Asciminib
(chronic myeloid leukaemia)

Addendum to Project A25-70
(dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

Project: A25-129 Version: 1.0 Status: 31 Oct 2025 DOI: 10.60584/A25-129_en

[1] Translation of the addendum *Asciminib (chronische myeloische Leukämie) – Addendum zum Projekt A25-70 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Asciminib (chronic myeloid leukaemia) – Addendum to Project A25-70

Commissioning agency

Federal Joint Committee

Commission awarded on

7 Oct 2025

Internal Project No.

A25-129

https://doi.org/10.60584/A25-129_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone:+49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Recommended citation

Institute for Quality and Efficiency in Health Care. Asciminib (chronic myeloid leukaemia); Addendum to Project A25-70 (dossier assessment) [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-129_en.

Keywords

Asciminib, Leukemia – Myelogenous – Chronic – BCR-ABL Positive, Benefit Assessment, NCT03106779

IQWiG employees involved in the addendum

- Raphaela Gorris
- Ivona Djuric
- Philip Kranz
- Fabian Lotz
- Veronika Schneck

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CML	chronic myeloid leukaemia
CTCAE	Common Terminology Criteria for Adverse Events
ESC	European Society of Cardiology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MDASI	MD Anderson Symptom Inventory
MedDRA	Medical Dictionary for Regulatory Activities
PGIC	Patient Global Impression of Change
(Ph^+ CML-CP)	Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase
PT	Preferred Term
SAE	Serious AE
SCORE	Systematic Coronary Risk Evaluation
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
TKI	tyrosine kinase inhibitor
VAS	visual analogue scale
WPAI	Work Productivity and Activity Impairment

1 Background

On 7 October 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-70 (Asciminib – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analyses presented by the pharmaceutical company (hereinafter referred to as the 'company') in the commenting procedure [2], taking into account the information in the company's dossier [3]:

- Reworking of the data for the total study population in the ASCEMBL study
- The number of patients recruited from outside Europe and therefore classified as in a low-risk category according to the European Society of Cardiology's (ESC) 10-year risk score for fatal cardiovascular disorders (ESC Systematic Coronary Risk Evaluation 2 [SCORE2])

The responsibility for this assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

As described in the dossier assessment A25-70 [1], the total population of the ASCEMBL study [4-14] was not suitable for assessing the added benefit of asciminib in adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph^+ CML-CP) previously treated with ≥ 2 tyrosine kinase inhibitors (TKIs), versus individualized treatment as the appropriate comparator therapy (ACT). This was largely due to the fact that, in the comparator arm of the study, ponatinib represented an additional and potentially more suitable individual treatment option for a relevant proportion of patients alongside bosutinib; however, this option was not available in the study. Furthermore, for at least 13% of patients in the comparator arm, it is not certain whether bosutinib was administered on-label. Overall, therefore, bosutinib was not the most appropriate individual treatment option for more than 20% of patients in the comparator arm of the study. The information provided by the company during the commenting procedure did not alter this assessment for the present addendum. The total population of ASCEMBL was therefore not suitable for comparison with the ACT.

Following the oral hearing, the company submitted further information regarding the number of patients recruited from outside Europe who, for this reason, were classified as in a low-risk category according to the ESC's 10-year risk score for fatal cardiovascular disorders (ESC SCORE2) [15].

In accordance with the terms of the commission, the following sections present an assessment of the total population of the ASCEMBL study comparing asciminib with bosutinib in adult patients with Ph^+ CML-CP previously treated with ≥ 2 TKIs, as well as an assessment of further information regarding the number of patients recruited outside Europe and therefore classified as in a low-risk category for fatal cardiovascular disorders according to ESC SCORE2.

In its comments, the company also presented results for a subpopulation of ASCEMBL [16]. According to the company, this subpopulation comprised those patients for whom bosutinib represented the only remaining treatment option, taking into account prior treatments, mutation status and comorbidities, and in the company's view, very narrow selection criteria. Information on this subpopulation can be found in the company's comments [2].

2.1 Study characteristics

A detailed description of ASCMBL, including information on the study design, intervention and characteristics of the study population, can be found in Appendix B of the full dossier assessment A25-70 [1].

