Asciminib
(chronic myeloid leukaemia)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ABL	Abelson murine leukaemia
ACT	appropriate comparator therapy
BCR	breakpoint cluster region
BCR::ABL1	breakpoint cluster region-Abelson gene
CML	chronic myeloid leukaemia
EU HTA	European health technology assessment
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IS	International Scale
MCyR	major cytogenetic response
MMR	major molecular response
NCCN	National Comprehensive Cancer Network
Ph^+ CML-CP	Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase
PT	Preferred Term
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
SOC	System Organ Class
TKI	tyrosine kinase inhibitor

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug asciminib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 28 May 2025.

Research question

The aim of this report is to assess the added benefit of asciminib compared with individualized treatment as the appropriate comparator therapy (ACT) in adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph^+ CML-CP) who have previously been treated with ≥ 2 tyrosine kinase inhibitors (TKIs).

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of asciminib

Therapeutic indication	**ACT**[a]
Adult patients with Ph^+ CML-CP previously treated with ≥ 2 TKIs	Individualized treatment[b, c, d] selecting from ▪ nilotinib ▪ dasatinib ▪ bosutinib and ▪ ponatinib

a. Presented is the respective ACT specified by the G-BA.
b. Editorial note: The term 'individualized treatment' is used by the G-BA instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
c. The treatment decision is made taking into account previous treatments, comorbidities and mutation status in particular. According to the G-BA, it is assumed for the given therapeutic indication that patients will (initially) be treated with BCR-ABL TKIs as part of remission-inducing therapy. For some patients, allogeneic stem cell transplantation can only be considered once remission has been achieved (and is therefore not part of the ACT).
d. For the implementation of individualized treatment in a study of direct comparison, the G-BA expects investigators to have a choice of several treatment options at their disposal, enabling them to make individualized treatment decisions (multi-comparator study). The decision on individualized treatment with regard to the comparator therapy was to be made before group allocation (e.g. randomization). The selection and, where applicable, restriction of treatment options must be justified under consideration of the named criteria. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.

ACT: appropriate comparator therapy; ABL: Abelson murine leukaemia; BCR: breakpoint cluster region; EU HTA: European health technology assessment; GBA-: Federal Joint Committee; TKI: tyrosine kinase inhibitor

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. To derive the added benefit, randomized controlled trials (RCTs) without any restrictions on study duration were used – in deviation from the company's inclusion criteria, which only included RCTs with a minimum study duration of 24 weeks.

Results

The ASCEMBL study included by the company did not allow for a comparison of asciminib versus the ACT, as no individualized treatment according to the G-BA's ACT was carried out in the comparator arm. This means that no suitable data were available for the comparison of asciminib with the G-BA's comparator therapy. ASCEMBL is described below, followed by an explanation of why it was not suitable for this benefit assessment.

Evidence presented by the company – ASCEMBL study

The ASCEMBL study is a completed multicentre, open-label RCT comparing asciminib with bosutinib. Adult patients with chronic myeloid leukaemia (CML) in the chronic phase who had previously been treated with 2 or more adenosine triphosphate-competitive TKIs were included. The prerequisite for inclusion in the study was treatment failure or intolerance to the last previous TKI therapy. Patients were not allowed to have a T351I or V299L mutation, nor should they have progressed to an accelerated phase or blast crisis of CML.

A total of 233 patients were included in ASCEMBL and randomly assigned in a 2:1 ratio to treatment with asciminib (N = 157) or bosutinib (N = 76). Randomization was stratified according to the presence of a major cytogenetic response (MCyR [complete or partial] versus no MCyR [minor, minimal or none]).

Treatment with asciminib and bosutinib was carried out in compliance with the respective summary of product characteristics (SmPC). Treatment with the study medication continued until disease progression, treatment failure, the occurrence of a T315I or V299L mutation, or for a maximum of 96 weeks after the first dose of the last randomized patient or up to 48 weeks after the last patient switched from bosutinib to asciminib, whichever was longer, provided that treatment was not discontinued prematurely. The study documents showed that continued treatment with asciminib or bosutinib beyond 96 weeks was possible and did occur (51% of patients in the asciminib arm and 19.7% in the bosutinib arm). For patients in the bosutinib arm, a switch to treatment with asciminib was also possible in the event of treatment failure.

