EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Scemblix (asciminib)
Treatment of chronic myeloid leukaemia
EU/3/20/2261
Sponsor: Novartis Europharm Limited

Note

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

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Product and administrative information

Product	
Designated active substance(s)	Asciminib
Other name(s)	Asciminib
International Non-Proprietary Name	-
Tradename	Scemblix
orphan condition	Treatment of chronic myeloid leukaemia
Sponsor's details:	Novartis Europharm Limited Vista Building Elmpark Merrion Road Dublin 4 D04 A9N6 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Novartis Europharm Limited
COMP opinion	20 February 2020
EC decision	24 March 2020
EC registration number	EU/3/20/2261
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Janet Koenig / Paula Boudewina van Hennik
Applicant	Novartis Europharm Limited
Application submission	22 June 2021
Procedure start	15 July 2021
Procedure number	EMA/H/C/005605/0000
Invented name	Asciminib
Proposed therapeutic indication	Treatment of patients with Philadelphia chromosome-positive chronic myelogenous leukaemia in chronic phase (Ph+ CML-CP), previously treated with two or more tyrosine kinase inhibitors (TKIs). Further information on Scemblix can be found in the European public assessment report (EPAR) on the Agency's website: ema.europa.eu/en/medicines/human/EPAR/scemblix
CHMP opinion	23 June 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Bozenna Dembowska-Baginska
Sponsor's report submission	24 September 2021
COMP opinion	14 July 2022

Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2020 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing asciminib was considered justified based on preliminary clinical data demonstrating anti-tumour response in patients affected by the condition;
- the condition is life threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections;
- the condition was estimated to be affecting approximately 1.2 in 10,000 persons in the European Union, at the time the application was made.
- In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing asciminib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating anti-tumour response in patients affected by the condition, who have failed all currently authorised therapies. The Committee considered that this constitutes a clinically relevant advantage.

Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor is proposing that chronic myeloid leukaemia (CML) is an orphan condition. CML is a myeloproliferative neoplasm. It is characterised by a balanced genetic translocation t(9;22)(q34;q11.2), involving a fusion of the Abelson gene (*ABL1*) from chromosome 9q34 with the breakpoint cluster region (*BCR*) gene on chromosome 22q11.2. This rearrangement is known as the Philadelphia chromosome. The molecular consequence of this translocation is the generation of a *BCR::ABL1* fusion oncogene, which in turn translates into a BCR::ABL1 oncoprotein. BCR::ABL1 positive cells are genetically unstable and are prone to develop multiple and heterogeneous genomic abnormalities, resulting in the transformation of the leukaemic phenotype from chronic to acute, hence leading to the progression from chronic (CP) to accelerated (AP) and blast (BP) phases. About 50% of patients with CML diagnosed in Europe are asymptomatic (Annals of Oncology (2017) 28 (Supplement 4): iv41–iv51).

Most (90%-95%) patients present in CML-CP. Common signs and symptoms of CML-CP, when present, result from anemia and splenomegaly. These include fatigue, weight loss, malaise, easy satiety, and left upper quadrant fullness or pain. Rare manifestations include bleeding with a low platelet count and/or platelet dysfunction), thrombosis (associated with thrombocytosis and/or marked leukocytosis), gouty arthritis (from elevated uric acid levels), priapism (usually with marked leukocytosis or thrombocytosis), retinal hemorrhages, and upper gastrointestinal ulceration and bleeding (from elevated histamine levels due to basophilia). Leukostatic symptoms (dyspnea, drowsiness, loss of coordination, confusion) due to leukemic cells sludging in the pulmonary or cerebral vessels, are uncommon in CP despite white blood cell (WBC) counts exceeding 100×109/L. Splenomegaly is the

most consistent physical sign detected in 20-40% of cases. Hepatomegalyis less common (less than 10%). Lymphadenopathy and infiltration of skin or other tissues are rare. When present, they favour Ph-negative CML or AP or BP of CML. Headaches, bone pain, arthralgias, pain from splenic infarction, and fever are more frequent with CML trans-formation. Most patients evolve into AP prior to BP, but 20% transition into BP without AP warning signals. Therefore, CML-AP might be insidious or present with worsening anemia, splenomegaly and organ infiltration; CML-BP presents as an acute leukemia (myeloid in 60%, lymphoid in 30%, megakaryocytic or undifferentiated in 10%) with worsening constitutional symptoms, bleeding, fever and infections.

