Summary Report of Benefit-Risk Assessment

SCEMBLIX FILM-COATED TABLET 20 MG, 40 MG

NEW DRUG APPLICATION

Active Ingredient(s)	Asciminib hydrochloride
Product Registrant	Novartis (Singapore) Pte Ltd
Product Registration Number	SIN16539P, SIN16540P
Application Route	Full evaluation
Date of Approval	05 July 2022

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A INTRODUCTION

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 (TKIs).

The active substance, asciminib, is an oral 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.

Scemblix is available as film coated tablets containing 20mg or 40mg of asciminib. Other ingredients in the tablet core are lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, magnesium stearate, and colloidal anhydrous silica. Ingredients in the film coating include lecithin, polyvinyl alcohol, talc, xantham gum, titanium dioxide, iron oxide red, iron oxide yellow (20mg only) and iron oxide black (40mg only).

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, asciminib, is manufactured at Novartis Pharma Schweizerhalle AG, Pratteln, Switzerland. The drug product, Scemblix Film Coated Tablets 20mg and 40mg, are manufactured at Novartis Pharma Stein AG, Stein, Switzerland.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance(s) and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Novartis Pharma Schweizerhalle AG was adequate to support the storage at below 30^{o}C with a re-test period of 36 months. The packaging consists of a polyethylene bag within a sealed quadruple laminated foil bag and then packed in drums.

Drug product:

The tablet is manufactured using dry granulation followed by film-coating. The process is considered a standard process.

The manufacturing site involved is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the

manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored at or below 25ºC. The container closure system consists of PCTFE-PVC/ Aluminium blisters containing 60 tablets.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of asciminib for the treatment of adult patients with Ph+ CML CP previously treated with two or more TKIs was based primarily on data from one pivotal study, A2301.

Study A2301 is an ongoing Phase III, multicentre, active-controlled, open-label, randomised study to compare the efficacy and safety of asciminib with bosutinib in the treatment of adult patients with CML-CP, who had received prior treatment with two or more adenosine triphosphate (ATP) binding site TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib), and had treatment failure or were intolerant to the most recent TKI. Patients with known presence of the T315I or V299L mutation were excluded from the study as bosutinib is not active at physiologically relevant concentrations against the T315I and V299L mutations.

A total of 233 patients in the study were randomised in a 2:1 ratio to receive asciminib 40 mg twice daily or bosutinib 500 mg once daily, stratified according to according to major cytogenetic response (MCyR) status at baseline. Patients continued treatment until unacceptable toxicity or treatment failure occurred. Patients randomised to the bosutinib arm who experienced treatment failure were offered the option to switch to asciminib treatment within 96 weeks after the last patient was randomised to the study. Patients who discontinued study treatment at any time during the study were to be followed up for survival and for progression to accelerated phase (AP)/ blast crisis (BC) for up to 5 years from the date when the last randomised patient received the first dose.

The primary efficacy endpoint was major molecular response (MMR) rate at Week 24, and the key secondary endpoint was MMR rate at Week 96. Other secondary efficacy endpoints included MMR rate by Week 24, complete cytogenetic response (CCyR) at and by Week 24, time to response, duration of response, time to treatment failure (TTF), progression-free survival (PFS) and overall survival (OS).

The full analysis set comprised 157 patients in the asciminib arm and 76 patients in the bosutinib arm. As of the cut-off date of 06 October 2021, all patients had completed the Week 96 visit or discontinued earlier. A total of 99 of the 233 patients (42.5%) were continuing the study treatment. The median duration of exposure was 103.1 weeks for asciminib and 30.5 weeks for bosutinib.

The patient demographics and baseline disease characteristics were generally well-balanced between the treatment arms. The median age was 52 years and 18.9% of the patients were ≥ 65 years of age. The majority of patients were White (74.7%), and 14.2% were Asian. The

proportions of patients who received 2, 3, 4 and ≥ 5 lines of prior TKI therapy were 48.1%, 31.3%, 14.6% and 6.0%, respectively. Approximately one-third (34.8%) of the patients were intolerant to the most recent TKI therapy, while 63.9% patients experienced treatment failure to the most recent TKI therapy prior to study entry. There were some imbalances in sex, prior lines of TKI treatment and reasons for discontinuation of prior TKI observed. Nevertheless, analyses based on logistic regression models showed that these imbalances did not have a significant impact on the primary efficacy results.