The primary outcome of the study was major molecular response (MMR) at Week 24. Secondary outcomes were overall survival and other outcomes in the categories morbidity, health-related quality of life and side effects.

ASCEMBL study unsuitable for the benefit assessment

ACT defined by the G-BA

The G-BA determined individualized treatment selecting from nilotinib, dasatinib, bosutinib and ponatinib as the ACT for the therapeutic indication in question. In its notes on the ACT, the G-BA pointed out that for implementation of individualized treatment in a study of direct comparison, the investigator is expected to have a selection of several treatment options at their disposal, enabling them to make individualized treatment decisions taking into account previous treatments, comorbidities and mutation status (multicomparator study). The selection and, where applicable, restriction of treatment options must be justified. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment. With the ASCEMBL study, the company presented a single-comparator study in which only bosutinib was available as a treatment in the comparator arm.

The company's argumentation regarding implementation of the ACT

The company argued that the ASCEMBL study provided evidence for the subpopulation of the asciminib therapeutic indication for which bosutinib represents an individualized treatment option, taking into account previous therapies, comorbidities and mutation status. It stated that at the time of study inclusion, approximately 24% of patients in the bosutinib arm had previously been treated with ponatinib, and ponatinib would no longer be a viable treatment option for them. The company said that for the remaining patients, the 2 drugs bosutinib and ponatinib would be equally suitable, but that it is known that ponatinib increases the risk of cardiovascular side effects, which is why bosutinib is preferable in cases where cardiovascular risk factors are present.

It continued that in addition to ponatinib, there were 2 other feasible options for individualized treatment: dasatinib and nilotinib. It stated that in total, dasatinib and nilotinib were not suitable for 86.8% of patients in the comparator arm due to previous therapies, mutation status or comorbidities, and bosutinib was the preferred individualized treatment option.

Evaluation of the implementation of the ACT

The company's reasoning that the G-BA's ACT was implemented in ASCEMBL for the subpopulation of patients for whom bosutinib represents an individualized treatment was not appropriate. The reasons for this are provided below.

Individualized treatment, ponatinib option

Approximately 76% of patients in the comparator arm had not received ponatinib therapy before the start of the study, meaning that ponatinib would have been a treatment option for these patients. In Module 4 A, the company stated that the 2 drugs bosutinib and ponatinib

are equally suitable as treatment options. However, the current guidelines do not describe bosutinib and ponatinib as equivalent treatment options in this therapeutic indication. Rather, treatment with ponatinib should at least be considered in cases where at least 2 other TKIs have failed or where resistance has developed following treatment with a 2nd-generation TKI (dasatinib, nilotinib, bosutinib) and where there are no specific mutations in the breakpoint cluster region-Abelson gene (BCR::ABL1), even if an alternative 2nd-generation TKI remains a treatment option. The company further argued that, according to the approved therapeutic indications for bosutinib and ponatinib, the patient population in ASCEMBL was equally eligible for bosutinib and ponatinib. However, according to the current SmPCs, ponatinib is an option for patients who are resistant to treatment or intolerant to only 1 of the 2 drugs dasatinib or nilotinib, whereas for treatment with bosutinib, according to the marketing authorization, both dasatinib and nilotinib must be unsuitable. This means that ponatinib can be used in treatment situations where bosutinib is not yet indicated because either dasatinib or nilotinib are still treatment options. Since ASCEMBL also included patients who had received only dasatinib or only nilotinib as a previous treatment, it cannot be assumed that bosutinib and ponatinib were equally suitable for all patients in the study.