The diagnosis of typical CML is simple and consists of documenting, in the setting of persistent unexplained leukocytosis (or occasionally thrombocytosis), the presence of the Philadelphia (Ph) chromosome abnormality, the t(9;22)(q34;q11), by routine cytogenetics, or the Ph-related molecular BCR::ABL1 abnormalities by fluorescence in situ hybridization (FISH) or by molecular studies (Jabbour E and Kantarjian, Am J Hematol (2020) 95:691–709).

The COMP has designated this condition in the past and continues to do so.

The approved therapeutic indication "*Scemblix is indicated for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors"* falls within the scope of the designated orphan condition "Treatment of chronic myeloid leukaemia".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

Patients present with splenomegaly which is the most common physical sign in 40-50% of patients, hepatomegaly is less common. Headaches, bone pain, arthralgias, pain from splenic infarction and fever are more frequent with CML transformation.

Life expectancy is linked to the type of CML the patient has been diagnosed with. A key factor in patient outcome is the recognition of disease progression from CP to BP as this affects prognosis. About 50% of patients are diagnosed as asymptomatic and rarely do they present initially as BP.

CML has become a chronic disease with a good prognosis. A study in 2016 reported that 50% of patients with CML die not from CML itself, but from secondary cancers and cardiovascular events (Pfirrmann M et al, Leukemia (2016) 30:48-56).

Survival rates have significantly improved over the last 20 years with overall survival rates as high as 90% at 5 years (Di Felice et al, BMC Cancer (2018) 18:1069).

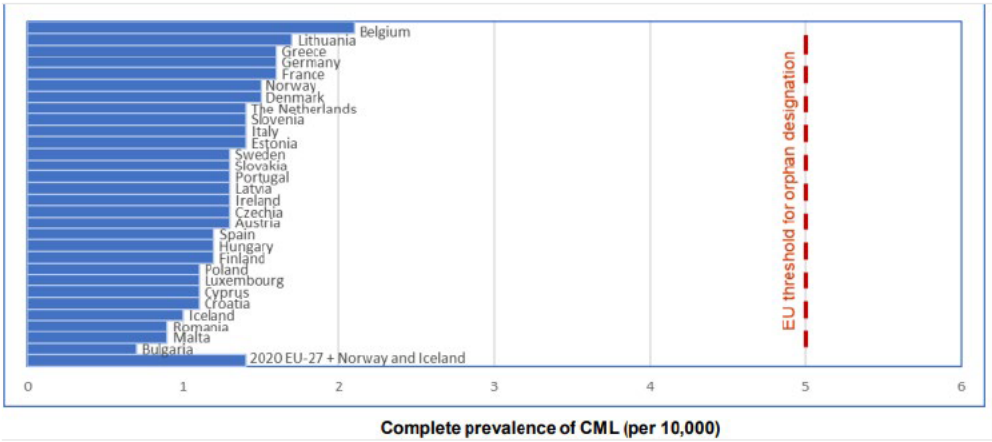
Number of people affected or at risk

The sponsor has identified sources of epidemiologic data on CML in the European population using a targeted literature search and an online search of other sources of data, such as population-based cancer databases and registries. These were presented in full in an appendix attached to the maintenance report. There was no consultation of the European Cancer Information System (ECIS).

The estimated complete prevalence in the 2020 EU-27 plus Iceland and Norway was 1.3 per 10,000. Among individual European countries ranging from 0.7 per 10,000 in Bulgaria to 2.0 per 10,000 in Belgium.

Following a request from COMP the sponsor provided a revised prevalence estimate of 1.4 in 10,000 based on population-based cancer databases and registries and current ECIS data. The sponsor noted that the literature review was updated. They also provided a graph showing the range across member states in Europe (Figure 1).

Figure 1. . Complete prevalence estimate of CML in the 2020 EU-27 plus Iceland and Norway



The COMP accepted this revised prevalence estimate of 1.4 in 10,000.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The following products can be identified to be authorised for the treatment of CML: hydroxyurea, interferon alfa-2b, imatinib, dasatinib, nilotinib, bosutinib, ponatinib.

