) patients. Among the patients with anaemia grade 3, the median time to first occurrence of reactions was 30 weeks (range: 0.4 to 207 weeks) with median duration of any occurring reaction of 0.9 weeks (95% CI, range: 0.43 to 2.14 weeks). Of the 46 patients with anaemia, Scemblix was temporarily withheld in 2 patients (0.6%) due to the adverse drug reaction.

8 Interactions

Agents that may increase asciminib plasma concentrations

Strong CYP3A4 inhibitors

Physiologically-based pharmacokinetic (PBPK) models predict that co-administration of Scemblix at 200 mg twice daily with a strong CYP3A4 inhibitor (clarithromycin) would increase asciminib AUCtau and Cmax by 77% and 49%, respectively.

Caution should be exercised during concomitant administration of Scemblix 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 Scemblix is not required.

Agents that may decrease asciminib plasma concentrations

Strong CYP3A4 inducers

Co-administration of a strong CYP3A4 inducer (rifampicin) decreased asciminib AUCinf by 14.9%, while increasing asciminib Cmax by 9% in healthy subjects receiving a single Scemblix dose of 40 mg.

PBPK models predict that co-administration of asciminib at 80 mg once daily with rifampicin would decrease asciminib AUCtau and Cmax by 52% and 23%, respectively, while co-

administration of asciminib at 200 mg twice daily with rifampicin would decrease asciminib AUCtau and Cmax by 63% and 47%, respectively.

Caution should be exercised during concomitant administration of Scemblix at all recommended doses with strong CYP3A4 inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, or St. John's wort *(Hypericum perforatum)*. Dose adjustment of Scemblix is not required.

Agents that may have their plasma concentrations altered by asciminib

CYP3A4 substrates with narrow therapeutic index

Co-administration of asciminib with a CYP3A4 substrate (midazolam) increased midazolam AUCinf and Cmax by 28% and 11%, respectively, in healthy subjects receiving Scemblix 40 mg twice daily.

PBPK models predict that co-administration of asciminib at 80 mg once daily would increase midazolam AUCinf and Cmax by 24% and 17%, respectively, while co-administration of asciminib at 200 mg twice daily would increase midazolam AUCinf and Cmax by 88% and 58%, respectively.

Caution should be exercised during concomitant administration of Scemblix 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 11 Clinical pharmacology). Dose adjustment of Scemblix is not required.

CYP2C9 substrates

Co-administration of asciminib with a CYP2C9 substrate (warfarin) increased S-warfarin AUCinf and Cmax by 41% and 8%, respectively, in healthy subjects receiving Scemblix 40 mg twice daily.

PBPK models predict that co-administration of asciminib at 80 mg once daily would increase S-warfarin AUCinf and Cmax by 52% and 4%, respectively, while co-administration of asciminib at 200 mg twice-daily would increase S-warfarin AUCinf and Cmax by 314% and 7%, respectively.

Caution should be exercised during concomitant administration of Scemblix at 80 mg total daily dose with CYP2C9 substrates known to have a narrow therapeutic index, including, but not limited to, phenytoin or warfarin (see section 11 Clinical pharmacology). Dose adjustment of Scemblix is not required.

Concomitant administration of Scemblix at 200 mg twice daily with CYP2C9 sensitive substrates and CYP2C9 substrates known to have a narrow therapeutic index should be avoided and alternative medications should be considered (see section 11 Clinical pharmacology). If co-administration cannot be avoided, the CYP2C9 substrates dose should be reduced. If co-administration with warfarin cannot be avoided, the frequency of international normalized ratio (INR) monitoring should be increased as the anti-coagulant effect of warfarin may be enhanced.

P-gp substrates

Coadministration of SCEMBLIX with a drug that is a substrate of P-gp may result in a clinically relevant increase in the plasma concentrations of P-gp substrates, where minimal concentration changes may lead to serious toxicities.

Substrates of OATP1B, of BCRP or of both transporters

PBPK models predict that co-administration of asciminib at 40 mg twice daily and 80 mg once daily with an OATP1B substrate (pravastatin) would increase pravastatin Cmax by 43% and

63% and AUCinf by 37% and 51%, respectively, while co-administration of asciminib at 200 mg twice daily would increase pravastatin Cmax and AUCinf by 141% and 137%, respectively.

