Asciminib
(CML, first-line and second-line therapy)

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 within the framework of this 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
ACT	appropriate comparator therapy
AE	adverse event
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ELN	European LeukemiaNet
ELTS	European Treatment and Outcome Study Long-Term Survival
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-GP5	Functional Assessment of Cancer Therapy-General Item 5
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IPD	individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRT	interactive response technology
MAR	missing at random
MCAR	missing completely at random
MMR	major molecular response
Ph+ CML-CP	Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase
PRO	patient-reported outcome
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
TFR	treatment-free remission
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 01 December 2025.

Research question

The aim of the present report is to assess the added benefit of asciminib in comparison with the appropriate comparator therapy (ACT) in adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML-CP).

The present benefit assessment refers exclusively to the first-line and second-line treatment. Patients who have already received two or more prior treatments were already addressed in benefit assessment A25-70 with the associated addendum A25-129.

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of asciminib

Research question	Therapeutic indication	ACT[a]
1	Adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in the chronic phase (Ph^+ CML-CP); first-line treatment	▪ Imatinib or ▪ nilotinib or ▪ dasatinib or ▪ bosutinib
2	Adult patients with Ph^+ CML-CP who have previously been treated with a tyrosine kinase inhibitor (TKI); second-line treatment	An individualized treatment[b, c, d] with a choice of: ▪ nilotinib, ▪ dasatinib, ▪ bosutinib, and ▪ ponatinib

a. Presented is the respective ACT specified by the G-BA.
b. The term 'individualized treatment' is used 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). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).

ACT: appropriate comparator therapy; ABL: Abelson murine leukaemia; BCR: breakpoint cluster region; EU: European Union; HTA: Health Technology Assessment; G-BA: Federal Joint Committee; TKI: tyrosine kinase inhibitor

For both questions, the pharmaceutical company (hereinafter referred to as 'the company') follows the ACT specified by the G-BA during the consultation on 15 February 2024. On 9 December 2025, following the submission of the dossier, the G-BA amended the ACT. As a result of this change, the treatment options imatinib, nilotinib or dasatinib have been expanded to include bosutinib as an ACT for research question 1. This benefit assessment has been conducted versus the adjusted ACT of 9 December 2025.

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. For research question 2, the company also considered RCTs in its

information retrieval that included patients who had received at least one prior treatment. However, only RCTs that included patients who had received exactly one prior treatment (second-line therapy) are relevant for research 2.

Research question 1: adult patients with Ph$^+$ CML-CP; first-line treatment

Study pool and study design – ASC4FIRST and ASC4START

The two studies ASCFIRST and ASC4START were included for the benefit assessment. ASC4FIRST and ASC4START are ongoing, multicentre, open-label RCTs. The ASC4FIRST study compared asciminib with a tyrosine kinase inhibitor (TKI) chosen by the investigator (imatinib, nilotinib, dasatinib or bosutinib), whilst ASC4START compared asciminib with nilotinib. The study included adult patients with newly diagnosed Ph$^+$ CML-CP.

A total of 405 patients were enrolled in the ASC4FIRST study and randomized in a 1:1 ratio to either treatment with asciminib (N = 201) or with a TKI (imatinib, nilotinib, dasatinib or bosutinib) selected by the investigator prior to randomization (N = 204). At the time this dossier was drawn up, bosutinib was not yet part of the ACT. The company therefore presented a subpopulation in which patients who had been assigned to treatment with bosutinib prior to randomization were not considered. As only 3.7% of patients in the total population had been assigned to treatment bosutinib in the ASC4FIRST study, it is not assumed that the exclusion of these patients had a significant impact on the results. Furthermore, the results of the ASC4FIRST study are summarized in a meta-analysis with the results from the ASC4START study (see the section ‘Meta-analytical summary of the studies ASC4FIRST and ASC4START’), which reduces the aforementioned proportion of patients to 1.5 per cent related to the total population relevant for the assessment.

A total of 568 patients in ASC4START were randomly assigned in a 1:1 ratio to treatment with asciminib (N = 284) or nilotinib (N = 284).

In both studies, treatment with asciminib and the TKIs in the comparator arm (ASC4FIRST: imatinib, nilotinib, dasatinib; ASC4START: nilotinib) was largely in compliance with the specifications of the respective SmPC. In both studies, treatment with the study medication was continued until disease progression, confirmed loss of major molecular response (MMR); according to European LeukemiaNet [ELN] criteria), intolerance, decision by the investigator, withdrawal of consent, transition to the treatment-free remission (TFR) phase, treatment failure (according to ELN criteria), death or the end of the study. Neither of the two studies provided for any switch between study arms. In both studies, subsequent therapies were allowed without restrictions after disease progression for patients in both study arms.

Primary outcome in the ASC4FIRST study was an MMR at Week 48; primary outcome in the ASC4START study was treatment discontinuation due to adverse events (AEs). Furthermore,

overall survival as well as outcomes of the categories morbidity, health-related quality of life and AEs were recorded in both studies.

Data cuts

ASC4FIRST

This benefit assessment uses the results from the 2nd data cut of 22 October 2024. This data cut took place after all patients had been treated with the study medication for 96 weeks or had previously discontinued the study medication.

ASC4START

The results of the second data cut on 15 May 2025 – which took place following 65 treatment discontinuations due to AEs – were used for the benefit assessment.

Meta-analytical summary of studies ASC4FIRST and ASC4START

Based on individual patient data (IPD), the company summarized the results of the studies ASC4FIRST and ASC4START in a meta-analysis. This meta-analysis was used for this benefit assessment.

Risk of bias

The risk of bias across outcomes was rated as low for both studies.

For the results on the outcomes overall survival, progression to blast crisis, SAEs, severe AEs and vascular diseases (serious AE), the ASC4FIRST and ASC4START studies each have a low risk of bias.

There is a high risk of bias in each of the results on the outcomes symptoms and health-related quality of life, recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) in the studies ASC4FIRST and ASC4START, as well as in the results on the outcome health status, recorded using the EQ-5D VAS in the ASC4FIRST study. This is particularly due to a high proportion of patients not considered in the analysis because of missing baseline values. In principle, the proportion of patients considered (approximately 54% to 59%) would be too small to allow the results to be used. However, the company also presented comprehensive analyses to examine the mechanism and the impact of the missing baseline values, as well as sensitivity analyses. These make it possible to assess the direction and strength of bias of an effect to such an extent that an added benefit can still be derived under certain conditions.

The results on the outcome discontinuation due to AEs are subject to a high risk of bias due to the lack of blinding in the case of a subjective decision on treatment discontinuation.

Summary assessment of the certainty of conclusions

Based on the results of the meta-analysis with two studies, at most proof, e.g. of an added benefit can be derived each with a high certainty of conclusions for the outcomes overall survival, progression to blast crisis, SAEs, severe AEs and vascular events (severe AEs).

The numerous uncertainties in the present data situation do not allow an upgrade of the certainty of conclusions for the results on patient-reported outcomes (PROs) despite the reproduction of the results. Therefore, at most hints, e.g. of an added benefit, can be derived for the results on these outcomes despite the existence of a meta-analysis.

Due to the high risk of bias in the results, at most indications, e.g. of an added benefit based can be derived for the results on the outcome discontinuation due to AEs on the basis of the meta-analysis.

Results

For the outcomes on symptoms, health status and health-related quality of life, a high proportion of patients were not considered in the analysis due to a lack of baseline values at the time of randomization. To address this issue, the company presented several additional analyses and three different analyses on these outcomes. In the analysis designated by the company as the main analysis, patients without a baseline value at the time of randomization were censored on Day 1. Consequently, the observed effects are based solely on patients with a baseline value at the time of randomization. Furthermore, the company presented two sensitivity analyses, one of which uses an expanded definition of the baseline (observed effects are based on patients for whom baseline values were recorded prior to the first administration of the study medication; patients without an extended baseline value were censored on Day 1), and one using multiple imputation for patients without a baseline value at the time of randomisation, using data from patients with a baseline value at randomization. The benefits assessment is based primarily on the results of the analysis designated by the company as the main analysis. An added benefit is only derived if the main analysis shows a statistically significant effect with at least minor extent, which is confirmed by both sensitivity analyses. Moreover, the extent of the added benefit in an outcome can only be quantified if the extent of the effects is identical across all three analyses.

Mortality

Overall survival

For the outcome overall survival, the meta-analysis of the studies ASC4FIRST and ASCA4START does not show any statistically significant difference between the treatment arms. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Progression to blast crisis

For the outcome progression to blast crisis, the meta-analysis of the studies ASC4FIRST and ASCA4START does not show any statistically significant difference between the treatment arms. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Symptoms

The added benefit is derived on the basis of the main analysis, taking into account the sensitivity analyses presented by the company.

EORTC QLQ-C30 – Fatigue, insomnia and constipation

For the outcomes fatigue, insomnia and constipation, recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START showed a statistically significant difference in favour of asciminib in the main analyses. However, the extent of the effect is no more than minor for each of these outcomes. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

EORTC QLQ-C30 – Nausea and vomiting

For the outcome nausea and vomiting, recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START showed a statistically significant difference in favour of asciminib in the main analyses and both sensitivity analyses. This results in a hint of added benefit of asciminib in comparison with the ACT.

EORTC QLQ-C30 - pain

For the outcome pain, recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START shows heterogeneous study results with no conclusive effects, as early as in the primary analysis. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

EORTC QLQ-C30 - dyspnoea

For the outcome dyspnoea, recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START showed no statistically significant difference between the treatment arms even in the main analyses. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

EORTC QLQ-C30 - appetite loss and diarrhoea

For the outcomes appetite loss and diarrhoea, recorded using the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START shows a statistically significant difference in favour of asciminib in the main analysis for each outcome; however, in at least one of the

sensitivity analyses presented by the company, there is either no statistically significant difference between the treatment arms or the study results are heterogeneous without conclusive effects. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Symptoms (Quality of Life Questionnaire CML 24 Items [EORTC QLQ-CML24])

No suitable data are available for the outcome symptoms, recorded using the EORTC QLQ-CML24. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

The outcome health status was only recorded in the ASC4FIRST study.

The main analysis showed a statistically significant difference in favour of asciminib for the outcome health status, recorded using the EQ-5D VA; however, the sensitivity analysis with multiple imputation for patients without a baseline value at the time of randomization presented by company showed no statistically significant difference. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

The added benefit is derived on the basis of the main analysis, taking into account the sensitivity analyses presented by the company.

EORTC QLQ-C30 – global health status, physical functioning, role functioning and cognitive functioning

For the outcomes global health status, physical functioning, role functioning and cognitive functioning, recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START shows, even in the main analysis, that there is no statistically significant difference between the treatment arms in each case, or that there are no conclusive effects given the heterogeneous study results. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

EORTC QLQ-C30 - emotional functioning

For the outcome emotional functioning, recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START showed a statistically significant difference in favour of asciminib in the main analysis; however, this difference was not observed in the sensitivity analysis with multiple imputation for patients without a baseline value at the time of randomization presented by company. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

EORTC QLQ-C30 - social functioning

For the outcome social functioning recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START showed a statistically significant difference in favour of asciminib in the main analyses and both sensitivity analyses. This results in a hint of added benefit of asciminib in comparison with the ACT.

EORTC QLQ-CML24

No suitable data were available for the outcomes on health-related quality of life, recorded with the EORTC QLQ-CML24. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

The meta-analysis of the studies ASC4FIRST and ASC4START showed no statistically significant difference between treatment arms for the outcomes SAEs and severe AEs. There was no hint of greater or lesser harm from asciminib in comparison with the ACT for either of the outcomes; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome discontinuation due to AEs, the meta-analysis of the studies ASC4FIRST and ASC4START showed a statistically significant difference in favour of asciminib. There is an indication of lesser harm from asciminib in comparison with the ACT.

PRO-CTCAE

No suitable data are available for the outcome PRO-CTCAE. There was no hint of greater or lesser harm from asciminib in comparison with the ACT; greater or lesser harm is therefore not proven.

Vascular disorders (severe AEs)

For the outcome vascular disorders (severe AEs), the meta-analysis of the studies ASC4FIRST and ASC4START showed a statistically significant difference to the disadvantage of asciminib. There is proof of greater harm from asciminib in comparison with the ACT.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3] (research question 1: adult patients with Ph+ CML-CP; first-line treatment)

On the basis of the results presented, the probability and extent of the added benefit of the drug asciminib versus the ACT is assessed as follows:

[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

Overall, mostly positive and one negative effects of asciminib were shown in comparison with the ACT.

On the positive side, there is a hint of added benefit with minor extent for nausea and vomiting in the morbidity category, and in the category health-related quality of life a hint of a non-quantifiable added benefit is shown for social functioning.

In the side effects category, there is a positive effect in discontinuations due to AEs with an indication of lesser harm with the extent "major". This is offset by a negative effect in the outcome vascular disorders (severe AEs), with proof of greater harm with the extent "considerable".

Overall, the positive effects of asciminib outweigh those of the ACT. In summary, there is a hint of minor added benefit of asciminib over the ACT for patients with Ph^+ CML-CP.

Research question 2: adult patients with Ph^+ CML-CP; second-line treatment

Results

Consistent with the findings of the company, the review of the completeness of the study pool did not produce any RCTs for this research question.