Characterization of the study population according to country-specific risk

In Module 4 A, the company stated, within its assessment of the implementation of the ACT in ASCEMBL, that treatment with nilotinib or dasatinib would not be an option for 87% of

patients in the total population. The company justified this on the basis of the documented comorbidities and risk factors for these patients. One of these risk factors was cardiovascular risk, which the company assessed using the ESC risk score. This score takes into account factors such as age, blood pressure, HDL and total cholesterol, patients' smoking status, and a country-specific risk assessment to evaluate individual cardiovascular risk. The company stated that as the country-specific classification according to the ESC only lists risk classifications for countries within Europe, a conservative assumption of low cardiovascular risk had been made for patients from countries outside Europe. Within the commenting procedure, the company provided information on the characterization of the study population according to country-specific risk as defined by the ESC, as well as on the proportion of patients from non-European countries. This information is presented in Appendix C. The data indicate that in both study arms, around 40% of patients were recruited from outside Europe, and it was therefore assumed that these patients had low cardiovascular risk. In the intervention arm, most patients were from Japan (8.3%), the United States (8.3%) and Brazil (7.6%). In the comparator arm, most patients were from the United States (11.8%), Brazil (9.2%) and Korea (6.6%). It remained unclear whether these patients had a low, moderate, high or very high cardiovascular risk.

Data cuts

This addendum presents the results for each outcome for their respective longest available observation period. For the outcomes of overall survival and progression to blast crisis, this corresponds to the prespecified final data cut-off date of 4 December 2024 (5 years after the first dose of the study medication was administered to the last randomized patient); for all other outcomes, it corresponds to the prespecified data cut-off date of 22 March 2023 (30 days after the end of study treatment).

Planned duration of follow-up

Table 1 shows the planned duration of patient follow-up for the individual outcomes.

Table 1: Planned duration of follow-up – RCT, direct comparison: asciminib vs. bosutinib

Study **Outcome category** **Outcome**	**Planned follow-up**
ASCEMBL	
Mortality	
Overall survival	Until death, lost to follow-up, withdrawal of consent or end of study[a] (whichever occurred first)
Morbidity	
Progression to blast crisis	Until death, lost to follow-up, withdrawal of consent or end of study[a] (whichever occurred first)
Health status (EQ-5D VAS), symptoms (PGIC, MDASI-CML)	Until treatment discontinuation or end of the study treatment
Health-related quality of life	Outcome not recorded[b]
Side effects	
All outcomes in the side effects category	30 days after the last dose of the study medication

a. 5 years after the first dose of the study medication was administered to the last randomized patient.
b. Outcomes from the category of health-related quality of life were not recorded. The company classifies the WPAI-CML instrument under the category of health-related quality of life (see Section 2.2.1).

CML: chronic myeloid leukaemia; MDASI: MD Anderson Symptom Inventory; PGIC: Patient Global Impression of Change; RCT: randomized controlled trial; VAS: visual analogue scale; WPAI: Work Productivity and Activity Impairment

The observation periods for the outcomes of morbidity (excluding progression to blast crisis) and side effects were systematically shortened, as data were recorded only for the duration of treatment with the study medication (+ 30 days for adverse events [AEs]). However, drawing a reliable conclusion on the total study period or the time to patient death would require recording these outcomes for the total period, as was done for survival and progression to blast crisis.

Information on the course of the study

Table 2 shows the patients' mean/median treatment duration and the mean/median observation period for individual outcomes.

Table 2: Information on the course of the study – RCT, direct comparison: asciminib vs. bosutinib (multipage table)