PBPK models predict that co-administration of asciminib at 40 mg twice daily and 80 mg once daily with an OATP1B, CYP3A4 and P-gP substrate (atorvastatin) would increase atorvastatin Cmax by 97% and 143% and AUCinf by 81% and 122%, respectively, while co-administration of asciminib at 200 mg twice daily would increase atorvastatin Cmax and AUCinf by 300% and 326%, respectively.

PBPK models predict that co-administration of asciminib at 40 mg twice daily and 80 mg once daily with a BCRP substrate (sulfasalazine) would increase sulfasalazine Cmax by 334% and 342% and AUCinf by 333% and 340%, respectively, while co-administration of asciminib at 200 mg twice daily would increase sulfasalazine Cmax and AUCinf by 353% and 359%, respectively.

PBPK models predict that co-administration of asciminib at 40 mg twice daily and 80 mg once daily with a BCRP and OATP1B substrate (rosuvastatin) would increase rosuvastatin Cmax by 453% and 530% and AUCinf by 190% and 202%, respectively, while co-administration of asciminib at 200 mg twice daily would increase rosuvastatin Cmax and AUCinf by 732% and by 311%, respectively.

Caution should be exercised during concomitant administration of Scemblix at all recommended doses with substrates of OATP1B, BCRP or both transporters, including, but not limited to sulfasalazine, methotrexate, pravastatin, atorvastatin, pitavastatin, rosuvastatin and simvastatin. Refer to OATP1B and BCRP substrates' dose reductions, as recommended in their prescribing information.

Concomitant administration of Scemblix at all recommended doses concomitantly with rosuvastatin should be avoided and alternative statins should be considered. If co-administration cannot be avoided, rosuvastatin dose should be reduced, as recommended in its prescribing information (see section 11 Clinical pharmacology).

QT prolonging agents

Caution should be exercised during concomitant administration of Scemblix at 80 mg total daily dose and medicinal products known to cause torsades de pointes, including, but not limited to, bepridil, chloroquine, clarithromycin, halofantrine, haloperidol, methadone, moxifloxacin or pimozide (see section 11 Clinical pharmacology).

Concomitant administration of Scemblix at 200 mg twice-daily dose and medicinal products known to cause torsades de pointes should be avoided (see section 11 Clinical pharmacology).

Drug-food interactions

The bioavailability of asciminib decreases on consumption of food (see sections 4 Dosage regimen and administration and 11 Clinical pharmacology).

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

Based on findings from animal studies, Scemblix can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women to inform a product-associated risk.

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

Pregnant women and females of reproductive potential should be advised of the potential risk to a fetus if Scemblix is used during pregnancy or if the patient becomes pregnant while taking Scemblix (see section 6 Warnings and precautions).

Data

Animal data

In embryo-fetal development studies, pregnant animals received oral doses of asciminib at 25, 150 and 600 mg/kg/day in rats and at 15, 50 and 300 mg/kg/day in rabbits during 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-fetal death at doses below or equal to 150 mg/kg/day. A dose-related increase in fetal weights at 25 and 150 mg/kg/day was observed. Fetal 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-fetal development were also observed at 150 mg/kg/day. The maternal no-observed-adverse-effect level (NOAEL) was 150 mg/kg/day and the fetal NOAEL was 25 mg/kg/day. At the fetal NOAEL of 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. At the fetal NOAEL of 25 mg/kg/day, the AUC exposures were below those achieved in patients at the 200 mg twice daily dose.

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-fetal mortality, and a low incidence of cardiac malformations, indicative of teratogenicity, were observed at 50 mg/kg/day. There was no effect on fetal growth. The NOAEL for maternal toxicity was 50 mg/kg/day and the fetal NOAEL was 15 mg/kg/day. At the fetal NOAEL of 15 mg/kg/day, the AUC exposures were equivalent to or below those achieved in patients at the 40 mg twice-daily or 80 mg once-daily doses, respectively. At the fetal NOAEL of 15 mg/kg/day, the AUC exposures were below those achieved in patients at the 200 mg twice-daily dose.

