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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Scemblix

Asciminib

Case no.: EMA/PAM/0000244440 (EMA/H/C/005605/P46)

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Steps taken for the assessment

Description	Date
Start of procedure	27.01.2025
CHMP Rapporteur Assessment Report	04.03.2025
CHMP members comments	n/a
Updated CHMP Rapporteur AR	18.03.2025
CHMP adoption of conclusions:	27.03.2025

Administrative information

Procedure resources	
Rapporteur:	**Name: Janet Koenig**

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1. Introduction

On 26-Dec-2024, the MAH submitted in accordance with article 46 of Regulation (EC) No 1901/2006, the final report of asciminib study CABL001A1401 as part of the post-authorisation measures.

This trial, Study A1401, was a special drug use-results surveillance study conducted in Japan to fulfil the regulatory requirement at the time of the asciminib approval in Japan. The study was conducted to access the safety and effectiveness of Scemblix tablets clinically administered in resistant or intolerant chronic myeloid leukemia.

Please note that only one paediatric patient was part of this study who was multi-resistant against dasatinib, nilotinib and ponatinib and also resistant against asciminib. Thus, information here assessed remains less informative regarding the use of asciminib in the paediatric population and reflects nearly exclusively real-world data experience in adults.

No new safety concern emerged from the paediatric patient during the short-term exposure of 83 days in this study. The study was completed on 04-Jul-2024.

2. Scientific discussion

2.1. Information on the development program

The objective of this procedure is to assess data provided from Study CABL001A1401, involving a paediatric population, and any impact these data have on the Sponsor's understanding of the safety and efficacy profile of asciminib.

Asciminib (film-coated tablets 20 mg and 40 mg) was granted marketing authorization in the EU/EEA through centralized procedure on 25-Aug-2022 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).

Asciminib (Scemblix) is also marketed in 79 countries worldwide in comparable indications. (The exact indication varies by country).

Asciminib is indicated for use as monotherapy in adults and it is available as film-coated tablet (FCT) for oral administration, with strengths equivalent to 20 mg and 40 mg asciminib.

No dose adjustment is required in patients with mild, moderate or severe renal or hepatic impairment receiving asciminib. However, caution should be exercised in patients with severe renal or hepatic impairment receiving the 200 mg twice daily dose (BID) of asciminib. No dose adjustment is required in patients of age 65 years or above.

Safety and efficacy in the pediatric population (below 18 years) has not been established.

A multi-center, open-label study to determine the dose and safety of oral asciminib in paediatric patients Ph+ CML-CP, previously treated with one or more TKI (ASC4KIDS) is currently ongoing; thus, results from this study are not available at present.

The paediatric aspect currently triggering this procedure is restricted to one patient only.

Study CABL001A1401, entitled "Special drug use-results surveillance of Scemblix tablets (resistant or intolerant chronic myeloid leukemia) was an observational study conducted in Japan as a post-marketing surveillance study to assess the safety and effectiveness of Scemblix tablets clinically

administered in resistant or intolerant patients with chronic myeloid leukemia. While Scemblix is only approved in adult patients, Study CABL001A1401 **enrolled only one paediatric subject aged <18 years).**

Thus, information and conclusions regarding paediatric population from this trial are very limited.

2.2. Information on the pharmaceutical formulation used in the study

Asciminib is an oral, potent inhibitor of BCR::ABL1 tyrosine kinase with a novel mechanism of action, specifically targeting the ABL myristoyl pocket. Asciminib functionally mimics the role of the myristoylated Gly2 residue by occupying the vacant site and restoring the negative regulation to the kinase activity. In non-clinical studies, asciminib has been shown to have activity against clinically observed point mutations in BCR::ABL1 that confer resistance to ATP-competitive TKIs. The product is available as film coated tablets of 20 mg and 40 mg dose strengths.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for **Study CABL001A1401**

Title of the study: *Special drug use-results surveillance of Scemblix tablets (resistant or intolerant chronic myeloid leukemia.*

2.3.2. Clinical study

The study design and rationale for Study CABL001A1401 are summarized in Table 1.