For the primary efficacy analysis, asciminib demonstrated a statistically significant and clinically meaningful improvement compared to bosutinib in terms of MMR at Week 24, with 25.5% in the asciminib arm and 13.2% in the bosutinib arm (treatment difference = 12.2%; 95% CI: 2.2, 22.3; p=0.029). This was supported by the subgroup analyses stratified by baseline cytogenetic response, sex, race, age, reason for discontinuation of prior TKI, number of prior TKI therapies and presence of BCR-ABL1 mutations, which demonstrated consistent treatment effect in favour of asciminib across subgroups. Sensitivity analyses also demonstrated consistent treatment benefit with asciminib, supporting the robustness of the results.

The key secondary endpoint, MMR rate at Week 96, showed a statistically significant and clinically meaningful improvement for asciminib compared to bosutinib, with 37.6% in the asciminib arm and 15.8% in the bosutinib arm (treatment difference = 21.7%; 95% CI: 10.5, 33.0; p=0.001).

The results of the secondary endpoints were supportive of the primary and key secondary efficacy results. Patients in the asciminib arm showed greater molecular responses as compared with patients on bosutinib at Week 96. There were higher proportions of patients on asciminib who achieved BCR-ABL1 International Scale (IS) ≤ 0.01% [MR4 (4-log reduction) or better] (17.2% vs 10.5%) and BCR-ABL1 IS ≤ 0.0032% [MR4.5 (4.5-log reduction) or better] (10.8% vs 5.3%) at Week 96 compared to patients on bosutinib. Median time to MMR was 16.1 weeks in the asciminib arm compared to 24.0 weeks in the bosutinib arm. Median duration of MMR had not been reached for both arms.

Among patients who were not in CCyR at baseline, there were higher proportions in the asciminib arm who achieved CCyR at Week 24 (40.8% vs 24.2%), Week 48 (39.8% vs 21.0%) and Week 96 (39.8% vs 16.1%) compared to the bosutinib arm, which were considered clinically relevant. Median duration of CCyR has not been reached for both arms.

The probability of patients experiencing treatment failure was lower in the asciminib arm (HR = 0.4; 95% CI: 0.3%, 0.6%; p<0.0001), and the proportion of patients experiencing treatment failure was 51.0% in the asciminib arm compared to 82.9% in the bosutinib arm. The median time to treatment failure was 2 years in the asciminib arm compared to 6 months in the bosutinib arm. Other endpoints of interest such as PFS and OS were immature at the data cut-off date.

Summary of key efficacy results

	Asciminib	**Bosutinib**
Primary endpoint		
MMR rate at Week 24, n	157	76
Response, n (%)	40 (25.5%)	10 (13.2%)
Common risk difference[a] (%)	12.2	
95% CI for difference	(2.2, 22.3)	
Cochrane-Mantel-Haenszel (CMH) test p-value[b]	0.029	
Key secondary endpoint		

MMR rate at Week 96, n	157	76
Response, n (%)	59 (37.6%)	12 (15.8%)
Common risk difference[a] (%)	21.7	
95% CI for difference	(10.5, 33.0)	
CMH test p-value[b]	0.001	
Secondary endpoints		
BCR-ABL1 ratio (% IS) categories at Week 96, n	157	76
≤0.0032%	17 (10.8%)	4 (5.3%)
>0.0032% - ≤ 0.01%	10 (6.4%)	4 (5.3%)
>0.01% - ≤ 0.1%	32 (20.4%)	4 (5.3%)
>0.1% - ≤ 1%	17 (10.8%)	4 (5.3%)
>1% - ≤ 10%	3 (1.9%)	2 (2.6%)
>10%	0	0
Missing/not evaluable	9 (5.7%)	1 (1.3%)
Discontinued due to lack of efficacy/ progressive disease/ death	39 (24.8%)	30 (39.5%)
Discontinued due to other reasons	30 (19.1%)	27 (35.5%)
CCyR rate at Week 24, n	103	62
Response, n (%)	42 (40.8%)	15 (24.2%)
Common risk difference[a] (%)	17.3	
95% CI for difference	(3.6, 31.0)	
CCyR rate at Week 96, n	103	62
Response, n (%)	41 (39.8)	10 (16.1)
Common risk difference[a] (%)	23.9	
95% CI for difference	(10.3, 37.4)	

Data cut-off date: 06 October 2021

[a] The common risk difference after adjusting for stratum: baseline MCyR status and its 95% CI were estimated using the Mantel-Haenszel method.