Table 1. Authorised products in Europe for the treatment of Chronic Myeloid Leukaemia.

Medicine name	Indication
Hydroxyurea	Approved in several EU countries for the use in patients with CML, although with local variations in the description of the indication.
IntronA (interferon alfa-2b)	Chronic myelogenous leukaemia *Monotherapy* Treatment of adult patients with Philadelphia chromosome or bcr/abl translocation positive chronic myelogenous leukaemia. Clinical experience indicates that a haematological and cytogenetic major/minor response is obtainable in the majority of patients treated. A major cytogenetic response is defined by < 34 % Ph+ leukaemic cells in the bone marrow, whereas a minor response is 34 %, but < 90 % Ph+ cells in the marrow. *Combination therapy* The combination of interferon alfa-2b and cytarabine (Ara-C) administered during the first 12 months of treatment has been demonstrated to significantly increase the rate of major cytogenetic responses and to significantly prolong the overall survival at three years when compared to interferon alfa-2b monotherapy.
Glivec (imatinib)	Glivec is indicated for the treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment.
Sprycel (Dasatinib)	SPRYCEL is indicated for the treatment of adult patients with: - newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase. - chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib.
Tasigna (nilotinib)	Tasigna is indicated for the treatment of: - adult and paediatric patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase, - adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available, - paediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.
Iclusig (Ponatinib)	Iclusig is indicated in adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate or who have the T315I mutation
Bosulif (bosutinib)	Bosulif is indicated for the treatment of adult patients with: - newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML). - CP, accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

"Scemblix is indicated for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP) previously treated with two or more tyrosine kinase inhibitors".

The target population for Scemblix overlaps with that for Iclusig (ponatinib) and Bosulif (bosutinib), therefore these two products are considered satisfactory treatments for the target population of Scemblix.

Inclusig is indicated in adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T3I5I mutation

Bosulif is indicated for the treatment of adult patients with:

Newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+CML)

CP, accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

The COMP also takes into consideration the current European Society for Medical Oncology (ESMO) treatment guideline (Hochhaus et al, Ann Oncol (2017) 28 (suppl 4): iv41–iv51).

Significant benefit

Novartis sought protocol assistance for the justification of significant benefit (EMEA/H/SA/3426/1/FU/2/2020/PA/II). The COMP agreed, in principle, with Novartis' approach to confirm the significant benefit of asciminib for the treatment of CML as stated below:

'In conclusion, the pivotal data will be derived from the phase III study (asciminib versus bosutinib). If the results from this study confirm the superiority over bosutinib leading to the positive benefit/risk balance for asciminib at the MAA (CHMP), and if the additional indirect comparison of clinical data (especially against ponatinib) will confirm the expectations, the COMP agrees that the Applicant`s approach to support the justification of significant benefit could in principle be acceptable and sufficient. The final assessment will depend on the totality of evidence presented in the dossier. However, if the sponsor intends to include RWE data, the attention of the sponsor is drawn to the limitations of such comparisons necessitating appropriate methodological preparation to be prospectively agreed with the EMA.'

Significant benefit versus bosutinib

Data to support significant benefit is based on the results of the primary analysis of the pivotal Phase III study [CABL001A2301] (ASCEMBL, hereafter referred to as Study A2301).

Trial A2301, was performed as a multi-center, open-label randomized study designed to compare the efficacy and safety of asciminib with that of bosutinib in the treatment of patients with CML-CP who received at least 2 prior ATP-binding site TKIs. Approximately 220 patients were to be randomized in a 2:1 ratio asciminib 40 mg BID or bosutinib 500 mg QD.

Patients with documented lack of efficacy as per study protocol (based on 2013 ELN recommendations, Baccarani et al 2013) in either treatment arm must discontinue study treatment. Patients on bosutinib meeting the lack of efficacy criteria were offered the option to switch to asciminib treatment (Figure 2). Patients discontinuing bosutinib due to any other reason including adverse events were not allowed to switch to asciminib. The efficacy and safety data collected during the switch to asciminib are analysed separately.

The primary objective of the study was major molecular response (MMR) rate at Week 24 and the key secondary objective MMR rate at 96 weeks.

The primary and key secondary analyses of this study were planned and performed, when all randomized patients had been on study treatment for 24 and 96 weeks, respectively, or discontinued earlier.