Table 1 Summary of study design

Purpose	Study CABL001A1401 was a non-interventional study to assess the safety and effectiveness of Scemblix tablets clinically administered in resistant or intolerant chronic myeloid leukemia. This study was a post-marketing surveillance study conducted as an additional pharmacovigilance activity in Japan, following marketing authorization for Scemblix.	
Primary objective(s) and variable(s)	**Objective(s)** • To assess the safety profile of the safety specifications (myelosuppression, infections, QT interval prolongation, pancreatitis, vascular occlusive events, photosensitivity)	**Variable(s)** • For the safety specifications (myelosuppression, infections, QT interval prolongation, pancreatitis, vascular occlusive events, photosensitivity), type, frequency AE, seriousness, severity of AE/treatment-related AE, AEs leading to interruption/discontinuation, changes in relevant laboratory parameters • Frequency of AEs/treatment-related AEs by patient characteristic factor

Secondary objectives and variables	**Objective(s)** • To assess the overall safety profile in R/I CML patients	• Type, frequency, seriousness, severity of AEs/treatment-related AEs, AEs leading to interruption/discontinuation in the safety analysis set
		• Frequency of AEs/treatment-related AEs summarized by patient characteristic factor
	• To assess the safety in patients with special characteristics (patients with renal impairment/hepatic impairment/cardiac impairment, elderly, children, pregnant/parturient women)	• Type, frequency, seriousness, severity of AEs/treatment-related AEs, AEs leading to interruption/discontinuation in patients with special characteristics (patients with concurrent renal impairment/hepatic impairment/cardiac impairment, elderly, children, pregnant/parturient women)
	• To assess the safety by treatment line	• Type, frequency, seriousness, severity and outcome of AEs/treatment-related AEs, factors affecting occurrence, AEs leading to interruption/discontinuation by treatment line
	• To assess the effectiveness in R/I CML patients	• Major molecular response (MMR) rates at/by Week 12, Week 24 and Week 48 • MMR rates by Week 48 by patient characteristics factor • MR4.0 and MR4.5 rates at/by Week 12, Week 24 and Week 48 • Complete cytogenetic response (CCyR) rates at/by Week 12, Week 24 and Week 48 • Complete hematological response (CHR) rates at/by Week 12, Week 24 and Week 48 • Rates of patients with BCR::ABL1 gene mutations
	• To assess the effectiveness in patients with special characteristics (patients with renal impairment/hepatic impairment/cardiac impairment, elderly, children, pregnant/parturient woman)	• MMR rates by Week 48 in patients with special characteristics (patients with concurrent renal impairment/hepatic impairment/cardiac impairment, elderly, children, pregnant/parturient women)
	• To assess the effectiveness by treatment line	• MMR rates at/by Week 12, Week 24 and Week 48 by treatment line • MR4.0 and Mr4.5 rates at/by Week 12, Week 24 and Week 48 by treatment line • CCyR rates at/by Week 12, Week 24 and Week 48 by treatment line • CHR rates at/by Week 12, Week 24 and Week 48 by treatment line