Study **Duration of the study phase** **Outcome category/outcome**	**asciminib** **N = 157**	**bosutinib** **N = 76**
ASCEMBL		
Treatment duration [months]	N = 156	N = 76
Median [min; max]	35.9 [ND]	7.0 [ND]
Mean (SD)	27.3 (19.12)	13.2 (14.42)
Observation period [months]		
Overall survival[a] (data cut-off 4 December 2024)	N = 157	N = 76
Median [min; max]	64.9 [0; 84]	61.8 [0; 84]
Mean (SD)	57.7 (22.03)	52.0 (25.44)
Progression to blast crisis (data cut-off 4 December 2024)	N = 157	N = 76
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Symptom severity and impact of symptoms on daily functioning (MDASI-CML)	N = 147	N = 69
Median [Q1; Q3]	11.6 [5.6; 22.1]	5.6 [3.7; 11.1]
Mean (SD)	14.1 (8.3)	8.6 (7.4)
Symptoms (PGIC)	N = 145	N = 69
Median [Q1; Q3]	11.6 [5.6; 22.1]	5.6 [3.7; 11.1]
Mean (SD)	14.3 (8.1)	8.6 (7.4)
Health status (EQ-5D VAS)	N = 147	N = 69
Median [Q1; Q3]	11.3 [5.6; 22.1]	5.6 [3.7; 11.1]
Mean (SD)	14.1 (8.2)	8.6 (7.4)
Health-related quality of life	Not recorded in the study[b]	
Side effects[c, d]	N = 156	N = 76
Median [min; max]	36.9 [1; 60]	13.4 [1; 56]
Mean (SD)	28.3 (19.12)	19.2 (16.20)

a. The observation period is calculated as the difference between the date of death or censoring and the date of randomization + 1. This value is then converted into months by dividing it by 30.4375. The censoring date corresponds to the date of the last contact prior to the data cut-off; patients who were alive at the time of the data cut-off are censored on the last contact date, regardless of any subsequent therapy.
b. No outcomes in the category of health-related quality of life were recorded. The company classifies the WPAI-CML instrument under the category of health-related quality of life (see Section 2.2.1).
c. According to the company: observation period during treatment with the randomized study medication; data not plausible, see the following section for further details.
d. The observation period is calculated as the difference between the date of the last follow-up for AEs and the date of the first administration of the study medication + 1. This value is then converted into months by dividing it by 30.4375. The date of the last follow-up for AEs is defined as the earliest of the following: (date of death, data cut-off date, or the last date on study medication + 30 days).

Table 2: Information on the course of the study – RCT, direct comparison: asciminib vs. bosutinib (multipage table)

Study **Duration of the study phase** **Outcome category/outcome**	**asciminib** **N = 157**	**bosutinib** **N = 76**
AE: adverse event; CML: chronic myeloid leukaemia; max: maximum; MDASI: MD Anderson Symptom Inventory; min: minimum; N: number of analysed patients; ND: no data; PGIC: Patient Global Impression of Change; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; WPAI: Work Productivity and Activity Impairment		

The median treatment duration with the study medication was approximately 36 months in the intervention arm, more than 5 times as long as in the comparator arm.

At the data cut-off date of 4 December 2024, the median observation period for the overall survival outcome was comparable between the 2 study arms, at approximately 65 months in the intervention arm and 62 months in the comparator arm. No data were available for the outcome of progression to blast crisis.

For all other outcomes, the observation period was linked to the end of treatment (for outcomes in the 'side effects' category, + 30 days) and was therefore systematically shortened. The median observation period for these outcomes was notably longer in the intervention arm than in the comparator arm.

The data on the observation period for the side effect outcomes in the comparator arm (treatment duration: 7 months; observation period: 13.4 months) indicate that, contrary to what was planned in the study protocol, these outcomes were monitored for longer than 30 days after the last dose of the initial study medication. It was assumed that patients who switched to treatment with asciminib in the comparator arm were monitored for outcomes in the side effects category beyond the period of treatment with the initial study medication (follow-up also included the period of treatment with asciminib following treatment switching). It would follow that patients in the comparator arm who switched to treatment with asciminib were followed up for a longer period than patients who did not switch to treatment with asciminib. This was taken into account during the assessment of the risk of bias of the results of the side effect outcomes (see Section 2.2.2).

Subsequent therapies

Table 3 shows the subsequent therapies patients received after discontinuing the study medication.

