Asciminib (Scemblix®) for the treatment of Philadelphia chromosome-positive (Ph+) chronic myeloid leukaemia (CML) in chronic phase (CP)

General information

Drug description	Indication [1]
Asciminib (Scemblix®) is a first-in-class BCR-ABL1 inhibitor specifically targeting the ABL myristoyl pocket (STAMP) [2]. Asciminib works differently from all current approved tyrosine kinase inhibitors by using a mechanism which may overcome resistance or side effects of treatment in patients on current tyrosine kinase inhibitors [3].	Asciminib (Scemblix®) is indicated for the treatment of adult patients with Philadelphia chromosome-positive CML in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors.

Current treatment [3]

- The current pharmacological treatment options for third-line treatment of CML-CP are:
  - Imatinib
  - Nilotinib
  - Dasatinib
  - Bosutinib
  - Ponatinib.

Regulatory status

EMA [1, 4]	FDA [5]
Approval status for this indication: On 23 June 2022, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Scemblix®. **UPDATE:** Date of issue of marketing authorisation valid throughout the European Union: 25/08/2022 The full indication is: ❖ Scemblix® is indicated for the treatment of adult patients with Philadelphia chromosome-positive CML in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors. **Other indications**: none ✓ **Orphan status** ✓ **Medicine is under additional monitoring**	**Approval status for this indication**: On 29 October 2021, the FDA granted accelerated approval to asciminib (Scemblix®) for patients with Philadelphia chromosome-positive CML (Ph+ CML) in CP, previously treated with two or more tyrosine kinase inhibitors. ✓ **Priority review** ✓ **Breakthrough designation** ✓ **Fast track designation** ✓ **Orphan drug designation** **Other indications**: ❖ Scemblix® is indicated for the treatment of adult patients with Ph+ CML in CP with the T315I mutation.

Costs

60 Scemblix® tablets 40 mg = € 4,457.14 (ex-factory price) [6]

Warnings and precautions [7]

- **Myelosuppression**
  - Severe thrombocytopenia and neutropenia events may occur.
  - Monitor complete blood counts regularly during therapy and manage by treatment interruption or dose reduction.
- **Pancreatic toxicity**

- Monitor serum lipase and amylase.
- Interrupt, then resume at reduced dose or discontinue Scemblix® based on severity.
- Evaluate for pancreatitis when lipase elevation is accompanied by abdominal symptoms.

❖ **Hypertension**
- Monitor blood pressure and manage hypertension as clinically indicated.
- Interrupt, dose reduce, or stop Scemblix® if hypertension is not medically controlled.

❖ **Hypersensitivity**
- May cause hypersensitivity reactions.
- Monitor patients for signs and symptoms and initiate appropriate treatment as clinically indicated.

❖ **Cardiovascular toxicity**
- Cardiovascular toxicity may occur.
- Monitor patients with history of cardiovascular risk factors for cardiovascular signs and symptoms.
- Initiate appropriate treatment as clinically indicated.

❖ **Embryo-foetal toxicity**
- Can cause foetal harm.
- Advise females of reproductive potential of the potential risk to a foetus and to use effective contraception.

Study characteristics [2, 7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ASCEMBL NCT03106779	233 2:1	asciminib 40 mg twice daily	bosutinib 500 mg once daily	major molecular response (MMR) rate at week 24	**ongoing**[1], randomised, open-label, active-controlled, multicenter, phase 3 trial	Ph+	Novartis Pharmaceuticals	[2]

Efficacy (I vs. C)

Week 24
MMR rate at week 24: 25.5% vs. 13.2%
Difference in MMR rates at week 24 after adjusting for MCyR status at baseline: 12.2% (95% CI, 2.19-22.30; 2-sided p=.029)
Cumulative incidence of MMR by week 24: 25.0% vs. 12.0%
CCyR rate at week 24 in patients without CCyR at baseline: 40.8% vs. 24.2%
Difference in CCyR rates at week 24 after adjusting for MCyR status at baseline: 17.3% (95% CI, 3.62-30.99)

Week 48
MMR rate at 48 weeks: 9% (95% CI, 22-37) vs. 13% (95% CI, 6.5-23)
Median duration of response: not yet been reached

Week 96
MMR rate at 96 weeks: 37.6% vs. 15.8%
Difference, adjusting for baseline MCyR: 21.7% (95% CI, 10.5%-33.0%; 2-sided p=.001)

Safety (I vs. C) (n=156)

Grade ≥3 AEs: n=79/156 (50.6%) vs. 46/76 (60.5%)
Treatment-related AEs (per investigator assessment): n=99/156 (63.5%) vs. 67/76 (88.2%)
Deaths during the study: n=4/156 (2.6%) vs. n=1/76 patient (1.3%)[2]

Week 96 update:
❖ No new on-treatment deaths were reported since the primary analysis.