The company further argued that bosutinib is the preferred option versus ponatinib in cases where cardiovascular risk factors are present. However, severe cardiovascular comorbidities were an exclusion criterion in ASCEMBL, and cardiovascular comorbidities and risk factors were observed in only a small number of patients in the bosutinib arm of the study. Cardiovascular risk factors and comorbidities are potentially decisive factors in favouring bosutinib over ponatinib. However, in this benefit assessment, the risk factors and comorbidities, for the vast majority of the study population, did not justify favouring bosutinib over ponatinib. Ponatinib represents an individualized treatment option for at least a relevant proportion of the patient population. In addition, approximately 24% of patients in the bosutinib arm received ponatinib as subsequent therapy after the end of the study treatment, which is why, at least for these patients, ponatinib can be assumed to be a suitable treatment option.

Individualized treatment, the options of dasatinib and nilotinib

The company argued that for approximately 87% of patients in the comparator arm, bosutinib was the preferred individualized treatment option over dasatinib and nilotinib. However, this was only certain for the 63% of patients who had previously been treated with both dasatinib and nilotinib or who had a mutation representing a contraindication versus dasatinib or nilotinib. The company argued that for a further 24%, dasatinib and nilotinib were not suitable due to potential comorbidities or risk factors. However, the company's approach to selecting these comorbidities or risk factors was not entirely comprehensible. It could not therefore be ruled out that the company overestimated the number of patients for whom dasatinib and nilotinib were not suitable.

As described above, treatment with bosutinib according to the marketing authorization requires that both dasatinib and nilotinib are unsuitable. According to the company data, which, as described above, may be overestimated, this applied to a maximum of 87% of the patients included. Treatment with bosutinib was therefore off-label for at least 13% of patients, as at least 1 of the 2 drugs would still have been a suitable treatment option for these patients.

Summary and consequences for the assessment

For approximately 76% of patients in the comparator arm of ASCEMBL, ponatinib is an additional individual treatment option, which was not available in the study. Furthermore, for at least 13% of patients in the comparator arm, bosutinib was not administered on-label. Overall, bosutinib was therefore not the most suitable individual treatment option for more than 20% of patients in the comparator arm of ASCEMBL; the study presented was therefore not suitable for comparison with the ACT. Patients in ASCEMBL who had already received all 3 alternative TKIs of the ACT (dasatinib, nilotinib, ponatinib) and for whom bosutinib was therefore the only remaining treatment option could potentially represent a relevant subpopulation for the benefit assessment. However, there was no information available on whether ASCEMBL included such a subpopulation and how many patients it comprised. The ASCEMBL study was therefore not suitable for the assessment of the added benefit of asciminib versus the G-BA's ACT.

Results on added benefit

Since no relevant study was available for the benefit assessment, there is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of asciminib.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Asciminib – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with Ph+ CML-CP previously treated with ≥ 2 TKIs	Individualized treatment[b, c, d] selecting from ▪ nilotinib ▪ dasatinib ▪ bosutinib and ▪ ponatinib	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Editorial note: The term 'individualized treatment' is used by the G-BA instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
c. The treatment decision is made taking into account previous treatments, comorbidities and mutation status in particular. According to the G-BA, it is assumed for the given therapeutic indication that patients will (initially) be treated with BCR-ABL TKIs as part of remission-inducing therapy. For some patients, allogeneic stem cell transplantation can only be considered once remission has been achieved (and is therefore not part of the ACT).
d. For the implementation of individualized treatment in a study of direct comparison, the G-BA expects investigators to have a choice of several treatment options at their disposal, enabling them to make individualized treatment decisions (multi-comparator study). The decision on individualized treatment with regard to the comparator therapy was to be made before group allocation (e.g. randomization). The selection and, where applicable, restriction of treatment options must be justified under consideration of the named criteria. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.