Table 2 summarizes prior TKI therapy in patients enrolled to Study A2301.

Figure 2. Trial design for Study A2301

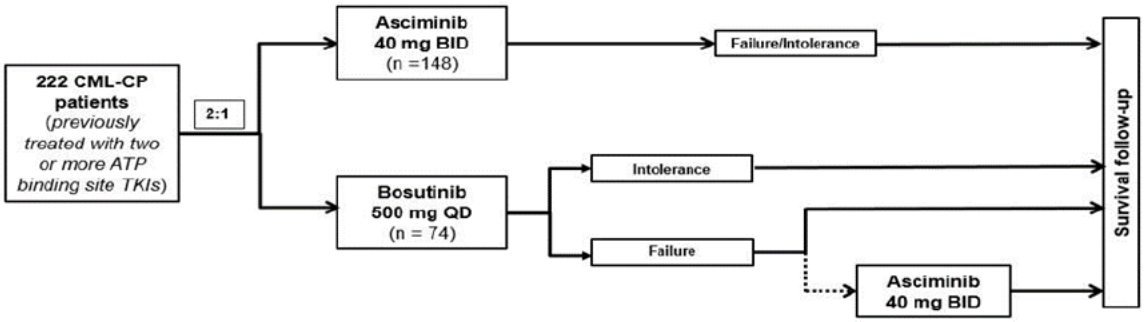


Table 2. TKI therapy prior to Study A2301

Characteristic	Asciminib N=157 n (%)	Bosutinib N=76 n (%)	All patients N=233 n (%)
Prior TKIs - n (%)			
Dasatinib	131 (83.4)	65 (85.5)	196 (84.1)
Imatinib	130 (82.8)	63 (82.9)	193 (82.8)
Nilotinib	104 (66.2)	56 (73.7)	160 (68.7)
Ponatinib	23 (14.6)	18 (23.7)	41 (17.6)
Other[1]	5 (3.2)	4 (5.3)	9 (3.9)
Radotinib	4 (2.5)	2 (2.6)	6 (2.6)
Number of prior TKIs - n (%)			
2	89 (56.7)	33 (43.4)	122 (52.4)
3	53 (33.8)	33 (43.4)	86 (36.9)
4	14 (8.9)	7 (9.2)	21 (9.0)
≥ 5	1 (0.6)	3 (3.9)	4 (1.7)
Number of lines of prior TKI therapy - n (%)			
2	82 (52.2)	30 (39.5)	112 (48.1)
3	44 (28.0)	29 (38.2)	73 (31.3)
4	24 (15.3)	10 (13.2)	34 (14.6)
≥ 5	7 (4.5)	7 (9.2)	14 (6.0)

Prior TKIs starting and completing prior to start of the study treatment are summarized.
Last TKI is based on start date of first dose.
A new line of therapy is considered each time a change in TKI occurred. Multiple entries for the same TKI are counted as separate lines of therapy if a different TKI is received between the different entries
[1] Other refers to investigational medications identified as BCR-ABL1 TKIs
Source: Table 14.3-2.1

The study met its primary objective; superiority was demonstrated for asciminib 40 mg BID relative to bosutinib 500 mg QD for the primary endpoint of major molecular response (MMR) rate at Week 24 (Table 3).

Table 3. MMR rates at Week 24 for Asciminib and Bosutinib in Study A2301

	Asciminib N=157	Bosutinib N=76
Response - n (%)	40 (25.48)	10 (13.16)
95% CI for response [1]	(18.87, 33.04)	(6.49, 22.87)
Unstratified difference in response rate (vs. bosutinib) (%)	12.32	
95% CI for difference in response rate [2]	(2.11, 22.53)	
Common risk difference (%) [3]	12.24	
95% CI for difference	(2.19, 22.30)	
CMH test p-value [4]	0.029	

[1] -Clopper-Pearson 95% 2-sided CI.
[2] Wald 95% 2-sided CI.
[3] The common risk difference after adjusting for stratum: baseline major cytogenetic response status (based on randomization data) and its 95% CI were estimated using the Mantel-Haenszel method.
[4] CMH 2-sided test was stratified by baseline major cytogenetic response status (based on randomization data).
Source: Table 14.2-1.1, Listing 14.2-1.1