[b] CMH 2-sided test stratified by baseline MCyR status.

Overall, Study A2301 met its primary and key secondary endpoints demonstrating superior MMR rate of asciminib over bosutinib at Week 24 and Week 96, respectively. These results were supported by the secondary endpoints which showed consistent treatment effect in favour of asciminib. The submitted data adequately supported the efficacy of asciminib for the intended population of adult patients with Ph+ CML CP previously treated with two or more TKIs. The PFS and OS data was immature and the benefits will be confirmed with longer follow-up. The registrant will be required to submit the final results of Study A2301 to confirm the clinical benefits of asciminib.

D ASSESSMENT OF CLINICAL SAFETY

The safety assessment was based primarily on the data from the pivotal study A2301 (156 patients in the asciminib arm and 76 patients in the bosutinib arm) and supported by a Phase I dose escalation study X2101. In the safety sets pooled from Study A2301 and Study X2101, there was a total of 356 patients with CML-CP/AP treated with any dose of asciminib. As of the safety data cut-off date of 06 January 2021, the median duration of exposure to study treatment in Study A2301 was longer in the asciminib arm (67.1 weeks) compared to the bosutinib arm (29.7 weeks), with total exposure of 204.3 patient-years and 61.2 patient-years, respectively. In the safety pool, the median duration of exposure to all doses of asciminib was 89.3 weeks, corresponding to 797.1 patient-years.

Overview of safety profile (Study A2301)

AE	Asciminib (N=156)	Bosutinib (N=76)
AE	142 (91.0%)	74 (97.4%)
Treatment-related AE	103 (66.0%)	68 (89.5%)

SAE	24 (15.4%)	18 (23.7%)
Treatment-related SAE	5 (3.2%)	9 (11.8%)
Discontinuations due to AE	11 (7.1%)	19 (25.0%)
Overall deaths	4 (2.6%)	1 (1.3%)
On-treatment deaths	2 (1.3%)	1 (1.3%)

Data cut-off date: 06 January 2021

Overview of safety profile (Safety pool – Asciminib all doses)

AE	Asciminib (N=356)
AE	342 (96.1%)
Treatment-related AE	279 (78.4%)
SAE	108 (30.3%)
Treatment-related SAE	26 (7.3%)
Discontinuations due to AE	34 (9.6%)
Overall deaths	14 (3.4%)
On-treatment deaths	9 (2.5%)

Data cut-off date: 06 January 2021

In Study A2301, adverse events (AEs) were reported less frequently in the asciminib arm compared to the bosutinib arm (91.0% vs 97.4%). The most frequently occurring AEs (≥ 10%) in the asciminib arm were thrombocytopenia (23.1%), neutropenia (19.2%), headache (18.6%), fatigue (13.5%), arthralgia (12.2%), hypertension (12.2%), nausea (11.5%), diarrhoea (11.5%), and nasopharyngitis (10.9%). The most frequently (≥ 10%) occurring AEs suspected to be study treatment-related in the asciminib arm were thrombocytopenia (19.9%) and neutropenia (15.4%).

Serious adverse events (SAEs) were reported less frequently in the asciminib arm compared to the bosutinib arm (15.4% vs 23.7%). All the SAEs suspected to be study treatment-related in the asciminib arm (thrombocytopaenia, febrile neutropenia, platelet count decreased, cerebral infarct, ejection fraction decreased, myocardial ischaemia) were reported as single cases. There were two on-treatment deaths in the asciminib arm vs one in the bosutinib arm. The on-treatment deaths in the asciminib arm were due to arterial embolism and ischemic stroke which were assessed by the investigator to be not related to the study treatment. The incidence of AEs leading to study treatment discontinuation was lower in the asciminib arm (7.1%) compared to the bosutinib arm (25.0%).

The identified adverse events of special interest (AESIs) with asciminib included myelosuppression, pancreatic toxicity, hypersensitivity, hepatotoxicity, hepatitis B virus reactivation, reproductive toxicity, gastrointestinal toxicity, phototoxicity, QTc prolongation, cardiac failure, oedema and fluid retention, ischemic heart disease and central nervous system conditions, and haemorrhage. In general, the incidences of AESIs were similar or reported more frequently in the bosutinib arm, except for thrombocytopenia which was reported more frequently in the asciminib arm than in the in bosutinib arm (29.5% vs 19.7%). Most thrombocytopenia events were of Grade 1 or 2 in severity and they did not translate into significant increase in risk of haemorrhage (11.5% in asciminib arm vs 10.5% in bosutinib arm). The AESIs were generally manageable through dose interruptions or dose adjustments. Consistent safety profile was also observed based on the updated analysis of the data from the pivotal study A2301 at the cut-off date of 06 October 2021. In addition, the findings from the safety sets pooled from Study A2301 and Study X2101 with longer duration of exposure were generally consistent with that observed in the pivotal study.