Transfer of results from patients from the RCT ASCEMBL to the target population not possible

Approach and reasoning of the company on the transferability of the study results

The company carries out an information retrieval for all pretreated patients, regardless of their line of treatment, and identifies the RCT ASCEMBL, which is already known from earlier benefit assessment procedures. The ASCEMBL study is an open-label, completed RCT comparing asciminib with bosutinib, which enrolled adult patients with Ph^+ CML-CP who had previously been treated with two or more TKIs. According to the company, the evidence from the ASCEMBL study is transferable to patients with Ph^+ CML-CP in the second-line of treatment, for whom bosutinib represents an individualized treatment option. The company justified this on the basis of treatment recommendations that are independent of treatment lines, as well as the fact that the EMA (European Medicines Agency) has granted authorization for all treatment lines without any directly comparative data from patients in the second-line. According to the predictive modelling carried out for MMR, it is expected that the degree of efficacy in patients who have received a single prior treatment will lie between the efficacy observed in treatment-naive patients and that observed in patients who have received at least

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].

two pretreatments. In terms of safety, patients who have previously been treated with only one TKI are thought to have a more favourable prognosis with regard to avoiding side effects, due to fewer comorbidities, compared with patients who have already been treated with at least two TKIs. It can therefore be assumed that the safety profile of asciminib in second-line treatment of adult patients with Ph^+ CML-CP is at least as favourable as that of patients who have been pretreated with at least two TKIs. Furthermore, new safety data from the single-arm study ASC2ESCELATE showed that the safety profile of asciminib was consistent with the previously established safety profile of asciminib also in patients with Ph^+ CML-CP who had been pretreated with a TKI.

Assessment of the data presented by the company

The company carried out an information retrieval for RCTs for the source population (patients pretreated with two or more TKIs) and the target population (patients in the second-line setting). However, there it did not conduct an information retrieval to identify all potentially relevant further investigations on the intervention and the ACT in the target population (patients in the second-line setting. The company only refers selectively to the single-arm study ASC2ESCELATE and only presents the analyses relating to MMR and discontinuation due to AEs in Module 4A. An appropriate processing of the data on patients who were pretreated with exactly one TKI did not take place. The insufficiently analysed data presented by the company are not suitable for a transfer of the results from patients who have been pretreated with two or more TKIs to patients in the second-line setting. Overall, the evidence from patients with Ph^+ CML-CP in the second-line treatment is insufficient to support the transferability of results from patients who have been pretreated with two or more TKIs to patients in the second-line treatment.

Furthermore, it is clear from the consultation held on 15 February 2024 that, according to the G-BA, it is not medically plausible to transfer evidence from patients who have previously been treated with two or more TKIs to patients who have previously been treated with exactly one TKI, as these involve different treatment situations and patient groups. CML is a progressive disease in which it is assumed that patient characteristics and the course of treatment change significantly as the number of previous treatments increases.

Regardless of this, the ASCEMBL study was classified as irrelevant to the benefit assessment of asciminib in adult patients with Ph+ CML-CP who have been pretreated with two or more TKIs in the previous benefit assessment procedure (A25-70), on the grounds that the ACT was considered not to have been implemented. It is therefore not possible to transfer the added benefit observed in patients who have been pretreated with two or more TKIs to patients in the second-line setting, regardless of the shortcomings regarding the company's information retrieval, the inadequate analysis of the data and the medical meaningfulness of such transfer.

Results on added benefit

For adult patients with Ph+ CML-CP in the second-line setting, there are no suitable data available to assess the added benefit of asciminib compared with the ACT. 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 significant added benefit (research question 2: adult patients with Ph+ CML-CP; second-line treatment)

Since the company presented no suitable data for assessing the added benefit of asciminib compared to the ACT in adult patients with Ph+ CML-CP receiving second-line treatment, the added benefit is not proven.

Probability and extent of added benefit – summary

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

Table 3: Asciminib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in the chronic phase (Ph^+ CML-CP); first-line treatment	▪ Imatinib or ▪ nilotinib or ▪ dasatinib or ▪ bosutinib	Hint of minor added benefit
2	Adult patients with Ph^+ CML-CP who have previously been treated with a tyrosine kinase inhibitor (TKI); second-line treatment	An individualized treatment[b, c, d] with a choice of: ▪ nilotinib ▪ dasatinib, ▪ bosutinib, and ▪ ponatinib	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The term 'individualized treatment' is used 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). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).

ACT: appropriate comparator therapy; ABL: Abelson murine leukaemia; BCR: breakpoint cluster region; EU: European Union; HTA: Health Technology Assessment; G-BA: Federal Joint Committee; TKI: tyrosine kinase inhibitor

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of asciminib in comparison with the ACT in adult patients with Ph+ CML-CP.

The present benefit assessment refers exclusively to the first-line and second-line treatment. Patients who have already received two or more pretreatments had already been the subject of benefit assessment A25-70 and the associated addendum A25-129 [3,4].

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of asciminib

Research question	Therapeutic indication	ACT[a]
1	Adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in the chronic phase (Ph^+ CML-CP); first-line treatment	▪ Imatinib or ▪ nilotinib or ▪ dasatinib or ▪ bosutinib
2	Adult patients with Ph^+ CML-CP who have previously been treated with a tyrosine kinase inhibitor (TKI); second-line treatment	An individualized treatment[b, c, d] with a choice of: ▪ nilotinib ▪ dasatinib, ▪ bosutinib, and ▪ ponatinib

a. Presented is the respective ACT specified by the G-BA.
b. The term 'individualized treatment' is used 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). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).

ACT: appropriate comparator therapy; ABL: Abelson murine leukaemia; BCR: breakpoint cluster region; EU: European Union; HTA: Health Technology Assessment; G-BA: Federal Joint Committee; TKI: tyrosine kinase inhibitor

For both research questions, the company followed the ACT specified by the G-BA during the consultation on 15 February 2024 [5]. On 9 December 2025, following the submission of the dossier, the G-BA amended the ACT. As a result of this change, the treatment options imatinib, nilotinib or dasatinib have been expanded to include bosutinib as an ACT for research question 1. This benefit assessment has been conducted versus the adjusted ACT of 9 December 2025.

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, 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. For research question 2, the company also considered RCTs in its information retrieval that included patients who had received at least one prior treatment. However, only RCTs that included patients who had received exactly one prior treatment (second-line therapy) are relevant for research 2.

I 3 Research question 1: adult patients with Ph+ CML-CP; first-line treatment

I 3.1 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: 10 October 2025)
- Bibliographical literature search on asciminib (last search on 04 November 2025)
- Search of trial registries/trial results databases for studies on asciminib (last search on 04 November 2025)
- Search on the G-BA website for asciminib (last search on 04 November 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on asciminib (last search on 15 December 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: asciminib vs. the ACT

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
CABL001J12301 (ASC4FIRST[c])	Yes	Yes	No	Yes [6,7]	Yes [8-10]	Yes [11]
CABL001J12302 (ASC4START[c])	No	Yes	No	Yes [12,13]	Yes [14-16]	No

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

ACT: appropriate comparator therapy; RCT: randomized controlled trial

The studies ASC4FIRST and ASC4START were used for the benefit assessment. The study pool was consistent with that selected by the company.

I 3.1.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: asciminib TKI[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
ASC4FIRST	RCT, open-label, parallel	Adult patients with newly diagnosed Ph+ CML-CP[c] ▪ with typical BCR::ABL1 transcripts [e14a2 and/or e13a2][d] ▪ ECOG PS of 0 or 1	Asciminib (N = 201) TKI[a] (N = 204) subpopulation thereof presented by the company[e]: asciminib (n = 197) TKI[e:] (N = 193)	Screening: 21 days treatment: until disease progression, confirmed loss of MMR[f], treatment failure[f], intolerance, decision by the investigator, withdrawal of consent, transition to the TFR phase[g], death or end of the study[h] follow-up[i]: outcome-specific, at most until death, withdrawal of consent or end of study	116 centres in: Australia, Austria, Belgium, Bulgaria, Canada, Czech Republic, China, Denmark, Finland, France, Germany, Hungary, India, Israel, Italy, Japan, Malaysia, the Netherlands, Norway, Portugal, Republic of Korea, Singapore, Slovakia, Spain, Sweden, Switzerland, Taiwan, United Kingdom, USA 10/2021–ongoing data cuts: 28 November 2023[j] 22 October 2024[k]	Primary: MMR at Week 48 secondary: overall survival, morbidity, health-related quality of life, AEs
ASC4START	RCT, open-label, parallel	Adult patients with newly diagnosed Ph+ CML-CP[c] ▪ with typical BCR::ABL1 transcripts [e14a2 and/or e13a2][d, l] ▪ ECOG PS of 0 or 1	Asciminib (N = 284) nilotinib (N = 284)	Screening: 21 days treatment: until disease progression, confirmed loss of MMR[f], treatment failure[f], intolerance, decision by the investigator, withdrawal of consent, death, transition to the TFR phase[g] or end of the study[h] follow-up[i]: outcome-specific, at most until death, withdrawal of consent or end of study	120 centres in: Argentina, Bulgaria, Canada, Czech Republic, France, Germany, Greece, Hungary, India, Italy, Jordan, Malaysia, Netherlands, Oman, Republic of Korea, Romania, Singapore, Slovakia, South Africa, Switzerland, Turkey, United Arab Emirates, United Kingdom, USA 11/2022–ongoing data cuts: 03 September 2024[m] 15 May 2025[n]	Primary: treatment discontinuation due to AEs secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, direct comparison: asciminib TKI[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
a. ASC4FIRST study: Prior to randomization, the investigator, in consultation with the patient and taking into account the current treatment paradigm as well as the patient characteristics and comorbidities, selects the TKI (imatinib, nilotinib, dasatinib or bosutinib) to be used if the patient is allocated to the comparator arm; ASC4START trial: nilotinib. b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment. c. Ph^+ CML-CP diagnosis according to the ELN 2020 criteria [17] with cytogenetic confirmation of the Philadelphia chromosome within the last 3 months; additionally, for the ASC4START study: a cryptic Ph chromosome should be detected by metaphase FISH. d. Quantified in the screening by means of standardised RQ-PCR. e. Patients who were assigned to treatment with imatinib, nilotinib or dasatinib prior to randomization. For explanation, see the following section. f. In accordance with ELN criteria [17]. g. Upon meeting certain remission criteria, patients were able to transition to a TFR phase; in the ASC4FIRST study, the TFR phase was only introduced with Amendment 4 to the study protocol after the relevant data cut; in ASC4START, the TFR phase was introduced with Amendment 2 to the study protocol before the data cut. h. ASC4FIRST: up to the relevant data cut, the study was scheduled to end after a maximum of 5 years; Amendment 4 to the study protocol extended the treatment duration to a maximum of 8 years from the date on which the last patient received the first dose of the study medication. In ASC4START, the end of the study was defined in Amendment 2 to the study protocol as a maximum of 5 years' treatment without TFR, or after 96 weeks of TFR, or after 48 weeks of re-treatment of the last patient following TFR in the event of MMR loss (including a 30-day safety follow-up period for all options). i. Outcome-specific information is described in Table 8. j. Primary analysis: once all patients have been treated with the study medication for 48 weeks or have discontinued it earlier. k. Secondary analysis: once all patients had been treated with the study medication for 96 weeks or had previously discontinued the study medication. l. If the central laboratory had not yet provided confirmation at the time of randomization, confirmation by means of a qualitative test carried out in an accredited local laboratory and validated in accordance with local regulations was sufficient. m. Interim analysis: following 46 treatment discontinuations due to AEs. n. Primary analysis: following 65 treatment discontinuations due to AEs. AE: adverse event; BCR::ABL1: breakpoint cluster region-Abelson gene; CML: chronic myeloid leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ELN: European LeukemiaNet; FISH: fluorescence in situ hybridization; MMR: major molecular response; n: subpopulation presented by company; N: number of randomized patients; Ph^+ CML-CP: Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase; RCT: randomized controlled trial; RQ-PCR: real-time quantitative polymerase chain reaction; TFR: treatment-free remission; TKI: tyrosine kinase inhibitor					

Table 7: Characteristics of the intervention – RCT, direct comparison: asciminib vs. TKI[a] (multipage table)

Study	Intervention	Comparison
ASC4FIRST	Asciminib 80 mg daily, orally	Imatinib 400 mg daily, orally or nilotinib 300 mg twice daily, orally or dasatinib 100 mg daily, orally
	Dose adjustments: ▪ dose increase not allowed ▪ dose reduction [b] to 40 mg daily in cases of AEs ▪ dose interruption for up to 28 days[c] ▪ treatment switches are not permitted	▪ dose increase[d]: for imatinib (to 600 mg daily) and for dasatinib (to 140 mg daily); no dose increase was permitted for nilotinib. ▪ dose reduction in the event of toxicity, in accordance with local marketing authorizations ▪ dose interruption for up to 28 days[c] ▪ treatment switches are not permitted
	Disallowed prior treatment ▪ other antineoplastic drugs, including chemotherapy and/or biologics for the treatment of CML[e], except hydroxyurea or anagrelide ▪ stem cell transplantation **disallowed concomitant treatment** ▪ other antineoplastic therapies including chemotherapies and biologic therapies[f] ▪ other TKIs for the treatment of CML ▪ TKI arm: contraindications as per local marketing authorization **allowed concomitant treatment** ▪ any supportive concomitant medication (e.g. antiemetics, anticoagulants, antithrombotics, blood and platelet transfusions[g]) ▪ hydroxyurea during the first 2 weeks of treatment ▪ bisphosphonates	
ASC4START	Asciminib 80 mg daily, orally	Nilotinib 300 mg twice daily, orally
	Dose adjustments: ▪ dose increase not allowed ▪ dose reduction [b] to 40 mg daily in cases of AEs ▪ dose interruption for up to 28 days[c] ▪ treatment switches are not permitted	▪ dose increase not allowed ▪ dose reduction to 200 mg twice daily ▪ dose interruption for up to 28 days[c] ▪ treatment switches are not permitted
	Disallowed prior treatment ▪ other antineoplastic drugs, including chemotherapy and/or biologics for the treatment of CML, except hydroxyurea or anagrelide ▪ stem cell transplantation **Disallowed concomitant treatment** ▪ other antineoplastic therapies including chemotherapies and biologic therapies[f] ▪ other TKIs for the treatment of CML	

Table 7: Characteristics of the intervention – RCT, direct comparison: asciminib vs. TKI[a] (multipage table)

Study	Intervention	Comparison
	Allowed concomitant treatment ▪ any supportive concomitant medication (e.g. antiemetics, anticoagulants, antithrombotics, blood and platelet transfusions[g]) ▪ hydroxyurea during the first 2 weeks of treatment ▪ bone-modifying drugs	

a. ASC4FIRST study: with a choice of imatinib, nilotinib or dasatinib prior to randomization by the investigator; ASC4START study: nilotinib.
b. A re-escalation to the protocol-specific dose was permitted only once, provided that the patient's condition had improved under on the reduced dose.
c. If there was a dose interruption of ≥ 28 days due to non-haematological toxicity, or ≥ 42 days due to haematological toxicity, the study treatment had to be discontinued.
d. At the investigator's discretion.
e. Prior treatment with imatinib, nilotinib, dasatinib or bosutinib for ≤ 2 weeks was permitted.
f. Except for antineoplastic therapies for newly diagnosed solid tumours, e.g. prostate cancer.
g. For patients with anaemia or thrombocytopenia.