The improved efficacy of asciminib over bosutinib has been shown in the pivotal trial submitted by the sponsor. It should be noted in addition that the subgroup analysis by line of therapy of randomized treatment confirmed the benefit of asciminib in heavily pretreated patients. A consistent treatment benefit with respect to the primary endpoint MMR rate at Week 24 was observed with asciminib compared

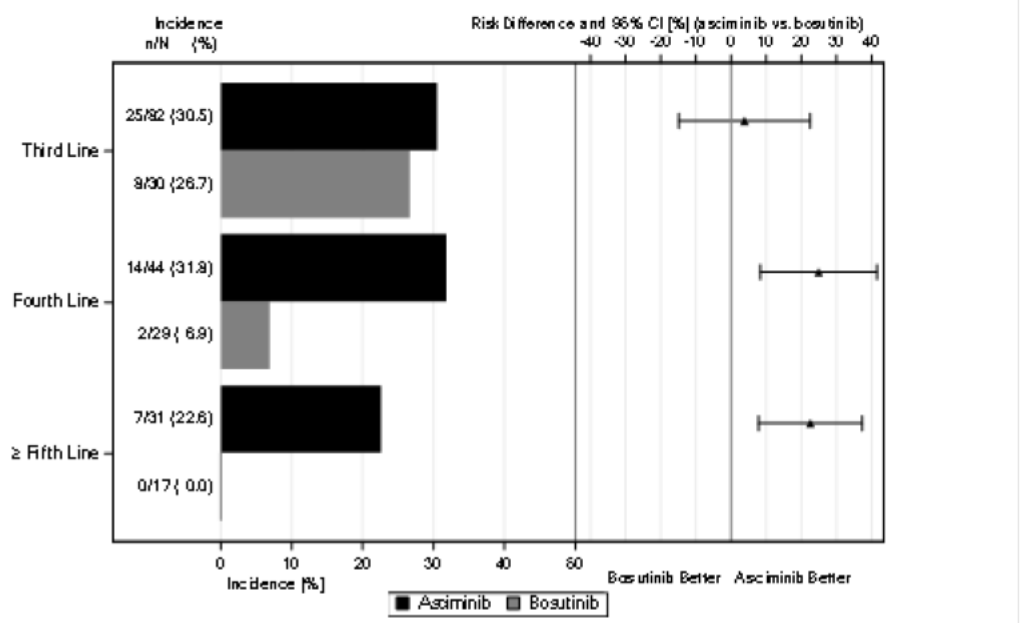
to bosutinib whether given as 3rd-line therapy (29.3% vs. 20.0%), 4th-line therapy (25.0% vs. 13.8%), or ≥ 5th-line therapy (16.1% vs. 0%). These results support the improved efficacy of asciminib over bosutinib irrespective of the number of previous lines of treatment with TKIs.

A clinically relevant two-fold increased MMR rate at Week 24 for asciminib compared to bosutinib was noted by the CHMP. This two-fold improvement in MMR is clinically relevant in this setting where the use of remaining TKIs may be limited and the option of allogeneic stem cell transplantation carries high risk of morbidity and mortality. The primary results from Study A2301, showed a clinically meaningful and statistically significant outcome, supporting the efficacy claim of asciminib in adult patients with Ph+ CML-CP, previously treated with two or more TKIs.

Additional 7.5 months of follow-up after the primary analysis cut-off date further support the clinical benefit of asciminib over bosutinib, as shown by a persistent MMR difference between asciminib and bosutinib. Asciminib continued to show a higher MMR rate across major prognostic factors of response when compared to bosutinib; Figure 3 shows the MMR rate by line of therapy.

The durability of response on asciminib is supported by a high probability of maintaining this level of response for at least 48 weeks.

Figure 3. MMR rate at Week 48, by line of therapy of randomized treatment (FAS)



Source: Study A2301 Supplement-Figure 14.2-1.1.3.2

The results from Study A2301 support a significant benefit over bosutinib based on a clinically relevant advantage.