Table 3: Information on subsequent therapies – RCT, direct comparison: asciminib vs. bosutinib (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy, n (%)**	
	asciminib **N = 157**	**bosutinib** **N = 76**
ASCEMBL (data cut-off 4 December 2024)		
Proportion of patients with at least one subsequent therapy[a]	131 (83.4)[b]	59 (77.6)[b]
Antineoplastic and immunomodulatory drugs		
asciminib	80 (61.1)	21 (35.6)[c]
ponatinib	22 (16.8)	18 (30.5)
bosutinib	17 (13.0)	15 (25.4)
fludarabine	11 (8.4)	5 (8.5)
hydroxycarbamide	11 (8.4)	8 (13.6)
imatinib	11 (8.4)	3 (5.1)
busulfan	9 (6.9)	3 (5.1)
dasatinib	9 (6.9)	9 (15.3)
cyclophosphamide	7 (5.3)	3 (5.1)
nilotinib	5 (3.8)	4 (6.8)
cytarabine	3 (2.3)	0 (0)
ruxolitinib	3 (2.3)	0 (0)
antithymocyte immunoglobulin	2 (1.5)	0 (0)
ciclosporin	2 (1.5)	0 (0)
antineoplastic study drugs	2 (1.5)	1 (1.7)
antithymocyte immunoglobulin (rabbit)	1 (0.8)	0 (0)
daunorubicin	1 (0.8)	0 (0)
idarubicin	1 (0.8)	0 (0)
methotrexate	1 (0.8)	0 (0)
mycophenolate mofetil	1 (0.8)	0 (0)
treosulfan	1 (0.8)	2 (3.4)
azacitidine	0 (0)	1 (1.7)
combinations of antineoplastic drugs	0 (0)	1 (1.7)
interferon	0 (0)	2 (3.4)
other antineoplastic drugs	0 (0)	1 (1.7)
pyrimidine analogues	0 (0)	1 (1.7)
radotinib	0 (0)	1 (1.7)
rituximab	0 (0)	1 (1.7)
venetoclax	0 (0)	1 (1.7)
mesna	1 (0.8)	0 (0)

Table 3: Information on subsequent therapies – RCT, direct comparison: asciminib vs. bosutinib (multipage table)

Study Drug class Drug	Patients with subsequent therapy, n (%)	
	asciminib N = 157	bosutinib N = 76

a. The information covers both subsequent therapy and continued treatment with the study medication.
b. Percentages based on the total population; further percentages are based on patients who have undergone at least one subsequent therapy.
c. Discrepancies between Module 4 A (n = 25, data cut-off date 22 March 2023) and the clinical study report (n = 21, data cut-off date 4 December 2024).

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

In ASCEMBL; treatment with the study medication continued until disease progression, treatment failure according to the criteria of the European LeukemiaNet, the occurrence of a T315I or V299L mutation, or for a maximum of 96 weeks after the first dose of the last randomized patient or up to 48 weeks after the last patient switched from bosutinib to asciminib, whichever was longer, provided that treatment was not discontinued prematurely. The study documents showed that continued treatment with asciminib or bosutinib beyond the maximum treatment duration in the study was possible and did occur (51% of randomized patients in the asciminib arm and 19.7% in the bosutinib arm).

Subsequent therapy is generally defined as the initiation of a new course of treatment following disease progression, treatment failure or discontinuation of treatment for other reasons (e.g. unacceptable toxicity). However, the company's figures on the number of patients who received at least one subsequent therapy also included those patients who, following the end of the planned treatment duration with the study medication described above, continued to receive asciminib (n = 80) or bosutinib (n = 15). The data on the proportion of patients who underwent at least one subsequent therapy could therefore only be interpreted to a limited extent.

In the comparator arm of ASCEMBL, patients who experienced treatment failure whilst on bosutinib, as defined by the European LeukemiaNet criteria [17], were eligible to switch to treatment with asciminib. According to the data provided by the company in the clinical study report, 21 (36%) of patients in the comparator arm switched to treatment with asciminib by the data cut-off date of 4 December 2024. Information on the timepoint of the treatment switch was not available. This was considered in the assessment of the risk of bias at outcome level (see Section 2.2.2). Furthermore, the subsequent therapies had no bearing on the assessment of ASCEMBL.

Risk of bias across outcomes (study level)

Table 4 shows the risk of bias across outcomes (risk of bias at study level).

Table 4: Risk of bias across outcomes (study level) – RCT, direct comparison: asciminib vs. bosutinib

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			
ASCEMBL	Yes	Yes	No	No	Yes	No[a]	High

a. A relevant difference in the proportion of study discontinuations between the treatment groups (asciminib 28.0% vs. bosutinib 40.8%) due to patient decision (asciminib 7% vs. bosutinib 18%) in the absence of blinding.