CML: chronic myeloid leukaemia; RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor; AE: adverse event

ASC4FIRST and ASC4START

ASC4FIRST and ASC4START are ongoing, multicentre, open-label RCTs. The ASC4FIRST study compared asciminib with a TKI chosen by the investigator (imatinib, nilotinib, dasatinib or bosutinib), whilst ASC4START compared asciminib with nilotinib. The study included adult patients with newly diagnosed Ph^+ CML-CP. The diagnosis was made in accordance with the ELN criteria [17], with cytogenetic confirmation of the Philadelphia chromosome within the last 3 months prior to the start of the study. In ASC4START, a cryptic Philadelphia chromosome was also to be detected using metaphase FISH hybridization. Prior treatment with hydroxyurea or anagrelide was permitted in both studies; in ASC4FIRST, prior treatment with imatinib, nilotinib, dasatinib or bosutinib was also allowed for a duration of ≤ 2 weeks prior to the start of the study. In addition, patients had to have a typical BCR:ABL1 transcript (e14a2 and/or e13a2).

A total of 405 patients were enrolled in the ASC4FIRST study and randomized in a 1:1 ratio to either treatment with asciminib (N = 201) or with a TKI (imatinib, nilotinib, dasatinib or bosutinib) selected by the investigator (N = 204). Randomization was stratified according to the European Treatment and Outcome Study Long-Term Survival (ELTS) score (low vs. medium vs. high) and the TKI selected prior to randomization, in accordance with the interactive response technology (IRT) (imatinib vs. second-generation TKIs [nilotinib, dasatinib or bosutinib]).

In ASC4START, a total of 568 patients in ASC4START were randomly assigned in a 1:1 ratio to treatment with asciminib (N = 284) or nilotinib (N = 284), stratified according to their ELTS score (low vs. medium vs. high).

Following a treatment period of at least 5 years up to a maximum of 6 years in the ASC4FIRST study, or at least 3 years up to a maximum of 5 years in the ASC4START study, patients may take part in an optional TFR phase, provided they meet certain remission criteria. Patients who enter the TFR phase and subsequently meet the criterion for TFR failure, or who, in the opinion of the investigator, require treatment, must move on to a treatment re-initiation phase. At the time of the data cuts relevant to the benefit assessment in the two studies, no patient in either study had yet entered the TFR phase.

In both studies, treatment with asciminib and the TKIs in the comparator arm (ASC4FIRST: imatinib, nilotinib, dasatinib; ASC4START: nilotinib) was largely in compliance with the specifications of the respective SmPC [18-21]. The treatment option with bosutinib in ASC4FIRST will not be addressed further below. The reason for this is that patients assigned to treatment with bosutinib prior to randomization were not included in the subpopulation presented by the company, which was used for the benefit assessment (see the following section).

In both studies, treatment with the study medication was continued until disease progression, confirmed loss of MMR; according to ELN criteria [17]), intolerance, decision by the investigator, withdrawal of consent, transition to the TFR phase, treatment failure (according to ELN criteria [17]), death or the end of the study. Neither of the two studies provided for any switch between study arms. Subsequent therapies were permitted without restrictions for patients in both study arms following disease progression (an overview of subsequent antineoplastic therapies is provided in Table 11).

Primary outcome in the ASC4FIRST study was MMR at Week 48; primary outcome in the ASC4START study was treatment discontinuation due to AEs. Furthermore, overall survival as well as outcomes of the categories morbidity, health-related quality of life and AEs were recorded in both studies.

Subpopulation of ASC4FIRST presented by the company

For research question 1, the G-BA specified the drugs imatinib, nilotinib, dasatinib or bosutinib as ACT. The ASC4FIRST study compared asciminib with all four treatment options specified by the G-BA. However, in its dossier the company only presented a subpopulation of ASC4FIRST (N = 197 vs. N = 193), in which patients who had been assigned to treatment with bosutinib prior to randomization were not considered. Overall, this only affected 4 patient in the intervention arm and 11 patients in the comparator arm. The company justified the consideration of this subpopulation on the grounds that bosutinib was not part of the ACT.

The company's approach is comprehensible, as bosutinib was only specified as a treatment option under the G-BA's ACT after this therapy had been adjusted (see Chapter I 2) following the submission of the dossier. As only 3.7% of patients in the total population had been assigned to treatment bosutinib in the ASC4FIRST study, it is not assumed that the exclusion of these patients had a significant impact on the results. Furthermore, the results of the ASC4FIRST study are summarized in a meta-analysis with the results from the ASC4START study (see the section 'Meta-analytical summary of the studies ASC4FIRST and ASC4START'), which reduces the aforementioned proportion of patients to 1.5 per cent related to the total population relevant for the assessment. Therefore, the subpopulation presented by the company was used for the benefit assessment.

Data cuts

ASC4FIRST

ASC4FIRST is an ongoing study. Two data cuts are available:

- First data cut: 28 November 2023 (primary analysis), once all patients have been treated with the study medication for 48 weeks or have discontinued it earlier
- Second data cut: 22 October 2024 (secondary analysis), once all patients had been treated with the study medication for 96 weeks or had previously discontinued the study medication

This benefit assessment uses the results for the second data cut of 22 October 2024. This concurs with the company's approach.

ASC4START

ASC4START is an ongoing study. Two data cuts are available:

- First data cut: 3 September 2024 (interim analysis) following 46 treatment discontinuations due to AEs
- Second data cut: 15 May 2025 (primary analysis) following 65 treatment discontinuations due to AEs

This benefit assessment uses the results for the second data cut of 15 May 2025. This concurs with the company's approach.

Planned duration of follow-up

Table 8 shows the planned duration of patient follow-up for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, direct comparison: asciminib vs. TKI[a]

Study **outcome category** **outcome**	**Planned follow-up**
ASC4FIRST	
Mortality	
Overall survival	Until death or study end
Morbidity	
Progression to blast crisis	Until death or study end
Symptoms (EORTC QLQ-C30, EORTC QLQ-CML24)	Until 12 weeks after the last dose of the study medication
Health status (EQ-5D VAS)	Until the last dose of the study medication
Health-related quality of life	
EORTC QLQ-C30, EORTC QLQ-CML24	Until 12 weeks after the last dose of the study medication
Side effects	
All outcomes of the side effects category[b] (except PRO-CTCAE)	Until 30 days after the last dose of the study medication
PRO-CTCAE	Until 12 weeks after the last dose of the study medication
ASC4START	
Mortality	
Overall survival	Until death or study end
Morbidity	
Progression to blast crisis	Until death or study end
Symptoms (EORTC QLQ-C30, EORTC QLQ-CML24)	Until 12 weeks after the last dose of the study medication
Health-related quality of life	
EORTC QLQ-C30, EORTC QLQ-CML24	Until 12 weeks after the last dose of the study medication
Side effects	
All outcomes of the side effects category[b] (except PRO-CTCAE)	Until 30 days after the last dose of the study medication
PRO-CTCAE	Until 12 weeks after the last dose of the study medication

a. ASC4FIRST study: imatinib, nilotinib or dasatinib by the investigator; ASC4START study: nilotinib.
b. SAEs related to the treatment were followed up for more than 30 days.

EORTC: European Organisation for Research and Treatment of Cancer; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-CML24: Quality of Life Questionnaire CML 24 Items; QLQ-C30: Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial; SAE: serious adverse event; TKI: tyrosine kinase inhibitor; VAS: visual analogue scale

In both studies, follow-up for the outcomes overall survival and progression to blast crisis was continued until death or the end of the study. With the exception of the outcome health status (only recorded in the ASC4FIRST study), the PROs on morbidity and health-related quality of life were planned to be followed up for up to 12 weeks after the last dose of the study

medication. For the outcome health status, follow-up was planned until the last dose of the study medication. The planned follow-up for the outcomes in the side effects category was up to 30 days after the last administration of the study medication. The patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), in contrast, should be followed up for up to 12 weeks after the last dose of the study medication.

The observation periods for outcomes in the categories morbidity, health-related quality of life, and side effects are systematically shortened in both studies except for the outcome progression to blast crisis, because these outcomes were surveyed only for the period of treatment with the study medication (or plus 30 days or 12 weeks). However, to draw a reliable conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

Patient characteristics

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, direct comparison: asciminib vs. TKI[a] (multipage table)

Study characteristic category	ASC4FIRST		ASC4START	
	asciminib	TKI[a]	asciminib	nilotinib
	N = 197	N = 193	N = 284	N = 284
Age [years], mean (SD)	51 (15)	50 (16)	48 (15)	49 (15)
Sex [F/M], %	35/65	39/61	38/62	44/56
Family origin, n (%)				
White	106 (54)	103 (53)	227 (80)	217 (76)
Asian	88 (45)	86 (45)	40 (14)	46 (16)
Black or African American	2 (1)	2 (1)	12 (4)	10 (4)
Other	0 (0)	0 (0)	1 (< 1)[b, c]	4 (1)[b, c]
Missing	1 (< 1)[c]	2 (1)[c]	4 (1)[c]	7 (2)[c]
ECOG PS at baseline, n (%)				
0	167 (85)	160 (83)	226 (80)	235 (83)
1	30 (15)	32 (17)	57 (20)	49 (17)
2	0 (0)	0 (0)	1 (< 1)	0 (0)
Missing	0 (0)	1 (< 1)	0 (0)	0 (0)
Time from first diagnosis of CML to randomization [weeks], median [min; max]	5.0 [1.9; 16.1]	4.9 [1.3; 14.9]	4.1 [0.0; 15.4]	4.5 [0.7; 16.0]
Blasts in the bone marrow [%], median [min; max][d]	1.2 [0.0; 14.0]	1.4 [0.0; 7.6]	2.0 [0.0; 23.8]	2.0 [0.0; 11.0]
Blasts and promyelocytes in the bone marrow [%], median [min; max][d]	4.1 [0.0; 29.0]	4.8 [0.0; 29.0]	6.0 [0.0; 30.4]	5.0 [0.0; 40.0]

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, direct comparison: asciminib vs. TKI[a] (multipage table)

Study characteristic category	ASC4FIRST		ASC4START	
	asciminib	TKI[a]	asciminib	nilotinib
	N = 197	N = 193	N = 284	N = 284
Ph+metaphases in the bone marrow, categorized [%], n (%)				
0	2 (1)	1 (< 1)	8 (3)	2 (< 1)
> 0–35	0 (0)	2 (1)	5 (2)	14 (5)
> 35–65	1 (< 1)	4 (2)	6 (2)	7 (3)
> 65–95	33 (17)	21 (11)	38 (13)	37 (13)
> 95	146 (74)	151 (78)	197 (69)	194 (68)
Missing	15 (8)	14 (7)	30 (11)	30 (11)
BCR::ABL1 ratio [% IS] at baseline, n (%)				
≤ 10	ND[e]	ND[e]	1 (< 1)	1 (< 1)
> 10	ND[e]	ND[e]	278 (98)	277 (98)
Missing	ND[e]	ND[e]	5 (2)	6 (2)
ELTS score (IRT), n (%)				
High	23 (12)	20 (10)	38 (13)	37 (13)
Moderate	54 (27)	53 (28)	75 (26)	75 (26)
Low	120 (61)	120 (62)	171 (60)	172 (61)
Any extramedullary involvement[f], n (%)				
No	184 (93)	178 (92)	252 (89)	248 (87)
Yes	13 (7)	13 (7)	32 (11)	36 (13)
Missing	0 (0)	2 (1)	0 (0)	0 (0)
TKI selected prior to randomization, n (%)				
Dasatinib	41 (21)	42 (22)	–	–
Imatinib	101 (51)	102 (53)	–	–
Nilotinib	55 (28)	49 (25)	284 (100)	284 (100)
Previous TKI[g], n (%)				
dasatinib	1 (< 1)	0 (0)	0 (0)	0 (0)
imatinib	20 (10)	9 (5)	0 (0)	0 (0)
Imatinib mesilate	3 (2)	1 (< 1)	0 (0)	0 (0)
None	173 (88)	183 (95)	284 (100)	284 (100)
Previous non-TKI treatment[h], n (%)	119 (60)	111 (58)	117 (41)[i]	112 (39)[i]
Treatment discontinuation, n (%)[j]	36 (18)	77 (40)	50 (18)	78 (28)
Study discontinuation, n (%)	ND[k]	ND[k]	4 (1)[l]	15 (5)[l]

Table 9: Characteristics of the study populations as well as study/treatment discontinuation – RCT, direct comparison: asciminib vs. TKI[a] (multipage table)

Study characteristic category	ASC4FIRST		ASC4START	
	asciminib	TKI[a]	asciminib	nilotinib
	N = 197	N = 193	N = 284	N = 284

a. Choice of imatinib, nilotinib or dasatinib prior to randomization.
b. Constituted of the categories 'Native Americans, 'Hawaiians or other Pacific Islanders' and 'multiple'.
c. Institute's calculation.
d. Figures for 196 versus 189 patients in ASC4FIRST and 270 versus 273 patients in ASC4START.
e. Data are available only for the total population; intervention arm vs. control arm [n (%)]
- ≤ 10 %: 1 (1) vs. 0 (0)
- > 10 %: 99 (99) vs. 102 (100).

f. According to the inclusion criteria, only patients with hepatosplenomegaly.
g. In ASC4FIRST, short-term treatment with imatinib, nilotinib, dasatinib or bosutinib was permitted for a maximum period of 2 weeks prior to the start of the study.
h. According to the study protocols for both studies, prior antineoplastic therapy was not permitted, with the exception of previous treatment with hydroxycarbamide and/or anagrelide.
i. Discrepancy between information in Module 4 and Module 5 of the dossier. The presented ~data were taken from additional analyses in Module 5.
j. Common reasons for treatment discontinuation in the intervention vs. the control arm (percentages based on randomized patients) were: AEs (6% vs. 13%) and inadequate treatment response (10% vs. 22%) in ASC4FIRST and AEs (7% vs. 16%) and inadequate treatment response (7% vs. 7%) in the ASC4START study). Furthermore, 2 vs. 3 of the randomized patients in the ASC4FIRST study and 0 vs. 2 of the randomized patients in the ASC4START study never started treatment.
k. In the total population, 12 (6%) in the intervention arm and 19 (9%) in the control arm had discontinued the study at the 96-week data cut. Information on the common reasons for study discontinuation is not available.
l. Information on the common reasons for study discontinuation is not available.