Overall, the safety profile of asciminib was considered acceptable for the intended population given the disease setting. The package insert has included adequate warnings and information

on clinical management of the AEs, as well as recommendations for dose modifications for adverse drug reactions to address the risks associated with asciminib.

E ASSESSMENT OF BENEFIT-RISK PROFILE

CML is a clonal myeloproliferative disorder of transformed, hematopoietic progenitor cells characterised by overproduction of immature myeloid cells and mature granulocytes in the spleen, bone marrow, and peripheral blood. Despite the availability of TKIs that have improved treatment outcomes in patients with CML, the therapeutic options are limited for those who experience treatment failure or are intolerant to previous TKI therapy. These patients are at higher risk of progressive disease and have worse prognosis.

The clinical benefit of asciminib in the treatment of adult patients with Ph+ CML CP previously treated with two or more TKIs has been demonstrated based on statistically significant and clinically meaningful higher MMR rate with asciminib compared with bosutinib at 24 weeks (25.5% vs 13.2%; difference of 12.2%; 95% CI 2.2, 22.3; p=0.029) and 96 weeks (37.6% vs 15.8%; difference of 21.7%; 95% CI 10.5, 33.0; p=0.001). The efficacy of asciminib was consistently supported by other secondary endpoints.

The safety profile of asciminib was considered acceptable relative to benefits. The most notable safety concerns with asciminib were myelosuppression, pancreatic toxicity, hypersensitivity and hypertension. The safety risks have been adequately described in the package insert, which included recommendations for dose modifications for adverse drug reactions.

Overall, the benefit-risk profile of asciminib in the treatment of adult patients with Ph+ CML-CP previously treated with two or more TKIs was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits of Scemblix have been demonstrated to outweigh the risks for the treatment of adult patients with Ph+ CML in CP previously treated with two or more TKIs and approval of the product registration was granted on 05 July 2022.

APPROVED PACKAGE INSERT AT REGISTRATION

NOVARTIS

1 Scemblix

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).

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.

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.

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

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	

Adverse drug reaction	Dosage modification
Elevation >2 x ULN[3]	Withhold Scemblix until resolved to <1.5 x ULN. • If resolved: resume Scemblix at reduced dose. If events 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 (see section 11 Clinical pharmacology).

Hepatic impairment

No dose adjustment is required in patients with mild, moderate or severe hepatic impairment receiving Scemblix (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 events 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. Hypokalaemia and hypomagnesaemia 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 events 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).

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) 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	Scemblixsafety 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
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

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	Scemblixsafety pool[3] N=356 (%) All grades	Frequency category[3] N=356 All grades
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						
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						

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	Scemblixsafety pool[3] N=356 (%) All grades	Frequency category[3] N=356 All grades
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
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 events (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;

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	Scemblixsafety pool[3] N=356 (%) All grades	Frequency category[3] N=356 All grades

[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.

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 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.

Caution should be exercised during concomitant administration of Scemblix 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.

Caution should be exercised during concomitant administration of Scemblix 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.

Caution should be exercised during concomitant administration of Scemblix 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.

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.

QT prolonging agents

Caution should be exercised during concomitant administration of Scemblix 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).

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.

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.

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 or 13-fold higher than those achieved in patients at the 40 mg twice-daily or 80 mg once-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 form of BCR-ABL1, asciminib inhibits cell growth with mean IC_{50} values of 0.61 ±0.21 nanomolar.

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

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 total daily dose of 80 mg.

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 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.

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, no clinically relevant interaction is expected for substrates of these transporters.

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.

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.

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).

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 higher when compared to asciminib free Cmax in patients at the 40 mg twice-daily, 80 mg once-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. 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 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. 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 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 and 6-fold higher than the exposure in patients on 40 mg twice daily and 80 mg once 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.

Novartis Pharma AG, Lichtstrasse 35, 4056 Basel, Switzerland