Significant benefit versus ponatinib

The sponsor provided an indirect comparison between asciminib and ponatinib for which the primary analysis is described in Annex 4 ("*Statistical Report for Matching-Adjusted Indirect Comparison Between CABL001A2301 and the ponatinib Ph+ ALL and CML Evaluation (PACE) Trial*"). The objective was to assess the treatment benefit of asciminib in comparison to ponatinib in patients treated with two or more prior TKIs. The primary endpoint was MMR by Week 24 and with MMR by Week 48 as

supportive endpoint. The method used was a Matching-adjusted indirect comparison (MAIC) in patients with Philadelphia chromosome-positive CML-CP previously treated with two or more TKIs. Furthermore, the sponsor has provided additional supportive and sensitivity analyses for the comparison at 24 weeks, 48 weeks and 96 weeks as separate documents.

The primary and supportive analyses are performed for CABL001A2301 asciminib treated patients (A2301-a) in the full analysis set (FAS). Additional sensitivity analyses are performed for a sub-group of patients in A2301-a FAS. Summary statistics reported for the ponatinib treated patients in PACE Cohort A (PACE-A) are used for comparison.

The PACE trial was the pivotal study for ponatinib approval conducted by Ariad Pharmaceuticals for Ph+ CML patients who had previously been treated with two or more TKIs. PACE enrolled 449 patients who were assigned to 1 of the 6 cohorts. All patients were treated with ponatinib. There were 203 patients in the cohort of CML-CP relapse or intolerant (R/I) to previous TKI treatments without T315I mutation (Cohort A). These 203 patients reflect a comparable population as the A2301 study and provide aggregated data (AD) for the MAIC comparison. In this document, PACE-A refers to these patients.

The information about the PACE study and trial results are extracted from the following three sources: 1. Cortes et al N Engl J Med (2013) 369(19):1783-96; 2. Cortes et al, Blood (2018) 132(4):393–404; 3. clinicaltrials.gov: NCT01207440.

The pivotal Phase III study CABL001A2301 provides individual patient level data (IPD) on the efficacy of asciminib. In particular, the 157 patients in the asciminib arm who are part of the FAS are included in the analysis. In this document, A2301-a cohort refers to these patients.

The comparison of asciminib versus ponatinib is based on a retrospective, non-randomized indirect comparison between patients in A2301-a cohort and a selected historical control group on ponatinib in PACE-A.

According to the sponsor, both CABL001A2301 and the PACE-A cohort enrolled patients from the same target population. Even if not exactly the same it can be agreed that the populations are similar. In both studies, patients were 18 years or older, had CML-CP, had prior use of TKI before enrolling into their respective studies, and were R/I to the previous TKI(s). For the MAIC, patients were matched on age, sex, and race, and on the prognostic clinical characteristics, i.e. number of prior TKIs, ECOG performance status, and major cytogenetic status at baseline. This design was in principle agreed with EMA in a protocol assistance in 2020.

Three eligibility criteria differ between CABL001A2301 and PACE-A. First, no patients who had prior use of ponatinib were enrolled in the PACE study. This is not the case for CABL001A2301. Second, PACE-A enrolled only patients who were R/I to dasatinib or nilotinib whereas CABL001A2301 enrolled patients who had two or more of any TKIs in their treatment history. Third, patients in complete cytogenetic response (CCyR) at baseline were not eligible in PACE, while in Study A2301 these patients were allowed. In total 67 patients in A2301-a would not have been eligible for PACE-A, which leaves 90 patients who could in theory be enrolled to PACE-A (Figure 4).

The 67 patients excluded from the analysis were:

19 in CCyR at baseline, who were excluded from A2301 CCyR analysis set;

35 with non-evaluable BMA at baseline (BMA missing at baseline, BMA with insufficient quality or BMA with less than 20 metaphases examined), who were also excluded from A2301 CCyR analysis set;

and 13 previously treated with ponatinib. The 90 patients form a sub-group in which MAIC is additionally conducted (sensitivity analysis) for both the week 24 and week 48 MMR results.