AE: adverse event; BCR::ABL1: breakpoint cluster region-Abelson gene; CML: chronic myeloid leukaemia; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ELTS: European Treatment and Outcome Study Long-Term Survival; f: female; IRT: interactive response technology; m: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; Ph^+: Philadelphia chromosome-positive; RCT: randomized controlled trial; SD: standard deviation; TKI: tyrosine kinase inhibitor

The demographic and clinical characteristics of the patients are largely balanced both between the subpopulation of the ASC4FIRST study presented by company and the ASC4START study, and between the study arms. The mean age of the patients was 50 (ASC4FIRST) and 49 (ASC4START) years at the time of study inclusion, and the majority were male (ASC4FIRST: 63%; ASC4START: 59%). In the subpopulation of the ASC4FIRST study, the patients were mainly white (54%) or of Asian (45%) family origin, whereas in the ASC4START study, the majority were white (76%). Overall, in ASC4FIRST and ASC4START, 62% and 60% of patients, respectively, had a low, 27% and 26% had a medium, and 11% and 13%, respectively, had a high ELTS score. The proportion of patients with any form of extramedullary involvement in the form of hepatosplenomegaly was 7% in the ASC4FIRST study, which is slightly lower than the 12% recorded in the ASC4FIRST study. Overall, more patients in the subpopulation of the

ASC4FIRST study received prior non-TKI therapy (hydroxycarbamide and/or anagrelide) than in the ASC4START study (ASC4FIRST: 59%; ASC4START: 40%). Prior treatment with a TKI within a maximum period of 2 weeks before the start of the study was permitted only in the ASC4FIRST study and was more common in the intervention arm than in the comparator arm (12% vs. 5%).

In both studies, the proportion of patients who discontinued treatment was higher in the intervention arm than in the comparator arm (ASC4FIRST: 18% versus 40%; ASC4START: 18% versus 28%). Treatment discontinuation in the comparator arm was more common in ASC4FIRST than in ASC4START (40% vs. 28%). Common reasons for treatment discontinuation in both studies were AEs and inadequate treatment response. In the ASC4FIRST study, information on the proportion of patients who discontinued the study was only available for the total population. Overall, 6% versus 9% of patients in the total population of the ASC4FIRST study and 1% versus 5% of those in the ASC4START study discontinued the study. Information on the common reasons for study discontinuation is not available.

Information on the course of the study

Table 10 shows the treatment duration of the patients and the observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: asciminib vs. TKI[a]

Study	**ASC4FIRST**		**ASC4START**	
duration of the study phase **outcome category** **outcome**	**asciminib** **N = 197**	**TKI[a]** **N = 193**	**asciminib** **N = 284**	**nilotinib** **N = 284**
Treatment duration [months]				
Median [Q1; Q3]	ND[b]	ND[b]	16.8 [13.0; 20.7][c]	15.8 [11.8; 19.9][c]
Mean (SD)	ND[b]	ND[b]	16.7 (6.0)[c]	15.4 (6.9)[c]
Observation period [d][months]				
Overall survival				
Median [min; max]	26.4 [0.0; 35.0]	24.9 [0.0; 33.6]	16.7 [1.2; 27.9]	16.6 [0.0; 29.4]
Mean (SD)	25.7 (5.3)	24.6 (6.1)	17.2 (5.0)	16.9 (5.2)
Morbidity				
Progression to blast crisis				
Median [min; max]	ND	ND	ND	ND
Mean (SD)	ND	ND	ND	ND
Symptoms (EORTC QLQ-C30)	N = 189[e]	N = 180[e]	N = 276[e]	N = 272[e]
Median [min; max]	22.0 [0.0; 24.9]	11.1 [0.0; 24.9]	11.1 [0.0; 22.6]	11.1 [0.0; 26.4]
Mean (SD)	15.9 (8.1)	12.6 (8.4)	10.0 (5.5)	9.6 (6.1)
Symptoms (EORTC QLQ-CML24)	No suitable data[f]		No suitable data[f]	
Health status (EQ-5D VAS)	N = 187[e]	N = 179[e]		
Median [min; max]	22.0 [0.0; 24.9]	11.1 [0.0; 24.9]	Not recorded	
Mean (SD)	15.9 (8.1)	12.5 (8.4)		
Health-related quality of life (EORTC QLQ-C30)	N = 189[e]	N = 180[e]	N = 276[e]	N = 272[e]
Median [min; max]	22.0 [0.0; 24.9]	11.1 [0.0; 24.9]	11.1 [0.0; 22.6]	11.1 [0.0; 26.4]
Mean (SD)	15.9 (8.1)	12.6 (8.4)	10.0 (5.5)	9.6 (6.1)
Side effects	N = 196	N = 190	N = 284	N = 282
Median [min; max]	26.6 [1.1; 35.6]	24.8 [1.3; 33.6]	16.9 [1.2; 29.0]	15.8 [1.1; 29.0]
Mean (SD)	24.7 (7.6)	21.1 (9.1)	16.8 (5.9)	15.6 (6.7)
PRO-CTCAE	No suitable data[f]		No suitable data[f]	

a. Choosing from imatinib, nilotinib or dasatinib prior to the randomization.
b. No data are available for the subpopulation presented in the dossier; in the total population, the duration of treatment in the intervention arm versus the control arm was: median [Q1; Q3]: 26.6 [23.6; 29.8] vs. 25.0 [13.7; 28.1]; mean (SD): 24.6 (7.9) vs. 21.1 (9.5).
c. Institute's calculation from data in weeks.
d. Information on how the observation period was calculated is not available.
e. Patients who have completed the questionnaire at least once.
f. For an explanation, see Section I 3.2.1.

EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; ND: no data; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; Q1: first quartile; Q3: third quartile; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-CML24: Quality of Life Questionnaire Chronic Myeloid Leukaemia 24 items; RCT: randomized controlled trial; SD: standard deviation; TKI: tyrosine kinase inhibitor; VAS: visual analogue scale

For the ASC4FIRST study, data on the duration of treatment are available only for the total population. Given the small discrepancy between the subpopulation and the total population, it is assumed that the data on treatment duration in the subpopulation presented by the company do not differ significantly from those of the total population. The data on the median treatment duration are comparable between the study arms within the studies: 26.6 months in the intervention arm and 25.0 months in the comparator arm for the total population of ASC4FIRST, and 16.8 months in the intervention arm and 15.8 months in the comparator arm for ASC4START.

The median follow-up duration for overall survival and for the outcomes of the side effects category is similar within the studies between the intervention arm and the comparator arm. None of the studies provides information on the follow-up period for the outcome progression to blast crisis.

The median follow-up duration for the PROs in the ASC4FIRST study is almost twice as long in the intervention arm (22.0 months) as in the comparator arm (11.1 months). In ASC4START, the median follow-up duration for PROs was 11.1 months in both study arms.

Information on subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies (≥ 2 patients in at least one study) – RCT, direct comparison: asciminib vs. TKI[a]

Drug class drug	Patients with subsequent therapy, n (%)			
	ASC4FIRST		ASC4START	
	asciminib N = 197	TKI[a] N = 193	asciminib N = 284	nilotinib N = 284
Patients with at least one subsequent therapy	26 (13.2)	65 (33.7)	43 (15.1)	70 (24.6)
Antineoplastic and immunomodulatory drugs[b]	26 (100)	65 (100)	43 (100)	70 (100)
Dasatinib	14 (53.8)	31 (47.7)	19 (44.2)	32 (45.7)
Dasatinib monohydrate	2 (7.7)	4 (6.2)	0 (0)	2 (2.9)
Imatinib	4 (15.4)	11 (16.9)	11 (25.6)	11 (15.7)
Nilotinib	3 (11.5)	11 (16.9)	10 (23.3)	7 (10)
Nilotinib hydrochloride monohydrate	0 (0)	0 (0)	3 (7.0)	2 (2.9)
Ponatinib	3 (11.5)	6 (9.2)	3 (7.0)	5 (7.1)
Ponatinib hydrochloride	0 (0)	2 (3.1)	1 (2.3)	0 (0)
Bosutinib	1 (3.8)	4 (6.2)	3 (7.0)	7 (10)
Cytarabine	1 (3.8)	2 (3.1)	0 (0)	1 (1.4)
Asciminib	0 (0)	12 (18.5)	0 (0)	17 (24.3)
Flumatinib mesylate	0 (0)	3 (4.6)	0 (0)	0 (0)
Hydroxycarbamide	0 (0)	3 (4.6)	2 (4.7)	1 (1.4)
Peginterferon alfa-2a	0 (0)	0 (0)	0 (0)	3 (4.3)
Methotrexate	0 (0)	1 (1.5)	1 (2.3)	1 (1.4)
1st subsequent therapy				
Antineoplastic and immunomodulatory drugs[b]	26 (100)	65 (100)	43 (100)	70 (100)
Dasatinib	13 (50.0)	26 (40.0)	16 (37.2)	29 (41.4)
Dasatinib monohydrate	2 (7.7)	4 (6.2)	0 (0)	2 (2.9)
Imatinib	3 (11.5)	10 (15.4)	10 (23.3)	10 (14.3)
Nilotinib	3 (11.5)	9 (13.8)	9 (20.9)	7 (10)
Nilotinib hydrochloride monohydrate	0 (0)	0 (0)	3 (7.0)	2 (2.9)
Bosutinib	1 (3.8)	3 (4.6)	3 (7.0)	7 (10)
Ponatinib	2 (7.7)	3 (4.6)	1 (2.3)	2 (2.9)
Flumatinib mesylate	0 (0)	3 (4.6)	0 (0)	0 (0)
Asciminib	0 (0)	2 (3.1)	0 (0)	6 (8.6)
Cytarabine	0 (0)	2 (3.1)	0 (0)	1 (1.4)
Hydroxycarbamide	0 (0)	2 (3.1)	1 (2.3)	1 (1.4)
Peginterferon alfa-2a	0 (0)	0 (0)	0 (0)	2 (2.9)

a. ASC4FIRST: choice of imatinib, nilotinib or dasatinib prior to randomization.
b. The following percentages are based on the number of patients with at least one subsequent therapy, Institute's calculation.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial, TKI: tyrosine kinase inhibitor

In both studies, treatment with the study medication was continued until disease progression, confirmed loss of MMR; according to ELN criteria [17]), intolerance, decision by the investigator, withdrawal of consent, transition to the TFR phase, treatment failure (according to ELN criteria [17]), death or the end of the study. In both studies, the study protocol did not impose any restrictions on subsequent therapies for disease progression.

Overall, 18% of patients in the intervention arm and 40% of patients in the comparator arm of the ASC4FIRST study had discontinued treatment prematurely by the second data cut (22 October 2024). In the ASC4START study, 18% of patients in the intervention arm and 28% of patients in the comparator arm had discontinued treatment prematurely by the second data cut (15 May 2025). In each case, the most common reasons were the occurrence of AEs or inadequate treatment response. 13.2% of patients in the intervention arm and 33.7% of patients in the comparator arm of the ASC4FIRST study had received a subsequent therapy by the second data cut (22 October 2024). In the ASC4START study, 15.1% of patients in the intervention arm and 24.6% of patients in the comparator arm had received a subsequent therapy by the second data cut (15 May 2025). Consequently, the majority of patients who discontinued treatment prematurely received a subsequent therapy.

As a first subsequent therapy, the majority of patients received another TKI, whilst a small proportion also received chemotherapeutic agents. In both studies, and in each of the two study arms, the most commonly used TKI was dasatinib, followed by nilotinib and imatinib respectively. 3.1% of patients in the comparator arm of the ASC4FIRST study and 8.6% of patients in the comparator arm of the ASC4START study received asciminib as their first subsequent therapy (based on the proportion of patients receiving subsequent therapy). When considering any subsequent therapy (beyond the first subsequent therapy), the proportion of patients treated with asciminib rises to 18.5% in ASC4FIRST and to 24.3% in ASC4START (based on the proportion of patients receiving subsequent therapy).