RCT: randomized controlled trial

The risk of bias across outcomes was rated as high for ASCEMBL. The reason for this was a relevant difference in the proportion of study discontinuations (28.0% vs. 40.8%) between the treatment arms in the absence of blinding. In the intervention arm, 7% of patients decided to discontinue the study, compared with 18% in the comparator arm (see also patient characteristics in Appendix B of the full dossier assessment A25-70 [1]). These study discontinuations occurred predominantly at an early timepoint in the study.

Limitations resulting from the open-label study design are described in Section 2.2.2 under the outcome-specific risk of bias.

2.2 Results

2.2.1 Presented outcomes

In this addendum, the following patient-relevant outcomes are presented for the total population of ASCEMBL:

- Mortality
  - Overall survival
- Morbidity
  - Progression to blast crisis
  - Health status, recorded using the EQ-5D visual analogue scale (VAS)

- Symptoms, recorded using the Patient Global Impression of Change (PGIC) and the MD Anderson Symptom Inventory including the additional module for CML (MDASI-CML)
  - Symptom severity, recorded using the MDASI-CML total symptom severity score
  - Impact of symptoms on daily functioning, recorded using the symptom interference score of the MDASI-CML

- Health-related quality of life
- Side effects
  - Serious AEs (SAEs)
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Other specific AEs

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

Table 5 shows for which outcomes data were available in the study presented.

Table 5: Matrix of outcomes – RCT, direct comparison: asciminib vs. bosutinib

Study	Outcomes										
	Overall survival	Progression to blast crisis	Symptoms (PGIC)	Symptom severity (MDASI-CML total symptom severity)	Impact of symptoms on daily functioning (MDASI-CML symptom interference)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs[b]
ASCEMBL	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (coded according to MedDRA): respiratory, thoracic and mediastinal disorders (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs), skin and subcutaneous tissue disorders (SOC, severe AEs), alanine aminotransferase increased (PT, severe AEs), aspartate aminotransferase increased (PT, severe AEs) and thrombocytopenia (PT, severe AEs).
c. Relevant outcomes in this category were not recorded. The company classifies the WPAI-CML instrument under the category of health-related quality of life (see Section 2.2.1).

AE: adverse event; CML: chronic myeloid leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; MDASI: MD Anderson Symptom Inventory; MedDRA: Medical Dictionary for Regulatory Activities; PGIC: Patient Global Impression of Change; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; WPAI: Work Productivity and Activity Impairment

General comments on the outcomes

Progression to blast crisis

In ASCEMBL, blast crisis was operationalized as a proportion of ≥ 30% blasts in the blood or bone marrow [17]. 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 [17]. The outcome was therefore patient relevant, and so was relevant for the benefit assessment.

Analyses of patient-reported outcomes on morbidity and health-related quality of life

In the study, the company recorded patient-reported outcomes with the instruments MDASI-CML, EQ-5D VAS, WPAI-CML (Work Productivity and Activity Impairment-CML) and PGIC. The prespecified operationalization in the statistical analysis plan was, in each case, the change versus baseline.

The analyses presented by the company regarding the time to first deterioration for the EQ-5D VAS (response criterion ≥ 15 points), for the total scores of the MDASI-CML (response criterion in each case ≥ 1.5 points) and for the PGIC (see below for the response criteria) were used for the assessment of ASCEMBL. The WPAI-CML was not used.

MDASI-CML

The MDASI-CML is a questionnaire designed to capture symptom severity and the impact of symptoms on daily functioning in people with CML. The respective total scores (total symptom severity and symptom interference) were included in the assessment for symptom severity and the impact of symptoms on daily functioning, and were assigned to the morbidity outcome category.

Symptoms recorded using the PGIC

The PGIC consists of a single question with which the patient assesses the change in CML symptoms compared to the start of treatment [5]. There are 7 possible responses ('very much improved', 'much improved', 'minimally improved', 'no change', 'minimally worse', 'much worse', 'very much worse'). The recording of symptoms using the PGIC was considered relevant to patients and the analysis was used in the benefit assessment.