9.2 Lactation

Risk summary

It is not known if asciminib is transferred into human milk after administration of Scemblix. There are no data on the effects of asciminib on the breastfed child or on milk production.

Because of the potential for serious adverse drug reactions in the breastfed child, breast-feeding is not recommended during treatment with Scemblix and for at least 3 days after the last dose.

9.3 Females and males of reproductive potential

Pregnancy testing

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with Scemblix.

Contraception

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

Infertility

There are no data on the effect of Scemblix on human fertility.

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, 13-fold or 2-fold higher than those achieved in patients at the 40 mg twice-daily, 80 mg once-daily or 200 mg twice-daily doses, respectively.

10 Overdosage

There is limited experience of Scemblix overdose. In clinical studies, Scemblix 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.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Antineoplastic agents. ATC code: L01EA06

Mechanism of action (MOA)

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

Pharmacodynamics (PD)

In vitro, asciminib inhibits the tyrosine kinase activity of ABL1 at mean IC_{50} values below 3 nanomolar. In patient-derived cancer cells, asciminib specifically inhibits the proliferation of cells harboring BCR-ABL1 with IC_{50} values between 1 and 25 nanomolar. In cells expressing the wild-type or the T315I mutant form of BCR-ABL1, asciminib inhibits cell growth with mean IC_{50} values of 0.61 ±0.21 and 7.64 ±3.22 nanomolar, respectively.

In mouse xenograft models of CML, asciminib dose-dependently inhibited the growth of tumors harbouring either the wild-type or the T315I mutant form of BCR-ABL1, with tumor regression being observed at doses above 7.5 mg/kg or 30 mg/kg twice daily, respectively.

Cardiac electrophysiology

Scemblix treatment is associated with an exposure-related prolongation of the QT interval. The correlation between asciminib concentration and the estimated maximum mean change from baseline of the QT interval with Fridericia's correction (ΔQTcF) was evaluated in 239 patients with Ph+ CML or Ph+ acute lymphoblastic leukemia (ALL) receiving Scemblix. Scemblix is not predicted to cause large mean increases in QTcF interval (i.e., >20 msec) following a dose of 40 mg twice daily, 80 mg once daily or 200 mg twice daily.

Pharmacokinetics (PK)

Absorption

Asciminib is rapidly absorbed, with median maximum plasma levels (Tmax) reached 2 to 3 hours after oral administration, independent of the dose. The geometric mean (geoCV%) of Cmax at steady state is 1781 ng/mL (23%) and 793 ng/mL (49%) following administration of Scemblix at 80 mg once-daily and 40 mg twice-daily doses, respectively. The geometric mean (geoCV%) of Cmax at steady state is 5642 ng/ml (40%) following administration of Scemblix at 200 mg twice-daily dose. The geometric mean (geoCV%) of AUCtau is 5262 ng*h/mL (48%) following administration of Scemblix at 40 mg twice-daily dose.

Asciminib bioavailability may be reduced by co-administration of oral medicinal products containing hydroxypropyl-β-cyclodextrin as an excipient. Co-administration of multiple doses of itraconazole containing hydroxypropyl-β-cyclodextrin at a total of 8 g per dose with a 40 mg dose of asciminib, decreased asciminib AUCinf 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 Dosage regimen and administration and 8 Interactions).

Distribution

Asciminib apparent volume of distribution at steady state is 111 L, 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/metabolism

Asciminib is primarily metabolized via CYP3A4-mediated oxidation (36%), UGT2B7- and UGT2B17-mediated glucuronidation (13.3% and 7.8%, respectively). Asciminib is the main circulating component in plasma (92.7% of the administered dose).

Elimination

Asciminib is mainly eliminated via fecal excretion, with a minor contribution of the renal route. PBPK models predict that asciminib biliary secretion via BCRP accounts for 31.1% of its total systemic clearance. Eighty and 11% of the asciminib dose were recovered in the feces and in the urine of healthy subjects, respectively, following oral administration of a single 80 mg dose of [^{14}C]-labelled asciminib. Fecal 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 terminal elimination half-life ($T_{1/2}$) of asciminib is between 7 and 15 hours.