The administration of a further TKI in the second line corresponds to the recommendations of the German Society for Haematology and Medical Oncology (DGHO) [22], with the choice depending on the reason for the treatment switch (resistance, relapse or intolerance). Patients with T315I mutation should preferably be administered asciminib or ponatinib. For patients without (this) mutation, there is a wider range of possible TKIs available (asciminib, bosutinib, dasatinib, nilotinib, ponatinib). In the event of intolerance to the previous treatment, a different TKI (asciminib, bosutinib, dasatinib, imatinib, nilotinib or ponatinib) should be administered following an assessment of cross-intolerance.

Based on the data provided, the use of subsequent therapies in the two studies is considered to be largely in line with treatment recommendations [22,23]. At the time the study was conducted, asciminib as a first subsequent therapy was not an approved treatment option.

Given the small proportion of patients who received asciminib in the second line, this has no consequences for the benefit assessment.

Meta-analytical summary of studies ASC4FIRST and ASC4START

The company summarizes the results of the studies ASC4FIRST and ASC4START in a meta-analysis. It justifies this on the basis of the great similarity between the study protocols, the almost identical inclusion and exclusion criteria and operationalizations of the outcomes, as well as an identical intervention. Differences between the RCTs would particularly exist in the included study centres from different countries and in the deviating treatment options in the control arm. Since the G-BA regards imatinib, dasatinib and nilotinib as equally appropriate comparator therapies in this therapeutic indication, it can be assumed that the three TKIs are comparable with one another and that the nilotinib comparator arm in the ASC4START study is also comparable with the subpopulation of the ASC4FIRST study who received imatinib, nilotinib or dasatinib. Due to the very similar study designs, it can be assumed that the two studies, ASC4FIRST and ASC4START, are sufficiently similar to allow a meta-analysis to be carried out. Accordingly, the company presents a meta-analysis based on IPD, in which patients from the nilotinib arm of the ASC4START study are counted amongst those treated with nilotinib in the ASC4FIRST trial.

The argumentation of the company is adequate. Although in addition to the similarities outlined by the company, there are also differences with regard to extramedullary involvement and prior TKI and non-TKI therapies of the patients included in the two studies (see the patient characteristics in Section I 3.2.1), these differences do not preclude a meta-analytical summary of the two studies. In the overall assessment – in line with the company's approach – the results of the meta-analysis are used for the present benefit assessment.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: asciminib vs. TKI[a]

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
ASC4FIRST	Yes	Yes	No	No	Yes	Yes	Low
ASC4START	Yes	Yes	No	No	Yes	Yes	Low

a. ASC4FIRST study: with a choice of imatinib, nilotinib or dasatinib prior to randomization; ASC4START study: nilotinib

RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor

The risk of bias across outcomes was rated as low for both studies.

Limitations resulting from the open-label study design are described in Section I 3.2.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

According to the company, the RCTs ASC4FIRST and ASC4START are multinational studies. In both studies, more than half of the patients were of white family origin, and a large proportion of the patients were from Europe without Germany (ASC4FIRST: 32.3%; ASC4START: 49.1%) or from Germany (ASC4FIRST: 8.7%; ASC4START: 22.0%). The company further states that the subgroup analyses carried out with regard to the characteristics 'family origin' and 'geographical region' had not revealed any effect modifications relevant to the conclusion. It can therefore be assumed that the results of the studies ASC4FIRST and ASC4START are transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - progression to blast crisis
  - symptoms, recorded using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30) und des EORTC Quality of Life Questionnaire Chronic Myeloid Leukaemia 24 items (QLQ-CML24)
  - health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded using the EORTC QLQ-C30 and the EORTC QLQ-CML24
- Side effects
  - serious AEs (serious adverse events [SAEs])
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs

- PRO-CTCAE
- other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 13 shows for which outcomes data were available in the included studies.

Table 13: Matrix of outcomes – RCT, direct comparison: asciminib vs. TKI[a]

Study	Outcomes											
	Overall survival	Progression to blast crisis	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-CML24)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-CML24)	SAEs	Severe AEs[b]	Discontinuation due to AEs	PRO-CTCAE	Vascular disorders (SOC, severe AEs[b])
ASC4FIRST	Yes	Yes	Yes	No[c]	Yes	Yes	No[c]	Yes	Yes	Yes	No[c]	Yes
ASC4START	Yes	Yes	Yes	No[c]	No[d]	Yes	No[c]	Yes	Yes	Yes	No[c]	Yes

a. ASC4FIRST study: with a choice of imatinib, nilotinib or dasatinib prior to randomization; ASC4START study: nilotinib.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. No suitable data available; see the following text sections for reasons.
d. Outcome not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-CML24: Quality of Life Questionnaire Chronic Myeloid Leukaemia 24 items; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; TKI: tyrosine kinase inhibitor; VAS: visual analogue scale

Notes on outcomes

Progression to blast crisis

In the studies ASC4FIRST and ASC4START, blast crisis was operationalized as the presence of ≥ 30% blasts in the blood or bone marrow aspirate. Alternatively, a blast crisis could be confirmed by biopsy as proof of extramedullary involvement (excluding hepatosplenomegaly). This operationalization was appropriate. Although the diagnosis is based solely on laboratory tests, a blast crisis resembles acute leukaemia, which is associated with, among other things, a worsening of general symptoms, haemorrhages, pyrexia and infections, and which is fatal if

left untreated [24]. The outcome was therefore patient relevant, and so was relevant for the benefit assessment.

Instruments used and analyses on PROs of the categories morbidity and health-related quality of life

The disease-specific additional module EORTC QLQ-CML24

In addition to the EORTC QLQ-C30, the company records outcomes on symptoms and health-related quality of life using the disease-specific additional module EORTC QLQ-CML24 [25,26]. The EORTC QLQ-CML24 is a disease-specific additional module to the EORTC QLQ-C30, which has been developed for patients with CML and is intended for use in conjunction with the EORTC QLQ-C30 core questionnaire. The additional module consists of 24 items, which are rated on a Likert scale from 1 (not at all) to 4 (very much). The EORTC QLQ-CML24 is divided into a total of 6 scales. The symptom burden scale comprises abdominal pain/spasms, dry mouth, skin problems, headaches, muscle/joint pain, hair loss, sweating, digestive disorders/heartburn, drowsiness, swelling, frequent urgency to urinate, eye disorders and muscle spasms. The following scales are used for health-related quality of life: problems with body image, impact on daily life, impact on worries/mood, satisfaction with care/information, and satisfaction with social life. To analyse the scales, the scores for the items in each scale are added together and converted into scores ranging from 0 to 100.

Response criteria

In Module 4A, the company presented responder analyses for the time to first deterioration for the outcomes symptoms (EORTC QLQ-C30 and EORTC QLQ-CML24), health status (EQ-5D VAS) and health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-CML24) using the following response criteria:

- EORTC QLQ-C30: deterioration by ≥ 10 points each (respective scale range 0 to 100)
- EORTC QLQ-CML24: deterioration by ≥ 15 points each (respective scale range 0 to 100)
- EQ-5D VAS: deterioration of ≥ 15 points (scale range 0 to 100)

The response criteria of the EORTC QLQ-C30, the EORTC QLQ-CML24 and the EQ-5D VAS were not prespecified according to the study design. The response criteria used for the analyses for the EORTC QLQ-C30 and the EQ-5D VAS are appropriate and were used for the benefit assessment. Unlike the responder analyses for the EORTC QLQ-C30, the company presented responder analyses for the proportion of patients with a deterioration by ≥ 15 points for the disease-specific additional module EORTC QLQ-CML24. For the benefit assessment procedure, only analyses on the response criterion 10 points are to be presented in the dossier for EORTC QLQ-C30 and the corresponding validated disease-specific additional modules [27]. The company did not present these for the EORTC QLQ-CML24. If a response threshold of 15 points

is considered in comparison with 10 points, this could result in relevant differences in 2 of the 6 scales of the EORTC QLQ-CML24. The analyses of the EORTC QLQ-CML24 presented by the company were therefore not used for this benefit assessment.

High proportion of missing values at the time of randomization

Discrepancy on the time of recording of the baseline values and approach of the company

For the time point of recording of the baseline values for the PROs, there are discrepancies in both studies between the study protocol and the statistical analysis plan (SAP). Whilst, according to the SAP, the baseline value should have been recorded at the time of randomization, the study protocol stipulated that the baseline value should be recorded prior to the first administration of the study medication (it is not clear from the study protocol whether the baseline value could be recorded only on the day of administration of the study medication or up to three days before). For both studies, the company presented additional analyses (referred to by the company as memoranda) showing the frequencies of baseline values at the various survey dates (prior to randomization vs. after randomization vs. after initiation of treatment vs. not available).

Overall, a baseline value for the EORTC QLQ-C30 was recorded in only 56% (ASC4FIRST) and 59% (ASC4START) of the patients, for the EORTC QLQ-CML24 in only 54% (ASC4FIRST) and 56% (ASC4START), and for the EQ-5D-VAS in only 54% (ASC4FIRST) of patients at the time of randomization (as defined in the SAP). Only after randomization, but before the first dose of the study medication was administered, the recordings for the EORTC QLQ-C30 took place in 21% (ASC4FIRST) and 28% (ASC4START) of patients; 20% (ASC4FIRST) and 25% (ASC4START) of patients were assessed using the EORTC QLQ-CML24, and 19% (ASC4FIRST) of patients were assessed using the EQ-5D-VAS (as defined in the study protocol). For the remaining patients, a baseline value was recorded only after the first administration of the study medication, or no baseline value was available. The reasons for baseline values being recorded too late or being missing are set out for these patients. On the basis of this information, the company concluded that the complete absence of baseline values, or baseline values that were only recorded after treatment initiation, is mainly due to administrative reasons.

In order to investigate the impact of missing values and the underlying mechanism, the company also presented further comprehensive analyses (at the date of the first data cut, 28 November 2023) for the ASC4FIRST study. According to the company, the assumption as to whether these data were missing at random (MAR) or missing completely at random (MCAR) should be assessed, and the suitability of the data for an imputation strategy using multiple imputation should be examined.

The company stated that, in the analysis of the ASC4FIRST study, demographic and clinical patient characteristics (age, sex, family origin, country, Eastern Cooperative Oncology Group

Performance Status (ECOG PS), TKI stratum and ELTS risk group) of patients with and without missing baseline values were compared with each other. Furthermore, the mean values of the PROs by baseline were compared for the two patient groups. Moreover, in one analysis, propensity score models were constructed using logistic regressions in order to estimate the probability of missing baseline values and to identify and analyse the differences between the models.

According to the company, a comparison of demographic and clinical patient characteristics reveals differences in terms of family origin, suggesting geographical and location-specific variations. A propensity score model showed that, despite the influence of ethnicity, the probability of missing baseline values was similar within the groups. From the company's perspective, the results suggest that the assumption that the missing baseline values were MAR is likely to be correct. On this basis, the company concluded that statistical methods which make an MAR assumption, such as multiple imputation, would constitute suitable sensitivity analyses.

The company stated that it would present three analyses for all PROs in order to assess the impact of missing values. In the analysis designated by the company as the main analysis, patients without a baseline value at the time of randomization were censored on Day 1. Consequently, the effects observed over time are based solely on patients with a baseline value at the time of randomization. Furthermore, the company presented two sensitivity analyses, one of which uses an expanded definition of the baseline (effects observed over time are based on patients for whom baseline values were recorded prior to the first administration of the study medication; patients without an extended baseline value were censored on Day 1), and one using multiple imputation for patients without a baseline value at the time of randomisation, using data from patients with a baseline value at randomization. To derive the added benefit, the company primarily used the main analysis and also considers the two sensitivity analyses in order to assess the robustness of the results.

Assessment of the company's approach

For the reasons set out above, the main analysis of PROs presented by the company considered only a total of 54% to 59% of the randomized patients. As a general rule, analyses that include less than 70% of the patients enrolled are not suitable for the benefit assessment.

However, as described above, the company presented comprehensive analyses on the missing baseline values at the time of randomization for the ASC4FIRST study. A comparison of patient characteristics between patients with and without baseline values at the time of randomization yielded comparable values for sex, age, ECOG PS and ELTS risk group. However, differences are shown in the characteristic family origin (see I Appendix E). For instance, the majority of patients without a baseline value at the time of randomization were of white

family origin (79%). The analyses presented also show that the countries with the highest numbers of patients with missing baseline values were Germany (N = 34), Canada (N = 21), France (N = 17), the USA (N = 16) and Italy (N = 13). By contrast, most Asian countries had a small proportion of patients without a baseline value at randomization.

A comparison of the mean values for PROs at baseline, Week 4 and Week 48 showed that, for selected domains of the EORTC QLQ-C30, the group without a baseline value had comparable or, in isolated cases, slightly lower scores at all time points compared with those with a baseline value; however, no consistent pattern was observed. In addition, the analyses presented examined how a replacement using multiple imputation and mean imputation affects the change from baseline in a mixed model. The results here tend to be similar.

Moreover, two propensity score models were constructed in order to estimate the probability of missing baseline values and to analyse the differences between the models. One model included age, sex, ECOG PS, TKI stratum, ELTS score (IRT) and family origin as variables. The second model considers the same variables, excluding the variable family origin. Information on the selection process for the considered variables is not available. It remains unclear whether the models actually include all the variables that might have an influence and are therefore complete. In the model in which ethnicity was included as a variable, the scores differ significantly between the groups (white vs. non-white). The average score for non-white patients was 0.20 where a baseline value was missing and 0.21 where a baseline value was available; for white patients, it was 0.62 where a baseline value was missing and 0.65 where a baseline value was available. In the model without the factor family origin, a clear difference in the scores was no longer observed (non-white: 0.41 and 0.44 respectively; white: 0.45 and 0.46 respectively). This suggests a link between the characteristic family origin and the likelihood of having a missing baseline value.