Study design	The study was an observational, multicenter, uncontrolled, central registration system, all-case, special drug use-results surveillance. The duration of the study was 48 weeks. The study was conducted in Japan in compliance with the Good Postmarketing Study Practice (GPSP) ordinance.
Rationale	Asciminib hydrochloride is a potent, orally bioavailable tyrosine kinase inhibitor (TKI) targeting the BCR-ABL myristoyl binding pocket with a novel mechanism of action. Asciminib does not work on the adenosine triphosphate (ATP) binding site and it remains active against cells expressing mutations that confer resistance to existing TKIs, which means asciminib is effective even in patients resistant to existing TKIs. Selectively inhibiting the ABL kinase family (ABL1, ABL2, BCR-ABL1), asciminib is safer and better tolerated than existing TKIs. A global phase III study (A2301) was conducted in resistant or intolerant CML A global phase III study (CABL001A2301, ASCEMBL) was conducted in resistant or intolerant CML patients in chronic phase (CP) previously treated with 2 or more TKIs. The primary analysis established the superiority of asciminib to bosutinib in terms of major molecular response (MMR) at Week 24 and also confirmed its efficacy, safety and tolerability in other variables. Thus, an application for marketing approval was submitted in Japan for an indication of "resistant or intolerant CML (hereafter called, R/I CML)," and approval was granted on 28-Mar-2022. Because CML drugs require long-term administration, it is necessary to collect data on the occurrence, severity, clinical courses of risks that affect continuous treatment with asciminib, identify factors etc. involved in occurrence and ensure that treatment is safely continued. This was the reason for the conduct of this post-marketing surveillance as an additional pharmacovigilance activity.
Study population	All patients treated with asciminib in clinical practice.
Key inclusion criteria	This study being a post-marketing surveillance study, no specific inclusion criteria were set, all patients treated with asciminib in the post-marketing setting were eligible.
Key exclusion criteria	This study being a post-marketing surveillance study, no specific exclusion criteria were set, all patients treated with asciminib in the post-marketing setting were eligible.
Study treatments	Study treatment in accordance with the Scemblix labelling (40 mg twice daily).
Key safety assessments	• Treatment-related adverse events • Adverse events corresponding to safety specifications: myelosuppression, infections, QT interval prolongation, pancreatitis, vascular occlusive events, photosensitivity • Laboratory tests as stated below: • Test type (Variables): Vital signs [Blood pressure, ECG (QTc interval)], Haematology (WBC count, differential WBC count (neutrophil, lymphocyte, basophil, eosinophil, monocyte), platelet count, Blood biochemistry (Amylase, lipase)
Data Analysis (cut-off date)	04-Jul-2024
Study population included	In this study, data of 550 patients were locked. Of these 550 patients, 529 patients were included in the safety analysis set, excluding 17 patients previously treated with asciminib, 3 patients with off-label use/disease not targeted by this study, 2 patients who did not receive asciminib, 2 patients whose start date of treatment with asciminib was unknown/not recorded, and 1 patient whose presence/absence of adverse events was unknown/not recorded (with some overlap in reasons for exclusion). The effectiveness analysis sets consisted of 461 patients in the molecular response analysis set, 128 patients in the cytogenetic response analysis set, and 387 patients in the hematological response analysis set, excluding patients whose assessment was "not

	measured/not recorded" (67, 400, and 141 patients, respectively) and 1 other patient (aged < 15 years) The median age (range) at the start of treatment with asciminib was 69.0 years (14-92 years), and more than half of the patients (58.2%, 308/529 patients) were aged ≥ 65 years. **The only paediatric patient aged 14 years participated in this trial is a male with CML, who was clinically resistant against dasatinib, nilotinib and ponatinib**
Exposure	The overall median duration (range) of treatment with asciminib was 336 days (1 to 336 days) in Study A1401, and the mean daily dose (standard deviation) was 79.2 mg (20 to 80 mg). **Asciminib treatment duration for the paediatric patient was 81 days (20 mg/twice a day for 48 days, 40 mg/twice a day for 33 days). Asciminib treatment was discontinued due to insufficient effect. No ADR's were observed.**
Efficacy Summary	The MMR rates (95% CI) by visit was 43.4% (38.8, 48.0) by Week 12, 55.7% (51.1, 60.3) by Week 24, 61.4% (56.8, 65.9) by Week 48. There were no noteworthy effectiveness findings in patients with special characteristics such as children, elderly, pregnant women, and patients with renal/hepatic impairments. The results demonstrated a certain level of effectiveness of asciminib in R/I CML patients in real-world clinical practice. **Asciminib was not effective in the single paediatric patient treated for 81 days without any clinical meaningful efficacy.**
Safety Summary	The incidence rate of ADRs was 33.3% (176/529 patients), with Grade ≥ 3 occurring in 11.7% (62/529 patients). The most common ADRs (reported in ≥ 1%) were platelet count decreased occurring in 5.1% (27/529 patients), neutropenia and rash each in 2.8% (15/529 patients), electrocardiogram QT prolonged in 2.5% (13/529 patients), chronic myeloid leukaemia and malaise each in 1.7% (9/529 patients), thrombocytopenia and diarrhoea each in 1.5% (8/529 patients), and headache, hypertension, and pleural effusion each in 1.1% (6/529 patients).There were no noteworthy safety findings in patients with special characteristics such as elderly, pregnant women, and patients with renal impairment, hepatic impairment, or cardiac dysfunction. Based on the above, there were no particular safety concerns with the asciminib treatment in patients with R/I CML in real-world clinical practice. **No ADRs were observed for the pediatric patient in Study.**

2.3.3. Discussion on clinical aspects

In this post-marketing surveillance, there were no particular concerns about the safety results in the targeted population of adult patients with resistant or intolerant chronic myeloid leukemia.