Figure 4. Sub-group definition for Study A2301

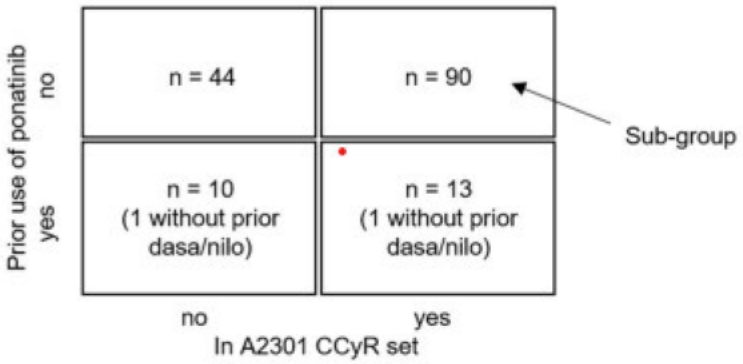


Table 4. Baseline characteristics between Study A2301 and PACE for MAIC comparison

Baseline characteristics		A2301-a FAS unadjusted	A2301-a subgroup unadjusted	PACE Cohort A
N		157	90	203
Age (years)	Minimum	24	25	22
	Median	52	51	61
	Maximum	83	79	94
Age [n (%)]	<= 61 years	119 (75.8)	70 (77.8)	102 (50)
Female [n (%)]		75 (47.8)	50 (55.6)	108 (53.2)
Race [n (%)]	American Indian / Alaska Native	1 (0.6)	1 (1.1)	1 (0.5)
	Asian	22 (14.0)	13 (14.4)	17 (8.4)
	Black / African American	8 (5.1)	8 (8.9)	7 (3.4)
	White	118 (75.2)	63 (70.0)	174 (85.7)
	Other / Unknown	8 (5.1)	5 (5.6)	4 (2)
ECOG [n (%)]	0	127 (80.9)	70 (77.8)	139 (68.5)
	1	28 (17.8)	18 (20.0)	60 (29.6)
	2	2 (1.3)	2 (2.2)	4 (2)
Time from diagnosis (years)	Minimum	0.52	0.52	0.45
	Median	3.83	3.72	7.85

Baseline characteristics		A2301-a FAS unadjusted	A2301-a subgroup unadjusted	PACE Cohort A
	Maximum	28.01	28.01	27.43
Time from diagnosis [n (%)]	<= 7.85 years	113 (72.0)	64 (71.1)	102 (50)
No. of prior TKI	Median	2	2	3
No. of prior TKI [n (%)]	1	0 (0)	0 (0)	4 (2)
	2	89 (56.7)	54 (60.0)	64 (31.5)
	>= 3	68 (43.3)	36 (40.0)	135 (66.5)
Cytogenetic status [n (%)]	Major	57 (36.3)	23 (25.6)	39 (19.2)
	Not Major	100 (63.7)	67 (74.4)	164 (80.8)

Source: CABL001A2301-MAIC-Table-1.1, CABL001A2301-MAIC-Table-1.2, Cortes (2013), clinicaltrials.gov: NCT01207440

PACE-A did not include patients who had complete cytogenetic response at enrolment, or had neither dasatanib nor nilotinib, or patients who had been treated with ponatinib before participating in the PACE study.

Primary analysis of MMR by week 24 based on A2301-a FAS

The results for the MAIC between A2301-a patients and PACE-A cohort to compare the efficacy in CML-CP patients without T315I mutation for the primary endpoint of MMR rate by week 24 are given in the table below.

Table 5. Treatment efficacy comparison: MMR rate by week 24 (Full analysis set)

Study	N	MMR (%) *	Difference (%)	95% CI (%) **
CABL001A2301 unadjusted	157	27.4		
CABL001A2301 MAIC-adjusted	75 #	20.4	1.4	(-9.2, 12.0)
PACE Cohort A	203	19		

* MMR by week 24
** Wald's confidence interval
# Effective sample size

Based on the weighting from the MAIC, the effective sample size decreased to 75 from initially 157 patients in A2301-a FAS. The MMR rate by week 24 decreased to 20.4% as compared to the observed 27.4% in A2301-a. Compared to the observed MMR rate of 19% in PACE-A, the difference is 1.4% with Wald's 95% confidence interval (CI) of (-9.2%, 12.0%). This indicates that the treatment effect of asciminib is comparable to that of ponatinib as third line TKI treatment for CML-CP patients who are R/I to their previous TKI treatments. These conclusions are supported by the supportive and sensitivity analyses, which consistently show numerically higher response rates for the adjusted MMR rates for asciminib (Table 6).