In principle, it is not possible to verify or demonstrate the mechanism underlying missing values. It is only possible to make assumptions based on the study design, the course of the study and the study data in order to arrive at an assessment. Given the present data situation and taking into account the analyses conducted by the company for the ASC4FIRST study, it seems reasonable to assume that the missing baseline values for the PROs are MAR. However, the company did not present these extended analyses for the ASC4START study, meaning that there is greater uncertainty regarding the MAR assumption. Overall, however, the data can be used for the benefit assessment under certain conditions:

Analogous to the company’s approach, the results of the analysis designated by the company as the main analysis (patients without a baseline value at the time of randomization were censored on Day 1) were primarily used. However, an added benefit can only be derived if there is a statistically significant effect of at least a minor extent in both the main analysis and the two sensitivity analyses (for the results of the sensitivity analyses, see I Appendix D).

Moreover, the extent of the added benefit in an outcome can only be quantified if the extent of the effects is identical across all three analyses.

Note on the outcome on the Functional Assessment of Cancer Therapy-General Item 5 (FACT-GP5) submitted by the company in Module 4 A

In Module 4A, the company presents analyses for the outcome patient-reported limitations due to AEs in accordance with the FACT-GP5, based on the survey of a single item of the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire (Item GP5: 'I am bothered by side effects of treatment'). However, recording data on the burden of side effects of therapy via this single item is not meaningful in terms of content. For individual patients, it is often impossible to distinguish whether the stress in a particular case is due to side effects of the treatment or to another cause, such as the symptoms of the underlying disease. For this reason, it is not possible to uniformly record the burden of side effects of the therapy. Therefore, the analyses presented by the company based on the individual question regarding the burden of side effects of the therapy were not suitable for the benefit assessment.

Notes on the outcomes in the side effects category

PRO-CTCAE

In the studies ASC4FIRST and ASC4START, side effects were also recorded with the PRO-CTCAE instrument. Overall, the PRO-CTCAE system is a valuable supplement to the usual survey and analysis of AEs. The system comprises a total of 78 symptomatic AEs of the CTCAE system, which are compiled into a questionnaire adapted to the respective study situation. The selection process for a survey should be planned a priori and carried out transparently. The selection of the individual symptomatic AEs must be transparent, e.g. the recording of all important potential AEs of the drugs in the intervention and the comparator arm. For a comprehensive description of the PRO-CTCAE system, see the corresponding explanations in benefit assessment A20-87 [28].

The study documents for ASC4FIRST and ASC4START, as well as Module 4A, point out that there is no official method regarding the choice of symptomatic AEs. In the studies, the company chose symptomatic AEs on the basis of three criteria:

1) symptomatic AEs, which, according to the marketing authorizations, may occur in at least 3 of the 4 TKIs in the comparator arm (ASC4FIRST) or under nilotinib (ASC4START)
2) Symptomatic AEs that may occur under treatment with asciminib according to the investigator's information
3) Symptomatic AEs of interest

According to the study documents, the following symptomatic AEs of the PRO-CTCAE system were recorded in ASC4FIRST:

- Fatigue
- Headache
- Rash
- Diarrhoea
- Vomiting
- Nausea
- Oedema
- Muscle pain
- Itching

In the ASC4START study, the following AEs were also recorded in addition to the symptomatic AEs recorded in the ASC4FIRST study:

- Cough
- Increased sweating

The company's approach is not suitable for ensuring that the side effects of asciminib, imatinib, nilotinib, dasatinib and bosutinib are documented with sufficient reliability. Approaches to selecting the items adequately are described by Tolstrup [29] or Taarnhøj [30] (see also A20-87 [28]). Furthermore, it is not comprehensible why the ASC4START study was the only one to additionally record the symptomatic AEs cough and increased sweating.

Overall, the outcome PRO-CTCAE is not used for the benefit assessment due to the points outlined above.

Recording of the progression of the underlying disease

According to the study documents and the information provided by the company in Module 4 A, progression of the underlying disease was not recorded as an SAE. According to the company, no additional presentation of AEs cleansed for progression events was therefore provided. However, the outcomes severe AEs and discontinuations due to AEs include events such as the preferred terms (PTs) anaemia, neutropenia and thrombocytopenia, which may be either side effects or may reflect the progression of the underlying disease (see I Appendix B.4). It cannot be conclusively clarified to what extent the events can be assigned to the outcome category of morbidity or side effects. Furthermore, for the outcome discontinuation due to AEs, the analyses of the ASC4START study report one patient in the intervention arm having a blast crisis. As these events occurred with similar frequency in both arms in the meta-analysis, it is not assumed that there is any relevant bias in the results for the outcomes in the side effects category.

Types of analysis

In the assessment of side effects, the number of patients in whom an event occurred is primarily relevant. However, when considering the time to event, effects may also result from an earlier or later occurrence of the event rather than on the basis of the proportions. Time-to-event analyses are of particular relevance in group comparisons with different mean observation periods because this approach takes the different observation periods in the analyses into account [31]. In Module 4A, the company presented time-to-event analyses for all outcomes of the side effects category. In the present situation, however, the median and mean observation periods between the two study arms are sufficiently comparable within the studies ASC4FIRST and ASC4START (see Table 10). For this reason, this assessment uses the relative risk as effect measure to derive the added benefit.

I 3.2.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: asciminib vs. TKI

Study		Outcomes											
	Study level	Overall survival	Progression to blast crisis	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-CML24)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-CML24)	SAEs	Severe AEs[b]	Discontinuation due to AEs	PRO-CTCAE	Vascular disorders (SOC, severe AEs[b])
ASC4FIRST	L	L	L	H[c]	–[d]	H[c]	H[c]	–[d]	L	L	H[e]	–[d]	L
ASC4START	L	L	L	H[c]	–[d]	–[f]	H[c]	–[d]	L	L	H[e]	–[d]	L

a. ASC4FIRST study: with a choice of imatinib, nilotinib or dasatinib prior to randomization; ASC4START study: nilotinib.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Large proportion of patients not considered in the analysis (> 10%); decrease in the return of questionnaires in the course of the study, and lack of blinding in subjective recording of outcomes.
d. No suitable data available; see Section I 3.2.1 for the reasoning.
e. Lack of blinding in subjective decision for discontinuation.
f. Outcome not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PRO-CTCAE: PROs version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-CML24: Quality of Life Questionnaire Chronic Myeloid Leukaemia 24 items; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; TKI: tyrosine kinase inhibitor; VAS: visual analogue scale

For the results on the outcomes overall survival, progression to blast crisis, SAEs, severe AEs and vascular diseases (serious AE), the ASC4FIRST and ASC4START studies each have a low risk of bias.

There is a high risk of bias in each of the results on the outcomes symptoms and health-related quality of life, recorded using the EORTC QLQ-C30 in the studies ASC4FIRST and ASC4START, as well as in the results on the outcome health status, recorded using the EQ-5D VAS in the ASC4FIRST study. On the one hand, this is due to the lack of blinding in subjective recording of outcomes and, on the other hand, to a high proportion of patients not considered in the analysis, as well as a decline in the response rate to the questionnaires over the course of the study. In principle, the proportion of patients considered (approximately 54% to 59%) would be too small to allow the results to be used. However, the company also presented comprehensive analyses to examine the mechanism and the impact of the missing baseline values, as well as sensitivity analyses, particularly for ASC4FIRST. These make it possible to assess the direction and strength of bias of an effect to such an extent that an added benefit can still be derived under certain conditions (see Section I 3.2.1). Furthermore, in addition to the low proportion of patients for whom baseline values were recorded, the varying response rates over the course of the study further limit the certainty of conclusions of the analyses (see Module 4 A). Thus, there are differentiated differences in response rates between the study arms as early as Week 24. The response rates for the EORTC QLQ-C30 were 70% vs. 57% (ASC4FIRST) and 74% vs. 67% (ASC4START), for the EORTC QLQ-CML24 69% versus 57% (ASC4FIRST) and 74% versus 66% (ASC4START), and for the EQ-5D VAS 69% versus 55% (ASC4FIRST).

The results on the outcome discontinuation due to AEs are subject to a high risk of bias due to the lack of blinding in the case of a subjective decision on treatment discontinuation.

No suitable data are available for the outcomes symptoms and health-related quality of life, recorded with the EORTC QLQ-CML24 in ASC4FIRST and ASC4START, nor for the outcome PRO-CTCAE; therefore, the risk bias was not assessed for these outcomes.

Summary assessment of the certainty of conclusions

Based on the results of the meta-analysis with two studies, at most proof, e.g. of an added benefit can be derived each with a high certainty of conclusions for the outcomes overall survival, progression to blast crisis, SAEs, severe AEs and vascular events (severe AEs).

The numerous uncertainties in the present data situation do not allow an upgrade of the certainty of conclusions for the results on PROs despite the reproduction of the results. Therefore, at most hints, e.g. of an added benefit, can be derived for the results on these outcomes despite the existence of a meta-analysis.

Due to the high risk of bias in the results, at most indications, e.g. of an added benefit based can be derived for the results on the outcome discontinuation due to AEs on the basis of the meta-analysis.

I 3.2.3 Results

Table 15 and Table 16 summarize the results of the comparison of asciminib versus the ACT for first-line treatment of adults with Ph^+ CML-CP. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves for all outcomes are shown in I Appendix B, and the forest plots for the meta-analyses calculated by the Institute for the outcomes in the side effects category are presented in I Appendix C. A comparison of the results of the main and sensitivity analyses for the outcomes on symptoms and health-related quality of life can be found in I Appendix D. Common AEs that occurred in ASC4FIRST and ASC4START are listed in I Appendix F.

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: asciminib versus TKI[a] (multipage table)

Outcome category outcome study	Asciminib N[b] median time to event in months [95% CI] patients with event n (%)	TKI[a] N[b] median time to event in months [95% CI] patients with event n (%)	Asciminib vs. TKI[a] HR [95% CI]; p-value[c]
Mortality			
Overall survival			
ASC4FIRST	197 NA 2 (1.0)	193 NA 4 (2.1)	0.48 [0.09; 2.65]; 0.393
ASC4START	284 NA 2 (0.7)	284 NA 1 (0.4)	1.98 [0.18; 21.89]; 0.568
Total			0.78 [0.21; 2.91]; 0.713[d]
Morbidity			
Progression to blast crisis			
ASC4FIRST	197 NA 1 (0.5)	193 NA 2 (1.0)	0.43 [0.04; 4.83]; 0.485
ASC4START	284 NA 3 (1.1)	284 NA 0 (0)	6.99 [0.23; 214.0]; 0.083
Total			1.87 [0.34; 10.28]; 0.462[d]
Symptoms (EORTC QLQ-C30 – time to first deterioration[e])			
Fatigue			
ASC4FIRST	197 22.1 [5.5; NC] 50 (25.4)	193 2.8 [1.8; 11.1] 62 (32.1)	0.62 [0.42; 0.91]; 0.009
ASC4START	284 NA [11.2; NC] 50 (17.6)	284 22.1 [11.8; NC] 58 (20.4)	0.74 [0.51; 1.09]; 0.214
Total			0.68 [0.52; 0.90]; 0.007[d]
Nausea and vomiting			
ASC4FIRST	197 NA 23 (11.7)	193 22.1 [11.0; NC] 42 (21.8)	0.42 [0.25; 0.71]; < 0.001
ASC4START	284 22.1 [22.1; NC] 39 (13.7)	284 NA [22.0; NC] 47 (16.5)	0.75 [0.49; 1.16]; 0.176
Total			0.59 [0.43; 0.82]; 0.001[d]
Pain			
ASC4FIRST	197 NA 37 (18.8)	193 5.6 [1.9; NC] 55 (28.5)	0.51 [0.33; 0.78]; < 0.001
ASC4START	284 11.1 [5.6; NC] 76 (26.8)	284 11.1 [2.8; NC] 79 (27.8)	0.90 [0.66; 1.23]; 0.453
Total		Heterogeneity:	p-value = 0.040

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: asciminib versus TKI[a] (multipage table)

Outcome category outcome study	Asciminib N[b]	Asciminib median time to event in months [95% CI] patients with event n (%)	TKI[a] N[b]	TKI[a] median time to event in months [95% CI] patients with event n (%)	Asciminib vs. TKI[a] HR [95% CI]; p-value[c]
Dyspnoea					
ASC4FIRST	197	22.2 [22.2; NC] 25 (12.7)	193	NA [22.1; NC] 36 (18.7)	0.55 [0.32; 0.94]; 0.019
ASC4START	284	22.1 [22.1; NC] 45 (15.8)	284	NA [11.8; NC] 50 (17.6)	0.86 [0.57; 1.29]; 0.524
Total					0.73 [0.53; 1.00]; 0.052[d]
Insomnia					
ASC4FIRST	197	NA 32 (16.2)	193	NA [11.1; NC] 40 (20.7)	0.61 [0.38; 0.97]; 0.073
ASC4START	284	22.1 [11.1; NC] 55 (19.4)	284	22.0 [11.1; NC] 64 (22.5)	0.74 [0.52; 1.07]; 0.122
Total					0.69 [0.52; 0.92]; 0.020[d]
Appetite loss					
ASC4FIRST	197	NA [22.2; NC] 19 (9.6)	193	NA [22.1; NC] 33 (17.1)	0.40 [0.22; 0.71]; 0.002
ASC4START	284	22.1 [22.1; NC] 31 (10.9)	284	NA [22.1; NC] 39 (13.7)	0.78 [0.48; 1.25]; 0.229
Total					0.59 [0.41; 0.85]; 0.004[d]
Constipation					
ASC4FIRST	197	NA 36 (18.3)	193	NA [11.1; NC] 35 (18.1)	0.80 [0.49; 1.29]; 0.496
ASC4START	284	22.1 [11.3; NC] 44 (15.5)	284	NA [11.1; NC] 60 (21.1)	0.63 [0.42; 0.93]; 0.026
Total					0.69 [0.51; 0.93]; 0.031[d]
Diarrhoea					
ASC4FIRST	197	NA 29 (14.7)	193	22.0 [6.7; NC] 45 (23.3)	0.49 [0.30; 0.79]; 0.004
ASC4START	284	NA [22.0; NC] 39 (13.7)	284	NA [22.2; NC] 53 (18.7)	0.72 [0.48; 1.09]; 0.055
Total					0.60 [0.44; 0.83]; < 0.001[d]
Symptoms (EORTC QLQ-CML24)	No suitable data[f]				