Linearity/non-linearity

Asciminib exhibits a slight dose over-proportional increase in steady-state exposure (AUC and Cmax) 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. In addition, asciminib reversibly inhibits CYP2C8 and CYP2C19 at plasma concentrations reached at 200 mg twice-daily dose.

Transporters

Asciminib is a substrate of BCRP and P-gp. Asciminib inhibits BCRP and P-gp, OATP1B1, OATP1B3, and OCT1 with Ki values of 24.3, 21.7, 2.46, 1.92, and 3.41 micromolar, respectively. Based on PBPK models, asciminib increases the exposure to OATP1B and BCRP substrates (see Section 8 Interactions). Based on PBPK models, no clinically relevant interaction is expected for P-gp substrates, while for OCT1 the clinical relevance is currently unknown at Scemblix 200 mg twice-daily dose.

Multiple pathways

Asciminib is metabolized 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 Scemblix exposure.

Asciminib inhibits several pathways including CYP3A4, CYP2C9, OATP1B, P-gp and BCRP. Scemblix may increase the exposure of medicinal products, which are substrates of these pathways (see Section 8 Interactions).

Special populations

Geriatric patients (65 years of age or above)

In ASCEMBL, 44 of the 233 (18.9%) patients were 65 years or older, while 6 (2.6%) were 75 years or older. In study X2101, 16 of the 48 (33.3%) patients were 65 years or older, while 4 (8.3%) were 75 years or older.

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.

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 AUCinf and Cmax 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 Scemblix (see section 4 Dosage regimen and administration).

Population pharmacokinetics models indicate an increase in asciminib median steady state $AUC_{0\text{-}24h}$ 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 to 6), moderate hepatic impairment (Child-Pugh B score 7 to 9) or severe hepatic impairment (Child-Pugh C score 10 to 15) was conducted. Asciminib AUCinf 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 Scemblix (see section 4 Dosage regimen and administration).

12 Clinical studies

Ph+ CML-CP

The clinical efficacy and safety of Scemblix in the treatment of patients with Philadelphia chromosome-positive myeloid leukemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors were demonstrated in the multi-center, randomized, active-controlled and open-label phase III study ASCEMBL. Patients with known presence of T315I and/or V299L mutations at any time prior to study entry were not included in ASCEMBL.

In this study, a total of 233 patients were randomized in a 2:1 ratio and stratified according to major cytogenetic response (MCyR) status at baseline to receive either Scemblix 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 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. The median duration of treatment was 103 weeks (range: 0.1 to 201 weeks) for patients receiving Scemblix and 31 weeks (range: 1 to 188 weeks) for patients receiving bosutinib.

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 ratio ≤0.1% by International Scale [IS]. Secondary endpoints were complete cytogenetic response rate (CCyR) at 24 and 96 weeks, defined as no metaphases in bone marrow with a minimum of 20 metaphases examined.

The main efficacy outcomes from ASCEMBL are summarized in Table 12-1.

Table 12-1 Efficacy results in Ph+ CML-CP patients previously treated with two or more tyrosine kinase inhibitors (ASCEMBL)

	Scemblix 40 mg twice daily	Bosutinib 500 mg once daily	Difference (95% CI)	p-value
MMR rate, % (95% CI) at 24 weeks	**N=157** 25.48 (18.87, 33.04)	**N=76** 13.16 (6.49, 22.87)	12.24[1] (2.19, 22.30)	0.029[2]
MMR rate, % (95% CI) at 96 weeks	37.58 (29.99, 45.65)	15.79 (8.43, 25.96)	21.74[1] (10.53, 32.95)	0.001[2]
CCyR rate, % (95% CI) at 24 weeks	**N=103**[3] 40.78 (31.20, 50.9)	**N=62**[3] 24.19 (14.22, 36.74)	17.3[1] (3.62, 30.99)	0.019[2,4]

CCyR rate, % (95% CI) at 96 weeks	39.81 (30.29, 49.92)	16.13 (8.02, 27.67)	23,87[1] (10.3, 37.43)	0.001[2,4]

[1]*On adjustment for the baseline major cytogenetic response status*
[2]*Cochrane-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*
[4]*Nominal p-value*

The predicted MMR rate at 24 weeks for the Scemblix 80 mg once-daily dose is comparable to the MMR rate at 24 weeks observed in ASCEMBL with the Scemblix 40 mg twice-daily dose, based on exposure-response analysis.