ACT: appropriate comparator therapy; ABL: Abelson murine leukaemia; BCR: breakpoint cluster region; EU HTA: European health technology assessment; GBA-: Federal Joint Committee; TKI: tyrosine kinase inhibitor

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment conducted in the context of the market launch in 2022, where the G-BA had determined a minor added benefit of asciminib. However, in the G-BA's assessment the added benefit was considered proven by the marketing authorization, regardless of the underlying data, due to the special situation for orphan drugs.

I 2 Research question

The aim of this report is to assess the added benefit of asciminib compared with individualized treatment as the appropriate comparator therapy (ACT) in adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph^+ CML-CP) who have previously been treated with ≥ 2 tyrosine kinase inhibitors (TKIs).

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of asciminib

Therapeutic indication	**ACT**[a]
Adult patients with Ph^+ CML-CP previously treated with ≥ 2 TKIs	Individualized treatment[b, c, d] selecting from ▪ nilotinib ▪ dasatinib ▪ bosutinib and ▪ ponatinib

a. Presented is the respective ACT specified by the G-BA.
b. Editorial note: The term 'individualized treatment' is used by the G-BA instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
c. The treatment decision is made taking into account previous treatments, comorbidities and mutation status in particular. According to the G-BA, it is assumed for the given therapeutic indication that patients will (initially) be treated with BCR-ABL TKIs as part of remission-inducing therapy. For some patients, allogeneic stem cell transplantation can only be considered once remission has been achieved (and is therefore not part of the ACT).
d. For the implementation of individualized treatment in a study of direct comparison, the G-BA expects investigators to have a choice of several treatment options at their disposal, enabling them to make individualized treatment decisions (multi-comparator study). The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). The selection and, where applicable, restriction of treatment options must be justified under consideration of the named criteria. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.

ACT: appropriate comparator therapy; ABL: Abelson murine leukaemia; BCR: breakpoint cluster region; EU HTA: European health technology assessment; GBA-: Federal Joint Committee; TKI: tyrosine kinase inhibitor

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. To derive the added benefit, randomized controlled trials (RCTs) without any restrictions on study duration were used – in deviation from the company's inclusion criteria, which only included RCTs with a minimum study duration of 24 weeks.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on asciminib (status: 13 March 2025)
- Bibliographical literature search on asciminib (last search on 13 March 2025)
- Search of trial registries/trial results databases for studies on asciminib (last search on 13 March 2025)
- search on the G-BA website for asciminib (last search on 13 March 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on asciminib (last search on 10 June 2025); for search strategies, see I Appendix A of the full dossier assessment

The review did not identify any relevant studies for assessing the added benefit of asciminib in comparison with the G-BA's ACT. This deviated from the company's assessment, which identified study CABL001A2301 (hereinafter referred to as ASCEMBL) for comparing asciminib with bosutinib [3-13].

The ASCEMBL study included by the company did not allow for a comparison of asciminib versus the ACT, as no individualized treatment according to the G-BA's ACT was carried out in the comparator arm. This means that no suitable data were available for the comparison of asciminib with the G-BA's comparator therapy. ASCEMBL is described below, followed by an explanation of why it was not suitable for this benefit assessment. Further details on the characterization of ASCEMBL, the intervention used and the patients included in the study are presented in Appendix B of the full benefit assessment.

Evidence provided by the company

ASCEMBL

The ASCEMBL study is a completed multicentre, open-label RCT comparing asciminib with bosutinib. Adult patients with chronic myeloid leukaemia (CML) in the chronic phase who had previously been treated with 2 or more adenosine triphosphate-competitive TKIs were included. The prerequisite for inclusion in the study was treatment failure or intolerance to the last previous TKI therapy. Treatment failure was determined based on the criteria of the European LeukemiaNet [14]. Patients with intolerance to the last TKI therapy could be included if they had a transcript level of the breakpoint cluster region-Abelson gene (BCR::ABL1) of > 0.1% International Scale (IS) at screening. Patients were not allowed to have

a T351I or V299L mutation, nor should they have progressed to an accelerated phase or blast crisis of CML.