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: asciminib versus TKI[a] (multipage table)

Outcome category outcome study	Asciminib N[b]	Asciminib median time to event in months [95% CI] patients with event n (%)	TKI[a] N[b]	TKI[a] median time to event in months [95% CI] patients with event n (%)	Asciminib vs. TKI[a] HR [95% CI]; p-value[c]
Health status (EQ-5D VAS – time to first deterioration[g])					
ASC4FIRST	197	NA [22.2; NC] 20 (10.2)	193	NA [22.1; NC] 32 (16.6)	0.49 [0.28; 0.86]; 0.011
ASC4START			Outcome not recorded		
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration[h]					
Global health status					
ASC4FIRST	197	22.2 [22.0; NC] 39 (19.8)	193	22.0 [5.4; NC] 49 (25.4)	0.70 [0.45; 1.09]; 0.052
ASC4START	284	22.1 [11.1; NC] 59 (20.8)	284	NA [11.1; NC] 63 (22.2)	0.89 [0.62; 1.27]; 0.529
Total					0.81 [0.61; 1.06]; 0.085[d]
Physical functioning					
ASC4FIRST	197	NA 25 (12.7)	193	22.1 [22.1; NC] 37 (19.2)	0.54 [0.32; 0.91]; 0.020
ASC4START	284	NA [11.2; NC] 49 (17.3)	284	NA 50 (17.6)	0.91 [0.61; 1.35]; 0.616
Total					0.75 [0.55; 1.02]; 0.069[d]
Role functioning					
ASC4FIRST	197	NA [22.2; NC] 34 (17.3)	193	NA [6.7; NC] 41 (21.2)	0.58 [0.36; 0.93]; 0.025
ASC4START	284	22.1 [11.1; NC] 64 (22.5)	284	22.1 [11.1; NC] 59 (20.8)	1.08 [0.76; 1.55]; 0.587
Total				Heterogeneity:	p-value = 0.037
Emotional functioning					
ASC4FIRST	197	NA 29 (14.7)	193	NA [22.1; NC] 37 (19.2)	0.68 [0.42; 1.12]; 0.128
ASC4START	284	NA [11.2; NC] 47 (16.5)	284	NA [11.1; NC] 59 (20.8)	0.65 [0.44; 0.96]; 0.120
Total					0.68 [0.50; 0.92]; 0.031[d]

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: asciminib versus TKI[a] (multipage table)

Outcome category outcome study	Asciminib N[b]	Asciminib median time to event in months [95% CI] patients with event n (%)	TKI[a] N[b]	TKI[a] median time to event in months [95% CI] patients with event n (%)	Asciminib vs. TKI[a] HR [95% CI]; p-value[c]
Cognitive functioning					
ASC4FIRST	197	NA [22.1; NC] 40 (20.3)	193	11.1 [10.9; 22.1] 50 (25.9)	0.73 [0.47; 1.12]; 0.134
ASC4START	284	11.1 [11.0; 22.1] 75 (26.4)	284	11.1 [5.6; NC] 77 (27.1)	0.92 [0.67; 1.26]; 0.626
Total					0.85 [0.65; 1.09]; 0.196[d]
Social functioning					
ASC4FIRST	197	NA 34 (17.3)	193	22.1 [5.4; NC] 46 (23.8)	0.65 [0.41; 1.01]; 0.043
ASC4START	284	22.1 [11.2; NC] 58 (20.4)	284	NA [11.0; NC] 64 (22.5)	0.76 [0.53; 1.09]; 0.203
Total					0.72 [0.54; 0.95]; 0.024[d]
EORTC QLQ-CML24	No suitable data[f]				

a. ASC4FIRST study: with a choice of imatinib, nilotinib or dasatinib prior to randomization; ASC4START study: nilotinib.
b. For the patient-reported outcomes: main analysis, in which patients without a baseline value upon randomization were censored on Day 1. In ASC4FIRST, 109 (55.3%) in the intervention arm vs. 108 (56.0%) in the control arm (for the EORTC QLQ-C30), and 105 (53.3%) in the intervention arm vs. 102 (52.8%) in the control arm (for the EQ-5D VAS) had a baseline value at randomization. In ASC4START, 168 (59.2%) in the intervention versus 165 (58.1%) in the control arm (for the EORTC QLQ-C30) had a baseline value at randomization.
c. ASC4FIRST: HR and 95% CI values from a stratified Cox proportional hazards model with stratification factors comprising the ELTS score (IRT) and the TKI selected prior to randomization (IRT), as well as the covariate treatment arm; p-value from a stratified log-rank test with factors ELTS score (IRT) and TKI selected prior to randomization (IRT). ASC4START: HR and 95% CI values from stratified Cox proportional hazards model with the stratification factor ELTS score (IRT) and the covariate treatment arm; p-value from stratified log-rank test with the factor ELTS score (IRT). The Firth correction was applied in the proportional hazards model where necessary due to extreme values of the hazard ratio when there were few or no events.
d. Calculated from a meta-analysis: HR and 95% CI values from stratified Cox proportional hazards model with stratification factors comprising ELTS score (IRT), TKI selected prior to randomization (IRT) and study, as well as the covariates treatment arm and baseline score; p-value from stratified log-rank test with stratification factors comprising ELTS score (IRT), TKI selected prior to randomization (IRT) and study
e. A score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100).
f. See Section I 3.2.1 of this dossier assessment for the reasoning.
g. A score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
h. A score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).

Table 15: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: asciminib versus TKI[a] (multipage table)

Outcome category outcome study	Asciminib		TKI[a]		Asciminib vs. TKI[a]
	N[b]	median time to event in months [95% CI] patients with event n (%)	N[b]	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[c]

CI: Confidence Interval; ELTS: European Treatment and Outcome Study Long-Term Survival; EORTC: European Organisation for Research and Treatment of Cancer; HR: Hazard Ratio; IRT: interactive response technology; N: number of analysed patients; n: Number of patients with (at least one) event; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-CML24: Quality of Life Questionnaire Chronic Myeloid Leukaemia (24 items); RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor; VAS: visual analogue scale

Table 16: Results (side effects) – RCT, direct comparison: asciminib vs. TKI[a]

Outcome category outcome study	Asciminib N	Asciminib patients with event n (%)	TKI[a] N	TKI[a] patients with event n (%)	Asciminib vs. TKI[a] RR [95% CI]; p-value[b]
Side effects					
AEs (supplementary information)					
ASC4FIRST	196	187 (95.4)	190	186 (97.9)	–
ASC4START	284	249 (87.7)	282	257 (91.1)	–
SAEs					
ASC4FIRST	196	29 (14.8)	190	35 (18.4)	0.80 [0.51; 1.26]; 0.530
ASC4START	284	47 (16.5)	282	42 (14.9)	1.11 [0.76; 1.63]; 0.683
Total[c]					0.97 [0.73; 1.30]; 0.839
Severe AEs[d]					
ASC4FIRST	196	87 (44.4)	190	101 (53.2)	0.84 [0.68; 1.03]; 0.088
ASC4START	284	102 (35.9)	282	114 (40.4)	0.89 [0.72; 1.10]; 0.289
Total[c]					0.86 [0.74; 1.00]; 0.051
Discontinuation due to AEs					
ASC4FIRST	196	10 (5.1)	190	25 (13.2)	0.39 [0.19; 0.79]; 0.006
ASC4START	284	23 (8.1)	282	44 (15.6)	0.52 [0.32; 0.70]; 0.006
Total[c]					0.47 [0.32; 0.70]; < 0.001
PRO-CTCAE	No suitable data[e]				
Vascular disorders (SOC, severe AEs[d])					
ASC4FIRST	196	13 (6.6)	190	7 (3.7)	1.80 [0.73; 4.41]; 0.247
ASC4START	284	17 (6.0)	282	6 (2.1)	2.81 [1.13; 7.03]; 0.021
Total[c]					2.26 [1.20; 4.29]; 0.012

a. ASC4FIRST study: with a choice of imatinib, nilotinib or dasatinib prior to randomization; ASC4START study: nilotinib.
b. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [32]).
c. Institute's calculation, meta-analysis with fixed effect according to Mantel and Haenszel.
d. Operationalized as CTCAE grade ≥ 3.
e. See Section I 3.2.1 of this dossier assessment for the reasoning.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TKI: tyrosine kinase inhibitor

For the outcomes overall survival, progression to blast crisis, SAEs, severe AEs and vascular disorders in the side effects category, at most proof can be derived on the basis of the

available information; the high risk of bias allows at most indications to be derived for the outcome discontinuation due to AEs; and at most hints, e.g. of an added benefit, can be determined for the outcomes symptoms, health status and outcomes in the category health-related quality of life (see also Sections I 3.2.1 and I 3.2.2).

Mortality

Overall survival

For the outcome overall survival, the meta-analysis of the studies ASC4FIRST and ASCA4START does not show any statistically significant difference between the treatment arms. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Morbidity

Progression to blast crisis

For the outcome progression to blast crisis, the meta-analysis of the studies ASC4FIRST and ASCA4START does not show any statistically significant difference between the treatment arms. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Symptoms

The added benefit is derived on the basis of the main analysis, taking into account the sensitivity analyses presented by the company (see Section I 3.2.1).

EORTC QLQ-C30

Fatigue, insomnia and constipation

For the outcomes fatigue, insomnia and constipation, recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START showed a statistically significant difference in favour of asciminib in the main analyses. However, the extent of the effect is no more than minor for each of these outcomes (see Table 20 of the full dossier assesment). There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Nausea and vomiting

For the outcome nausea and vomiting, recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START showed a statistically significant difference in favour of asciminib in the main analyses and both sensitivity analyses (see Table 20 of the full dossier assesment). This results in a hint of added benefit of asciminib in comparison with the ACT.

Pain

For the outcome pain, recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START shows heterogeneous study results with no conclusive effects, as early as in the primary analysis. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Dyspnoea

For the outcome dyspnoea, recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START showed no statistically significant difference between the treatment arms even in the main analyses. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Appetite loss and diarrhoea

For the outcomes appetite loss and diarrhoea, recorded using the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START shows a statistically significant difference in favour of asciminib in the main analysis for each outcome; however, in at least one of the sensitivity analyses presented by the company, there is either no statistically significant difference between the treatment arms or the study results are heterogeneous without conclusive effects (see Table 20 of the full dossier assesment). There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-CML24)

No suitable data are available for the outcome symptoms, recorded using the EORTC QLQ-CML24. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

The outcome health status was only recorded in the ASC4FIRST study.

The main analysis showed a statistically significant difference in favour of asciminib for the outcome health status, recorded using the EQ-5D VA; however, the sensitivity analysis with multiple imputation for patients without a baseline value at the time of randomization presented by the company showed no statistically significant difference (see Table 21 of the full dossier assesment). There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Health-related quality of life

The added benefit is derived on the basis of the main analysis, taking into account the sensitivity analyses presented by the company (see Section I 3.2.1).

EORTC QLQ-C30

Global health status, physical functioning, role functioning and cognitive functioning

For the outcomes global health status, physical functioning, role functioning and cognitive functioning, recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START shows, even in the main analysis, that there is no statistically significant difference between the treatment arms in each case, or that there are no conclusive effects given the heterogeneous study results. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Emotional Functioning

For the outcome emotional functioning, recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START showed a statistically significant difference in favour of asciminib in the main analysis; however, this difference was not observed in the sensitivity analysis with multiple imputation for patients without a baseline value at the time of randomization presented by company (see Table 20 of the full dossier assesment). There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Social functioning

For the outcome social functioning recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START showed a statistically significant difference in favour of asciminib in the main analyses and both sensitivity analyses (see Table 20 of the full dossier assesment). This results in a hint of added benefit of asciminib in comparison with the ACT.

EORTC QLQ-CML24

No suitable data were available for the outcomes on health-related quality of life, recorded with the EORTC QLQ-CML24. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome SAEs, the meta-analysis of the studies ASC4FIRST and ASCA4START does not show any statistically significant difference between the treatment arms. There was no hint of greater or lesser harm from asciminib in comparison with the ACT; greater or lesser harm is therefore not proven.

Severe AEs

For the outcome severe AEs, the meta-analysis of the studies ASC4FIRST and ASCA4START does not show any statistically significant difference between the treatment arms. There was

no hint of greater or lesser harm from asciminib in comparison with the ACT; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome discontinuation due to AEs, the meta-analysis of the studies ASC4FIRST and ASC4START showed a statistically significant difference in favour of asciminib. There is an indication of lesser harm from asciminib in comparison with the ACT.

PRO-CTCAE

No suitable data are available for the outcome PRO-CTCAE. There was no hint of greater or lesser harm from asciminib in comparison with the ACT; greater or lesser harm is therefore not proven.

Vascular disorders (severe AEs)

For the outcome vascular disorders (severe AEs), the meta-analysis of the studies ASC4FIRST and ASC4START showed a statistically significant difference to the disadvantage of asciminib. There is proof of greater harm from asciminib in comparison with the ACT.

I 3.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for this assessment:

- age (≥ 18 years to < 65 years versus ≥ 65 to < 75 years versus ≥ 75 years)
- Sex (female versus male)
- ELTS score according to IRT (low vs. medium vs. high)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup. Furthermore, results for PROs are only presented if the effect modification is statistically significant in the sensitivity analyses and if the statistically significant and relevant effects in at least one subgroup have been confirmed by both sensitivity analyses.