In ASCEMBL, 12.7% of patients treated with Scemblix and 13.2% of patients receiving bosutinib had one or more BCR-ABL1 mutation detected at baseline. MMR at 24 weeks was observed in 35.3% and 24.8% of patients receiving Scemblix with or without any BCR-ABL1 mutation at baseline, respectively. 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 randomized treatment represented the third, fourth, fifth or more line of TKI was 29.3%, 25%, and 16.1% in patients treated with Scemblix and 20%, 13.8%, and 0% in patients receiving bosutinib, respectively.

The MMR rate at 48 weeks was 29.3% (95% CI: 22.32, 37.08) in patients receiving Scemblix and 13.2% (95% CI: 6.49, 22.87) in patients receiving bosutinib. The Kaplan Meier estimated proportion of patients receiving Scemblix and maintaining MMR for at least 72 weeks was 96.7% (95% CI: 87.4, 99.2).

Ph+ CML-CP harboring the T315I mutation

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

In this study, a total of 185 patients with Ph+ CML-CP without (N=115) or with (N=70) the T315I mutation received Scemblix at doses ranging from 10 to 200 mg twice daily or 80 to 200 mg once daily. Among these, 48 patients with Ph+ CML-CP harboring the T315I mutation received Scemblix at a dose of 200 mg twice daily. Patients continued treatment until unacceptable toxicity or treatment failure occurred.

Patients with Ph+ CML-CP harboring the T315I mutation who received Scemblix at a dose of 200 mg twice daily were 77.1% male and 22.9% female with median age of 56.5 years (range: 26 to 86 years). Of 48 patients, 33.3% were 65 years or older, while 8.3% were 75 years or older. The patients were Caucasian (47.9%), Asian (25%) and Black (2.1%). Seventy-five percent and 25% of patients had ECOG performance status 0 or 1, respectively. Patients who had previously received 1, 2, 3, 4 and 5 or more TKIs were 16.7%, 31.3%, 35.4%, 14.6% and 2.1%, respectively. The median duration of treatment was 108 weeks (range: 2 to 215 weeks).

MMR by 24 weeks was achieved in 42.2% of the evaluable patients (N=45) treated with Scemblix (95% CI: 27.7-57.8%)

13 Non-clinical 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, 100-fold or 30-fold higher when compared to asciminib free Cmax in patients at the 40 mg twice-daily, 80 mg once-daily or 200 mg twice-daily doses, 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, hematopoietic system, adrenal gland, and gastro-intestinal 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, 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 on 40 mg twice daily or 80 mg once daily. AUC exposures were below (rats), equivalent (dogs) or approximately 2-fold higher (monkeys) than the exposure in patients on 200 mg twice daily. These changes were fully reversible.

Effects on the hematopoietic system (reduction in red blood cells mass, increased splenic or bone marrow pigment and increased reticulocytes) were consistent with a mild and regenerative, extravascular, hemolytic anemia 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. AUC exposures were below (rats), equivalent (dogs) or approximately 2-fold higher (monkeys) than the exposure in patients on 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-fold or 22-fold higher than those achieved in patients on 40 mg twice daily or 80 mg once daily, respectively. AUC exposure was 4-fold higher than those achieved in patients on 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 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 neither *in vitro* nor *in vivo*. Carcinogenicity studies have not been conducted with asciminib.

Reproductive toxicity

For information on reproductive toxicity, see section 9 Pregnancy, lactation, females and males of reproductive potential.

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 Cmax in plasma was 15-fold, 6-fold or 2-fold higher than the exposure in patients on 40 mg twice daily, 80 mg once daily or 200 mg twice daily, respectively.

14 Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Do not store above 25 °C.

Instruction for Patients: Please store this product in the refrigerator (2 - 8 ºC) if you are unable to store it under 25°C.

Store in the original package in order to protect from moisture.

Scemblix must be kept out of the reach and sight of children.

Presentation

For both 20 mg and 40 mg strengths: Tablets are packed in PCTFE-PVC blisters with Alu foil, in a box of 60 tablets.

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