In addition, this surveillance demonstrated a certain level of effectiveness of asciminib in adults. This study did not provide any relevant efficacy and safety results for the paediatric population since asciminib was not effective in this subject, who was also resistant or intolerant to other previous drugs (dasatinib, nilotinib and ponatib). Unfortunately, the type of mutation is not reported.

In summary, with respect to this case alone, no conclusion on the benefit and risk of Asciminib in the paediatric population can be drawn. The negative outcome in the single patient indicates the importance

of receiving data from the ongoing paediatric multi-center RCT as agreed in the PIP to characterise reliably efficacy and safety in CMP patients below the age of 18 years.

3. Overall conclusion and recommendation

Considering the limited efficacy and safety data in paediatric patients available from Study CABL001A1401, it is acknowledged that no changes to the current Scemblix Core Data Sheet and to the approved EU and UK SmPC are proposed as a result of this study.

In accordance with article 46 of Regulation (EC) No 1901/2006, the MAH submitted the final report of asciminib study CABL001A1401 as part of the post-authorisation measures.

No regulatory action required at present.

Since only one paediatric patient was included, the relevance of this data is marginal and the assessment in the paediatric population will further depend on the ongoing paediatric multi-center trial as agreed in the PIP.

4. Request for supplementary information

None.

Annex I Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

None

Clinical study

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report
Special drug use-results surveillance of Scemblix Tablets (resistant or intolerant chronic myeloid leukemia, CABL001A1401)	CABL001A1401	Completion of the study (LPLV): Feb.,28th, 2024. End of study (database lock date): July, 4th, 2024	Dec., 26th, 2024

Annex II - Overview regarding the details of the paediatric investigation plan PIP P/0052/2020 as agreed with the PECO:

Waiver

Condition:

Treatment of chronic myeloid leukaemia

(CML) The waiver applies to:

- the paediatric population from birth to less than 3 years of age;
- age-appropriate oral solid dosage form, film-coated tablet, oral use;
- on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

Paediatric investigation plan

Condition:

Treatment of chronic myeloid leukaemia (CML).

Indication(s) targeted by the PIP

Treatment of Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP) previously treated with one or more tyrosine kinase inhibitors (TKIs).

Subset(s) of the paediatric population concerned by the paediatric development

From 3 to less than 18 years of age.

Pharmaceutical form(s)

Age-appropriate oral solid dosage form, film-coated tablet.

Measures

Area	Number of measures	Description
Quality-related studies	1	Study 1 Development of an age appropriate oral formulation.
Non-clinical studies	0	Not applicable.
Clinical studies	1	Study 2 Open-label, multiple dose trial to evaluate pharmacokinetics, safety, activity, acceptability/palatability of asciminib in children from 3 to less than 18 years of age with Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP) previously treated with one or more tyrosine kinase inhibitors (TKIs).

Area	Number of measures	Description
Extrapolation, modelling and simulation studies	3	Study 3 Physiologically based PK (PBPK)study to predict the initial dose of asciminib for study 2 in children from 3 to less than 18 years of age with Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP) previously treated with one or more tyrosine kinase inhibitors (TKIs). Study 4 Population-PK/PD model of nilotinib adult data to predict paediatric nilotinib response in order to further support the applicability of efficacy extrapolation for TKIs, such as asciminib in children from 3 to less than 18 years of age with Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP) previously treated with one or more tyrosine kinase inhibitors (TKIs). Study 5 Extrapolation study to support the use of asciminib in paediatric patients from 3 to less than 18 years of age with Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP) previously treated with one or more tyrosine kinase inhibitors (TKIs).
Other studies	1	Study 6 Systematic review of the literature to assess the similarity of response to TKIs (dasatinib, imatinib and nilotinib) between adult and paediatric patients with CML when treated with the same BCR-ABL1 TKI at a comparable exposure.
Other measures	0	Not applicable.

Follow-up, completion and deferral of PIP

Concerns on potential long term safety/efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By March 2026
Deferral for one or more measures contained in the paediatric investigation plan:	Yes