Based on the described methods, no relevant effect modification by the characteristics age, sex or ELTS score according to IRT was identified for the outcomes for which suitable data are available.

I 3.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1,31].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section I 3.2 (see Table 17).

Determination of the outcome category for outcomes on symptoms and side effects

The dossier does not provide any details as to whether the following outcomes on symptoms and on side effects were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms – EORTC QLQ-C30 (fatigue, nausea and vomiting, insomnia and constipation)

For the outcomes fatigue, nausea and vomiting, insomnia and constipation, insufficient information is available to classify the severity category as serious/severe. These outcomes were therefore each assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Discontinuation due to AEs

In Module 4 A, the company additionally presents analyses on discontinuation due to severe AEs (CTCAE grade ≥ 3) for the outcome discontinuation due to AEs. These analyses show that the majority of the AEs that occurred and led to discontinuation of treatment were severe AEs. Thus, in the meta-analysis of the studies ASC4FIRST and ASC4START, the proportion of severe AEs leading to discontinuation of treatment was 64%. The outcome discontinuation due to AEs was therefore assigned to the outcome category serious/severe side effects.

Table 17: Extent of added benefit at outcome level: asciminib vs. TKI[a] (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Asciminib vs. TKI[a]** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	Median: NA vs. NA HR: 0.78 [0.21; 2.91]; p = 0.713	Lesser benefit not proven/added benefit not proven
Morbidity		
Progression to blast crisis	Median: NA vs. NA HR: 1.87 [0.34; 10.28]; p = 0.462	Lesser benefit not proven/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30 – time to first deterioration)[d]		
Fatigue	Median: 22.1 or NA vs. 2.8–22.1 HR: 0.68 [0.52; 0.90]; p = 0.007	Outcome category: non-serious/non-severe symptoms/late complications lesser benefit not proven/added benefit not proven[e]
Nausea and vomiting	Median: NA or 22.1 vs. 22.1 or NA HR: 0.59 [0.43; 0.82]; p = 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: “minor”
Pain	Heterogeneous results[f]	Lesser benefit not proven/added benefit not proven
Dyspnoea	Median: 22.1-22.2 vs. NA HR: 0.73 [0.53; 1.00]; p = 0.052	Lesser benefit not proven/added benefit not proven
Insomnia	Median: NA or 22.1 vs. NA or 22.0 HR: 0.69 [0.52; 0.92]; p = 0.020	Outcome category: non-serious/non-severe symptoms/late complications lesser benefit not proven/added benefit not proven[e]
Appetite loss	Median: NA or 22.1 vs. NA HR: 0.59 [0.41; 0.85]; p = 0.004	Lesser benefit not proven/added benefit not proven[g]
Constipation	Median: NA or 22.1 vs. NA HR: 0.69 [0.51; 0.93]; p = 0.031	Outcome category: non-serious/non-severe symptoms/late complications lesser benefit not proven/added benefit not proven[e]
Diarrhoea	Median: NA vs 22.0 or NA HR: 0.60 [0.44; 0.83]; p < 0.001	Lesser benefit not proven/added benefit not proven[g]
Symptoms (EORTC QLQ-CML24)	No suitable data	

Table 17: Extent of added benefit at outcome level: asciminib vs. TKI[a] (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Asciminib vs. TKI[a]** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Health status (EQ-5D VAS – time to first deterioration)[b]	Median: NA vs. NA HR: 0.49 [0.28; 0.86]; p = 0.011	Lesser benefit not proven/added benefit not proven[g]
Health-related quality of life		
EORTC QLQ-C30 – time to 1st deterioration		
Global health status	Median: 22.1-22.2 vs 22.0 or NA HR: 0.81 [0.61; 1.06]; p = 0.085	Lesser benefit not proven/added benefit not proven
Physical functioning	Median: NA vs 22.1 or NA HR: 0.75 [0.55; 1.02]; p = 0.069	Lesser benefit not proven/added benefit not proven
Role functioning	Heterogeneous results[f]	Lesser benefit not proven/added benefit not proven
Emotional functioning	Median: NA vs. NA HR: 0.68 [0.50; 0.92]; p = 0.031	Lesser benefit not proven/added benefit not proven[g]
Cognitive functioning	Median: NA or 11.1 vs. 11.1 HR: 0.85 [0.65; 1.09]; p = 0.196	Lesser benefit not proven/added benefit not proven
Social functioning	Median: NA or 22.1 vs. 22.1 or NA HR: 0.72 [0.54; 0.95]; 0.024 probability: hint	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"[i]
EORTC QLQ-CML24	No suitable data	
Side effects		
SAEs	14.8 %–16.5 % vs. 18.4 %–14.9 % RR: 0.97 [0.73; 1.30]; p = 0.839	Greater/lesser harm not proven
Severe AEs	35.9 %–44.4 % vs. 40.4 %–53.2 % RR: 0.86 [0.74; 1.00]; p = 0.051	Greater/lesser harm not proven
Discontinuation due to AEs	5.1 %–8.1 % vs. 13.2 %–15.6 % RR: 0.47 [0.32; 0.70]; p < 0.001 probability: indication	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: major
PRO-CTCAE	No suitable data	
Vascular disorders (severe AEs)	6.0 %–6.6 % vs. 2.1 %–3.7 % RR: 2.26 [1.20; 4.29]; RR: 0.44 [0.23; 0.83][j] p = 0.012 probability: "proof"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.9$ greater harm, extent: considerable

Table 17: Extent of added benefit at outcome level: asciminib vs. TKI[a] (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Asciminib vs. TKI[a]** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
a. ASC4FIRST study: with a choice of imatinib, nilotinib or dasatinib prior to randomization; ASC4START study: nilotinib. b. Information on the probability, provided there are statistically significant differences in both the main analysis and both sensitivity analyses. c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u). d. Main analysis: patients without a baseline value at the time of randomization were censored on Day 1. e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. f. No common effect estimation and no conclusive effects can be provided due to heterogeneous data. g. At least one sensitivity analysis shows no statistically significant difference between the treatment arms or no conclusive effects in the heterogeneous study results (see I Appendix D). h. Recorded only in the ASC4FIRST study. i. Quantification is not possible, as the extent varies between the main analysis and the sensitivity analyses (see Table 20 of the full dossier assesment). j. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QQLQ-CML24: Quality of Life Questionnaire Chronic Myeloid Leukaemia (24 items); RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TKI: tyrosine kinase inhibitor; VAS: visual analogue scale		

I 3.3.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 18: Positive and negative effects from the assessment of asciminib in comparison with the ACT

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
–	–
Outcomes with shortened observation period	
Morbidity non-serious/non-severe symptoms/late complications ▪ nausea and vomiting: hint of an added benefit – extent: "minor"	–
Health-related quality of life ▪ social functioning: hint of added benefit – extent: “non quantifiable”	–
Serious/severe side effects ▪ discontinuation due to AEs: indication of lesser harm – extent: "major"	Serious/severe side effects ▪ vascular disorders (severe AEs): proof of greater harm – extent "considerable"
No suitable data were available for the outcomes on symptoms and health-related quality of life, recorded with the EORTC QLQ-CML24 and for the outcomes on PRO-CTCAE.	
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Event; QLQ-CML24: Quality of Life Questionnaire Chronic Myeloid Leukaemia (24 items)	

Overall, mostly positive and one negative effects of asciminib were shown in comparison with the ACT.

On the positive side, there is a hint of added benefit with minor extent for nausea and vomiting in the morbidity category, and in the category health-related quality of life a hint of a non-quantifiable added benefit is shown for social functioning.

In the side effects category, there is a positive effect in discontinuations due to AEs with an indication of lesser harm with the extent “major”. This is offset by a negative effect in the outcome vascular disorders (severe AEs), with proof of greater harm with the extent “considerable”.

Overall, the positive effects of asciminib outweigh those of the ACT. In summary, there is a hint of minor added benefit of asciminib over the ACT for patients with Ph^+ CML-CP.

The assessment described above deviates from that of the company, which derived proof of considerable added benefit for adult patients with Ph^+ CML-CP in the first-line treatment.

I 4 Research question 2: adult patients with Ph+ CML-CP; second-line treatment

I 4.1 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: 10 October 2025)
- Bibliographical literature search on asciminib (last search on 04 November 2025)
- Search of trial registries/trial results databases for studies on asciminib (last search on 04 November 2025)
- Search on the G-BA website for asciminib (last search on 04 November 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on asciminib (last search on 15 December 2025); for search strategies, see I Appendix A of the full dossier assessment

Consistent with the findings of the company, the review of the completeness of the study pool did not produce any RCTs for this research question.

Research question 2 is limited to pretreated patients with Ph+ CML-CP in second-line treatment. In contrast, the company extends its information retrieval to all pretreated patients, regardless of their line of treatment, and identifies the RCT ASCEMBL [33], which is already known from earlier benefit assessment procedures [34]. The ASCEMBL study is a completed, open-label RCT comparing asciminib with bosutinib, which enrolled adult patients with Ph+ CML-CP who had previously been treated with two or more TKIs. According to the company, the results from the ASCEMBL study is transferable to patients with Ph+ CML-CP in the second-line setting, for whom bosutinib represents the individualized treatment option.

The data submitted by the company are not suitable to draw conclusions regarding the added benefit of asciminib compared with individualized treatment choosing from nilotinib, dasatinib, bosutinib or ponatinib for research question 2. The evidence presented by the company is described below, and the reasons for its unsuitability for the benefit assessment are provided.

Transfer of results from patients from the RCT ASCEMBL to the target population not possible

Approach and reasoning of the company on the transferability of the study results

The company described that the results for patients with Ph^+ CML-CP from the RCT ASCEMBL, who had been pretreated with two or more TKIs, can be transferred to patients in the second-line setting. It justifies this by referring to treatment recommendations that are independent of specific lines of treatment, and also points out that, in its consultations, the G-BA specified the same ACT for patients with one pretreatment and for patients with two or more pretreatments. Furthermore, even in the absence of directly comparative data from patients in the second-line setting, the EMA granted authorization for all lines of treatment on the basis of the studies ASCEMBL, ASC4FIRST and ASC2ESCALATE [35]. According to the predictive modelling carried out for MMR, it is expected that the degree of efficacy in patients who have received a single prior treatment will lie between the efficacy observed in treatment-naive patients and that observed in patients who have received at least two pretreatments. In terms of safety, patients who have previously been treated with only one TKI are thought to have a more favourable prognosis with regard to avoiding side effects, due to fewer comorbidities, compared with patients who have already been treated with at least two TKIs. It can therefore be assumed that the safety profile of asciminib in second-line treatment of adult patients with Ph^+ CML-CP is at least as favourable as that of patients who have been pretreated with at least two TKIs. Furthermore, new safety data from the single-arm study ASC2ESCELATE showed that the safety profile of asciminib was consistent with the previously established safety profile of asciminib also in patients with Ph^+ CML-CP who had been pretreated with a TKI.

Assessment of the data presented by the company

The data submitted by the company are not suitable to draw conclusions regarding the added benefit of asciminib compared with individualized treatment choosing from nilotinib, dasatinib, bosutinib or ponatinib for research question 2. The reasons for this are provided below.

The company carried out an information retrieval for RCTs for the source population (patients pretreated with two or more TKIs) and the target population (patients in the second-line setting). However, it did not conduct an information retrieval to identify all potentially relevant further investigations on the intervention and the ACT in the target population (patients in the second-line setting) which support the transfer of the results. The company only refers selectively to the single-arm study ASC2ESCELATE [36] and only presents the analyses relating to MMR and discontinuation due to AEs in Module 4A. Consequently, there was no adequate information retrieval and no processing or comparison of data relating to the baseline population (more than two prior treatments) and the target population (second-line treatment).

Furthermore, it is clear from the consultation held on 15 February 2024 [5] that, according to the G-BA, it is not medically plausible to transfer evidence from patients who have previously been treated with two or more TKIs to patients who have previously been treated with exactly one TKI, as these involve different treatment situations and patient groups. CML is a progressive disease in which it is assumed that patient characteristics and the course of treatment change significantly as the number of previous treatments increases. The company did not explicitly address this aspect in its comments on the transfer of evidence, nor does it present any data that would refute the G-BA's assessment.

Overall, based on the data presented by the company, it is therefore not possible to transfer the findings from patients who have been pretreated with two or more TKIs to patients in the second-line therapy.

I 4.2 Results on added benefit

For adult patients with Ph^+ CML-CP in the second-line setting, there are no suitable data available to assess the added benefit of asciminib compared with the ACT. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

In its dossier, the company presented no suitable data for the assessment of the added benefit of asciminib versus the ACT for adult patients with Ph^+ CML-CP in the second-line treatment. An added benefit of asciminib versus the ACT is therefore not proven for research question 2.

The assessment described above deviates from that of the company, which derived an indication of minor added benefit for adult patients with Ph^+ CML-CP in the second-line treatment based on the evidence transfer.

I 5 Probability and extent of added benefit – summary

Table 19 summarizes the result of the assessment of the added benefit of asciminib in comparison with the ACT.

Table 19: Asciminib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in the chronic phase (Ph^+ CML-CP); first-line treatment	▪ Imatinib or ▪ nilotinib or ▪ dasatinib or ▪ bosutinib	Hint of minor added benefit
2	Adult patients with Ph^+ CML-CP who have previously been treated with a tyrosine kinase inhibitor (TKI); second-line treatment	An individualized treatment[b, c, d] with a choice of: ▪ nilotinib ▪ dasatinib, ▪ bosutinib, and ▪ ponatinib	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The term 'individualized treatment' is used 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). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).

ACT: appropriate comparator therapy; ABL: Abelson murine leukaemia; BCR: breakpoint cluster region; EU: European Union; HTA: Health Technology Assessment; G-BA: Federal Joint Committee; TKI: tyrosine kinase inhibitor

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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