Activity impairment (WPAI-CML question 6)

The WPAI is a questionnaire developed to measure the impairment of work productivity and of activities outside of work [18]. The WPAI uses question 6 to record restrictions on daily activity over the past 7 days. In Module 4 A, the company presented the results for the WPAI-CML only as supplementary information, as the G-BA had not taken the results for question 6 of the WPAI into account in its benefit assessment of asciminib as a drug for rare diseases [12]. The company assigned the WPAI-CML overall to the outcome category of health-related quality of life. In deviation from the company's assessment, question 6 of the WPAI-CML was assigned to the morbidity category. Notwithstanding this, the WPAI-CML was not used for assessment, as the activity impairment of the patients was adequately captured by the MDASI-CML's symptom interference score (impact of symptoms on daily functioning).

2.2.2 Risk of bias

Table 6 describes the risk of bias for the results of the relevant outcomes.

Table 6: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: asciminib vs. bosutinib

Study		Outcomes										
	Study level	Overall survival	Progression to blast crisis	Symptoms (PGIC)	Symptom severity (MDASI-CML total symptom severity)	Impact of symptoms on daily functioning (MDASI-CML symptom interference)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs[b]
ASCEMBL	H	H[c]	H[c]	H[d, e]	H[d, e]	H[d, e]	H[d, e]	-[f]	H[e, g]	H[e, g]	H[g, h]	H[e, g]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (coded according to MedDRA): respiratory, thoracic and mediastinal disorders (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs), skin and subcutaneous tissue disorders (SOC, severe AEs), alanine aminotransferase increased (PT, severe AEs), aspartate aminotransferase increased (PT, severe AEs) and thrombocytopenia (PT, severe AEs).
c. In the comparator arm, at the data cut-off of 4 December 2024, n = 21 patients (35.6%) had switched from bosutinib to asciminib following confirmed treatment failure (see Section 2.1 and the running text that follows).
d. Lack of blinding in subjective outcome recording; a sharp and uneven decline in questionnaire response rates over the course of the study.
e. Incomplete observations for potentially informative reasons because of differing follow-ups.
f. Relevant outcomes in this category were not recorded. The company classifies the WPAI-CML instrument under the category of health-related quality of life (see Section 2.2.1).
g. Potentially selective follow-up of the AEs in the comparator arm.
h. Lack of blinding in subjective decision for discontinuation.

AE: adverse event; CML: chronic myeloid leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; H: high; MDASI: MD Anderson Symptom Inventory; MedDRA: Medical Dictionary for Regulatory Activities; PGIC: Patient Global Impression of Change; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; WPAI: Work Productivity and Activity Impairment

Given the high risk of bias already identified at the study level (see Section 2.1), the outcome-specific risk of bias was assessed as high for all outcomes. Further factors contributing to the high risk of bias at the outcome level are described below.

The results on overall survival and progression to blast crisis had a high risk of bias because a high proportion of patients (33%) switched from the control arm to treatment with asciminib. No information was available regarding the timepoints at which the patients switched treatment. In Module 4, the company presented a sensitivity analysis for the outcome overall survival, in which patients were censored at the time of treatment switching. This approach was inadequate as it may lead to potentially biased effect estimates due to informative censoring. The primary analysis, in which the intention-to-treat principle was implemented and which included the longest possible follow-up period, was used for the benefit assessment.

The risk of bias for the results for patient-reported outcomes (PGIC, MDASI-CML, EQ-5D VAS) was assessed as high due to the open-label study design. Furthermore, the risk of bias of these outcomes, as well as of all outcomes in the side effects category (excluding discontinuation due to AEs), was assessed as high due to incomplete observations for potentially informative reasons because of differing follow-ups between the treatment groups. Additionally, the response rates for the questionnaires declined over the course of the study and varied significantly between the study arms. For the outcomes in the side effects category, the potentially selective follow-up of AEs in the comparator arm, extending well beyond the planned 30-day follow-up period following the last administration of the medication, also contributed to the high risk of bias (see Section 2.1).

The risk of bias for the results on the outcome discontinuation due to AEs was rated as high due to the subjective decision to discontinue in an unblinded study design. The certainty of results for this outcome was additionally limited by the fact that premature treatment discontinuation may also be for reasons other than AEs. These reasons represented a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected.