A total of 233 patients were included in ASCEMBL and randomly assigned in a 2:1 ratio to treatment with asciminib (N = 157) or bosutinib (N = 76). Randomization was stratified according to the presence of a major cytogenetic response (MCyR [complete or partial] versus no MCyR [minor, minimal or none]).

Treatment with asciminib and bosutinib was carried out in accordance with the respective summary of product characteristics (SmPC) [15,16]. Treatment with the study medication continued until disease progression, treatment failure according to the criteria of the European LeukemiaNet [14], the occurrence of a T315I or V299L mutation, or for a maximum of 96 weeks after the first dose of the last randomized patient or up to 48 weeks after the last patient switched from bosutinib to asciminib, whichever was longer, provided that treatment was not discontinued prematurely. The study documents showed that continued treatment with asciminib or bosutinib beyond 96 weeks was possible and did occur (51% of patients in the asciminib arm and 19.7% in the bosutinib arm). For patients in the bosutinib arm, a switch to treatment with asciminib was also possible in the event of treatment failure according to the criteria of the European LeukemiaNet [14].

The primary outcome of the study was major molecular response (MMR) at Week 24. Secondary outcomes were overall survival and other outcomes in the categories morbidity, health-related quality of life and side effects.

ACT defined by the G-BA

The G-BA determined individualized treatment selecting from nilotinib, dasatinib, bosutinib and ponatinib as the ACT for the therapeutic indication in question. In its notes on the ACT, the G-BA pointed out that for implementation of individualized treatment in a study of direct comparison, the investigator is expected to have a selection of several treatment options at their disposal, enabling them to make individualized treatment decisions taking into account previous treatments, comorbidities and mutation status (multicomparator study). The selection and, where applicable, restriction of treatment options must be justified. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment. With the ASCEMBL study, the company presented a single-comparator study in which only bosutinib was available as a treatment in the comparator arm.

The company's argumentation regarding implementation of the ACT

All patients in the comparator arm of ASCEMBL received treatment with bosutinib. The other treatment options covered by the ACT, nilotinib, dasatinib and ponatinib, were not available. In Module 4 A, the company argued that the ASCEMBL study provided evidence for the

subpopulation of the asciminib therapeutic indication for which bosutinib represents an individualized treatment option, taking into account previous therapies, comorbidities and mutation status. The company justified this as follows:

It stated that at the time of study inclusion, approximately 24% of patients in the bosutinib arm had previously been treated with ponatinib, and ponatinib would no longer be a viable treatment option for them. The company said that for the remaining patients, the 2 drugs bosutinib and ponatinib would be equally suitable. It described that on the one hand, patients with a T351I mutation (for whom ponatinib is the only treatment option from the 4 TKIs available) were excluded from the study. On the other hand, according to guidelines and the SmPCs, there are no absolute contraindications with regard to comorbidity that would argue against the use of either of the 2 drugs. The company added that it is, however, known that ponatinib increases the risk of cardiovascular side effects, which is why bosutinib is preferable in cases where cardiovascular risk factors are present [17].

It continued that in addition to ponatinib, there were 2 other feasible options for individualized treatment: dasatinib and nilotinib. At the time of study enrolment, 59.2% of patients in the bosutinib arm had already received dasatinib or nilotinib a previous treatment. According to the company, a further 3.9% of patients had a mutation that constituted a contraindication for the administration of dasatinib or nilotinib. Furthermore, from the company's perspective, dasatinib or nilotinib were not a viable treatment option for 23.7% of patients who had received either dasatinib or nilotinib as a previous treatment, due to individual comorbidities or risk factors. To this end, the company identified drug-specific risk factors and comorbidities from the SmPCs and guidelines (cardiac disorders, diabetes mellitus and other metabolic diseases, thrombosis, cataracts and other eye disorders for both active ingredients; for nilotinib, additionally the presence of a very high cardiovascular risk, nervous system disorders, other vascular disorders such as peripheral arterial occlusive disease, arteriosclerosis; for dasatinib, additionally diseases of the respiratory tract), which would exclude the aforementioned patients from treatment with dasatinib or nilotinib. It stated that in total, dasatinib and nilotinib were therefore not suitable for 86.8% of patients in the comparator arm due to previous therapies, mutation status or comorbidities, and bosutinib was the preferred individualized treatment option.