Table 6. Treatment efficacy comparison: Primary analysis by week 24, supportive analysis by week 48, and sensitivity analyses

Table 1-1 Summary of MAIC efficacy comparisons between asciminib and ponatinib

	Observed MMR		MAIC-adjusted MMR		
	Ponatinib	Asciminib			
Endpoint (Analysis)	PACE-A [% (n)]	A2301-a [% (n)]	A2301-a [% (ESS *)]	Difference ** (%)	95% CI *** (%, %)
MMR by week 24 (Primary)	19 (203)	27.4 (157)	20.4 (75)	1.4	(-9.2, 12.0)
MMR by week 48 (Supportive)	27 (203)	35.0 (157)	29.0 (75)	2.0	(-10.0, 14.0)
MMR by week 24 (Sensitivity)	19 (203)	31.1 (90)	25.0 (38)	6.0	(-8.8, 20.8)
MMR by week 48 (Sensitivity)	27 (203)	38.9 (90)	32.7 (38)	5.7	(-10.4, 21.8)

* ESS = Effective Sample Size
** Difference = (MAIC-adjusted A2301-a MMR) – (PACE-A observed MMR)
*** CI = Wald's confidence intervals for the differences

Source: CABL001A2301-MAIC-Table-2.1, CABL001A2301-MAIC-Table-2.2, CABL001A2301-MAIC-Table-2.3, CABL001A2301-MAIC-Table-2.4, Cortes (2013), Cortes (2018)

The COMP asked the sponsor to further justify that no important prognostic or predictive factors have been omitted in their comparison. Furthermore, the sponsor was asked to clarify that the additional registry-based study which was considered at the time of protocol assistance had not been pursued following the feedback by the CHMP. In addition, the sponsor was invited to highlight any patients who had been treated with ponatinib or refractory to it at baseline in their main study.

The sponsor notified the COMP that the registry-based study (Study A2002) had been proposed due to the limited published information on patients with CML-CP treated with TKIs in the third line and beyond setting. The study included information from three cancer registries: Czech Republic, Netherlands and Sweden. The primary objective was to describe the effectiveness of each of the TKIs received in CML-CP patients treated with two or more prior TKIs. The main limitations when interpreting the data from this study are the low number of patients treated with each TKI and the absence of pre-planned efficacy assessments, which made it impossible to analyze the impact of the baseline disease characteristics on the response. The sponsor decided not to submit the data for this reason.

The COMP had previously noted that the MAIC was overall of good quality from a reporting point of view and that the sponsor had done a good job at describing what they did and what the results looked like. The sponsor clarified that two baseline variables were not used in the MAIC: 1) the reason of discontinuation of the last TKI (resistance/intolerance: 2) any BCR::ABL1 mutation detected at baseline.

More information was also provided on the patients previously treated with ponatinib. In the A2301 study (ASCEMBL), ponatinib was the last TKI prior to study entry for 20 patients randomized to asciminib and for 17 randomized to bosutinib. The MMR rates at Week 96 for asciminib and 11.8% (2 out of 17 patients) for bosutinib among these patients are presented in Table 7 below. Importantly, at week 96 molecular assessment, more patients whose last TKI was ponatinib were observed as still on treatment and meeting response milestones in the asciminib arm (40%, 8 out of 20 patients) when compared with the bosutinib arm (23.5%, 4 out of 17 patients), in this exploratory subgroup analysis.

Table 7. MMR rate at week 96 in patients whose last TKI was ponatinib

	Asciminib		Bosutinib	
	N	n (%)	N	n (%)
All patients	20	4 (20)	17	2 (11.8)
Resistant to ponatinib	12	1 (8.3)	12	0 (0)
Intolerant of ponatinib	8	3 (37.5)	5	2 (40)

The COMP accepted that based on this data asciminib could offer significant benefit in patients treated in third line or later, irrespective of ponatinib pre-treatment. As a result, the COMP agreed to recommend maintaining the orphan designation.

COMP position adopted on 14 July 2022

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of chronic myeloid leukaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1.4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections;
- although satisfactory methods for the Treatment of the condition have been authorised in the European Union, the assumption that Scemblix may be of significant benefit is supported with data showing that Scemblix offers benefit in patients treated in third line or later, irrespective of ponatinib pre-treatment.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Scemblix, asciminib, for treatment of chronic myeloid leukaemia (EU/3/20/2261) is not removed from the Community Register of Orphan Medicinal Products.