[1] The ASCEMBL trial is currently ongoing; estimated study completion date is 12/2024.
[2] In the asciminib arm, 2 deaths occurred on treatment (defined as death occurring during treatment or within 30 days after the end of treatment) from arterial embolism and ischemic stroke (1 each). Two deaths occurred after asciminib discontinuation during survival follow-up (both from CML). In the bosutinib arm, 1 patient died on treatment from septic shock.

HRQoL [10]:

- HRQoL was assessed in the intent to treat population with the MD Anderson Symptom Inventory – chronic myeloid leukaemia (MDASI-CML), an exploratory endpoint.
- Additional HRQoL measures were included in ASCEMBL and are reported elsewhere. Analyses included mixed model repeated measures (MMRM).
- MMRM analyses on MDASI-CML demonstrated that asciminib patients maintained or improved from baseline on all items (demonstrating improvement on 20 out of 26 items), symptom total score, and symptom distress score.
- Notable item improvements from baseline included fatigue, mood, and feeling of being upset.
- HRQL was similar to baseline in the bosutinib arm on symptom total score, symptom distress score, and all items, except for nausea and diarrhoea, with treatment differences favouring asciminib.
- Questionnaire compliance rates at week 24 were high and similar between treatment arms (83.1% vs 82.0%).
- Asciminib patients showed improvement in treatment-related symptoms and HRQoL compared with baseline and relative to bosutinib, within the first 24 weeks of treatment, confirming earlier findings.

ESMO-MCBS version 1.1 [11, 12][3]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The ESMO-MCBS was not applicable because the primary endpoint "major molecular response (MMR) rate at week 24" could not be assessed.											

Risk of bias (RCT) [13]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	-	No, open-label	unclear[4]	yes[5]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CCyR= complete cytogenetic response, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CML=chronic myeloid leukemia, CP=chronic phase, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, HRQOL=health-related quality of life, I=intervention, Int.=intention, MCyR=major cytogenetic response, MDASI-CML=MD Anderson Symptom Inventory – chronic myeloid leukemia, MG=median gain, MMR=major molecular response, MMRA= mixed model repeated measures, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, Ph+=Philadelphia chromosome-positive, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, STAMP=Specifically Targeting the ABL Myristoyl Pocket

References:

1. European Medicines Agency (EMA). Medicines. Imbruvica. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/imbruvica-1].
2. Réa D, Mauro MJ, Boquimpani C, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood 25 NOVEMBER 2021, VOLUME 138, NUMBER 21. [Available from: https://doi.org/10.1182/blood.2020009984].

[3] **Disclaimer**: Though not finally validated, but feasibility tested in [12], the original ESMO MCBS v1.1. was found to be widely applicable also for haematological malignancies. Hence, from October 2022, ESMO assessments were also carried out for haematological indications in new fact sheets and updates.
[4] The ASCEMBL trial is ongoing.
[5] Industry-funded.

3. National Institute for Health Research (NIHR). Asciminib for chronic myeloid leukaemia – chronic phase -third line. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/23792-Asciminib-for-Chronic-Myeloid-Leukaemia-V1.0-MAY2020-NON-CONF.pdf].
4. European Medicines Agency (EMA). Medicines. EPAR. Scemblix.
5. U.S. Food and Drug Administration (FDA). FDA approves asciminib for Philadelphia chromosome-positive chronic myeloid leukemia [Available from: FDA approves asciminib for Philadelphia chromosome-positive chronic myeloid leukemia.
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
7. U.S. Food and Drug Administration (FDA). Scemblix. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215358s000Orig2lbl.pdf].
8. Rea D, Mauro MJ, Hochhaus A, et al. Efficacy and safety results from ASCEMBL, a phase 3 study of asciminib versus bosutinib (BOS) in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) after ≥2 prior tyrosine kinase inhibitors (TKIs): Week 96 update. Meeting Abstract 2022 ASCO Annual Meeting.
9. U.S. National Library of Medicine, ClinicalTrials.gov. Study of Efficacy of CML-CP Patients Treated With ABL001 Versus Bosutinib, Previously Treated With 2 or More TKIs [Available from: https://clinicaltrials.gov/ct2/show/NCT03106779].
10. Mauro MJ, Boquimpani C, Réa D, et al. CML-417: ASCEMBL Phase 3 Health-Related Quality of Life (HRQL) Comparison of Asciminib and Bosutinib for Patients with Chronic Myelogenous Leukemia in Chronic Phase (CML-CP), Previously Treated with 2 or More Tyrosine Kinase Inhibitors (TKI). CHRONIC MYELOID LEUKEMIA Volume 21, Supplement 1, S336, 2021.
11. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.
12. Kiesewetter B , Cherny NI, Boissel N, al. e. EHA evaluation of the ESMO—Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS v1.1) for haematological malignancies. ESMO Open 2020;5.
13. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].