At the end of its reasoning, the company also referred to a G-BA procedure in which a single-comparator study was also used and individualized treatment was the ACT (A23-03, as well as addendum A23-47) [18,19].

Evaluation of the implementation of the ACT

The company's reasoning that the G-BA's ACT was implemented in ASCEMBL for the subpopulation of patients for whom bosutinib represents an individualized treatment was not appropriate. The reasons for this are provided below.

Individualized treatment, ponatinib option

Approximately 76% of patients in the comparator arm had not received ponatinib therapy before the start of the study, meaning that ponatinib would have been a treatment option for these patients. In Module 4 A, the company stated that the 2 drugs bosutinib and ponatinib are equally suitable as treatment options. However, the current guidelines do not describe bosutinib and ponatinib as equivalent treatment options in this therapeutic indication. According to the publication Hochhaus 2020 [17], ponatinib, as a 3rd-generation TKI, should be considered for all suitable patients who have resistance to 2nd-generation TKIs (bosutinib, dasatinib, nilotinib), even if an alternative 2nd-generation TKI is still a treatment option. According to the current recommendations of the European LeukemiaNet [20], ponatinib and asciminib are the treatment options of first choice in cases of treatment resistance after second-line therapy, provided that comorbidities and BCR::ABL1 mutations allow this. The National Comprehensive Cancer Network (NCCN) guideline also designates ponatinib as a suitable treatment option for chronic phase CML with treatment failure or intolerance versus at least 2 other TKIs [21]. According to the current recommendation of the German Society for Haematology and Medical Oncology (DGHO), the early use of ponatinib or asciminib should be considered in cases of resistance after treatment with a 2nd-generation TKI and without specific BCR::ABL1 mutations, as the use of an alternative 2nd-generation TKI is rarely successful in terms of molecular response rates [22].

The company further argued that, according to the approved therapeutic indications for bosutinib and ponatinib, the patient population in ASCEMBL was equally eligible for bosutinib and ponatinib. However, according to the current SmPCs, ponatinib is an option for patients who are resistant to treatment or intolerant to only 1 of the 2 drugs dasatinib or nilotinib, whereas for treatment with bosutinib, according to the marketing authorization, both dasatinib and nilotinib must be unsuitable [16,23]. This means that ponatinib can be used in treatment situations where bosutinib is not indicated because either dasatinib or nilotinib are still treatment options. Since ASCEMBL also included patients who had received only dasatinib or only nilotinib as a previous treatment, it cannot be assumed that bosutinib and ponatinib were equally suitable for all patients in the study (see also below).

The company further argued that bosutinib is the preferred option versus ponatinib in cases where cardiovascular risk factors are present. However, severe cardiovascular comorbidities (including myocardial infarction, angina pectoris and coronary artery bypass within the last 6 months, as well as clinically significant cardiac arrhythmias, risk factors for torsade de

pointes or concomitant medication with a known risk for torsade de pointes) were exclusion criteria in the ASCEMBL study. Furthermore, only a few patients in the bosutinib arm of the study had cardiovascular comorbidities and risk factors (10.5% with cardiovascular disorders, another 10.5% with type 2 diabetes mellitus and 7.9% with obesity). Cardiovascular risk factors and comorbidities are potentially decisive factors in favouring bosutinib over ponatinib. However, in this benefit assessment, the risk factors and comorbidities, for the vast majority of the study population, did not justify favouring bosutinib over ponatinib. Ponatinib represents a potentially suitable individualized treatment option for at least a relevant proportion of the patient population. In addition, approximately 24% of patients in the bosutinib arm received ponatinib as subsequent therapy after the end of the study treatment, which is why, at least for these patients, ponatinib can be assumed to be a suitable treatment option.

Individualized treatment, the options of dasatinib and nilotinib

The company argued that for approximately 87% of patients in the comparator arm, bosutinib was the preferred individualized treatment option over dasatinib and nilotinib. It stated that 63% of patients had been previously treated with both dasatinib and nilotinib or had a mutation that is a contraindication for dasatinib or nilotinib. The company argued that for a further 24%, dasatinib and nilotinib were not suitable due to potential comorbidities or risk factors. However, the company's approach to selecting these comorbidities or risk factors was not entirely comprehensible. In Module 4 A, it named individual Preferred Terms (PTs) for comorbidities and risk factors. In Module 4 A Appendix G-1, the company then listed relevant comorbidities as selection criteria, but only according to the higher-level System Organ Classes (SOCs). It could not therefore be ruled out that the company overestimated the number of patients for whom dasatinib and nilotinib were not suitable.

As described above, treatment with bosutinib according to the marketing authorization requires that both dasatinib and nilotinib are unsuitable [16]. According to the company data, which, as described above, may be overestimated, this applied to a maximum of 87% of the patients included. Treatment with bosutinib was therefore off-label for at least 13% of patients, as at least 1 of the 2 drugs would still have been a suitable treatment option for these patients.

Summary and consequences for the assessment

For approximately 76% of patients in the comparator arm of ASCEMBL, ponatinib is an additional and, according to the guidelines, potentially more suitable individual treatment option, which was not available in the study. Furthermore, for at least 13% of patients in the comparator arm, bosutinib was not administered on-label. Overall, bosutinib was therefore not the most suitable individual treatment option for more than 20% of patients in the comparator arm of ASCEMBL; the study presented was therefore not suitable for comparison

with the ACT. Patients in ASCEMBL who had already received all 3 alternative TKIs of the ACT (dasatinib, nilotinib, ponatinib) and for whom bosutinib was therefore the only remaining treatment option could potentially represent a relevant subpopulation for the benefit assessment. However, there was no information available on whether ASCEMBL included such a subpopulation and how many patients it comprised. The ASCEMBL study was therefore not suitable for the assessment of the added benefit of asciminib versus the G-BA's ACT.

I 4 Results on added benefit

No suitable data were available to assess the added benefit of asciminib in comparison with individualized treatment as the ACT in adult patients with Ph^+ CML-CP previously treated with ≥ 2 TKIs. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of the added benefit of asciminib in comparison with the ACT.

Table 5: Asciminib – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with Ph^+ CML-CP previously treated with ≥ 2 TKIs	Individualized treatment[b, c, d] selecting from ▪ nilotinib ▪ dasatinib ▪ bosutinib and ▪ ponatinib	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Editorial note: The term 'individualized treatment' is used by the G-BA instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
c. The treatment decision is made taking into account previous treatments, comorbidities and mutation status in particular. According to the G-BA, it is assumed for the given therapeutic indication that patients will (initially) be treated with BCR-ABL TKIs as part of remission-inducing therapy. For some patients, allogeneic stem cell transplantation can only be considered once remission has been achieved (and is therefore not part of the ACT).
d. For the implementation of individualized treatment in a study of direct comparison, the G-BA expects investigators to have a choice of several treatment options at their disposal, enabling them to make individualized treatment decisions (multi-comparator study). The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). The selection and, where applicable, restriction of treatment options must be justified under consideration of the named criteria. If only a single-comparator study is submitted, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.

ACT: appropriate comparator therapy; ABL: Abelson murine leukaemia; BCR: breakpoint cluster region; EU HTA: European health technology assessment; GBA-: Federal Joint Committee; TKI: tyrosine kinase inhibitor

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit for asciminib on the basis of the ASCEMBL study.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment conducted in the context of the market launch in 2022, where the G-BA had determined a minor added benefit of asciminib. However, in the G-BA's assessment the added benefit was considered proven by the marketing authorization, regardless of the underlying data, due to the special situation for orphan drugs.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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