2.2.3 Results

Table 7 summarizes the results for the comparison of asciminib with bosutinib in patients with Ph^+ CML-CP previously treated with ≥ 2 TKIs. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The results on common AEs, SAEs, severe AEs and discontinuation due to AEs are presented in Appendix A. The Kaplan-Meier curves on the presented outcomes can be found in Appendix B.

Table 7: Results (mortality, morbidity, side effects) – RCT, direct comparison: asciminib vs. bosutinib (multipage table)

Study Outcome category (data cut-off) Outcome	asciminib N	asciminib Median time to event in months [95% CI][a] Patients with event n (%)	bosutinib N	bosutinib Median time to event in months [95% CI][a] Patients with event n (%)	asciminib vs. bosutinib HR [95% CI][b]; p-value[c]
ASCEMBL					
Mortality (data cut-off 4 December 2024)					
Overall survival	157	NA[d] 16 (10.2)	76	NA [75.72; NC][d] 9 (11.8)	0.79 [0.35; 1.78]; 0.564
Morbidity (data cut-off 4 December 2024)					
Progression to blast crisis	157	–[e] 5 (3.2)	76	–[e] 5 (6.6)	0.37 [0.09; 1.50]; 0.146
Morbidity (data cut-off 22 March 2023)					
Symptoms (PGIC – time to first deterioration[f])	157	NA 19 (12.1)	76	NA 13 (17.1)	0.58 [0.29; 1.19]; 0.138
Symptom severity (MDASI-CML total symptom severity – time to first deterioration[g])	152	NA 19 (12.5)	70	NA [22.11; NC] 21 (30.0)	0.31 [0.17; 0.59]; < 0.001
Impact of symptoms on daily functioning (MDASI-CML symptom interference – time to first deterioration[g])	152	NA 36 (23.7)	70	NA [5.95; NC] 24 (34.3)	0.56 [0.33; 0.94]; 0.029
Health status (EQ-5D VAS - time to first deterioration[h])	150	NA 46 (30.7)	69	NA [3.68; NC] 24 (34.8)	0.77 [0.47; 1.27]; 0.300
Health-related quality of life	Relevant outcomes not recorded in the study[i]				

Table 7: Results (mortality, morbidity, side effects) – RCT, direct comparison: asciminib vs. bosutinib (multipage table)

Study Outcome category (data cut-off) Outcome	asciminib		bosutinib		asciminib vs. bosutinib
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95% CI][b]; p-value[c]
Side effects (data cut-off 22 March 2023)					
AEs (supplementary information)	156	0.41 [0.26; 0.95] 142 (91.0)	76	0.08 [0.03; 0.20] 74 (97.4)	–
SAEs	156	NA [50.10; NC] 34 (21.8)	76	NA [25.10; NC] 20 (26.3)	0.53 [0.30; 0.94]; 0.027
Severe AEs[j]	156	9.26 [3.25; 21.19] 93 (59.6)	76	3.48 [1.84; 8.31] 52 (68.4)	0.69 [0.49; 0.98]; 0.033
Discontinuation due to AEs	156	NA 13 (8.3)	76	NA [25.10; NC] 21 (27.6)	0.20 [0.10; 0.41]; < 0.001
Respiratory, thoracic and mediastinal disorders (SOC, severe AEs[j])	156	NA 1 (0.6)	76	NA [32.62; NC] 5 (6.6)	0.04 [0.00; 0.34]; < 0.001
Gastrointestinal disorders (SOC, severe AEs[j])	156	NA 8 (5.1)	76	NA 12 (15.8)	0.22 [0.09; 0.55]; < 0.001
Skin and subcutaneous tissue disorders (SOC, severe AEs[j])	156	NA 1 (0.6)	76	NA 8 (10.5)	0.06 [0.01; 0.45]; < 0.001
Alanine aminotransferase increased (PT, severe AEs[j])	156	NA 1 (0.6)	76	NA 11 (14.5)	0.04 [0.01; 0.31]; < 0.001
Aspartate aminotransferase increased (PT, severe AEs[j])	156	NA 3 (1.9)	76	NA 5 (6.6)	0.23 [0.05; 0.95]; 0.027
Thrombocytopenia (PT, severe AEs[j])	156	NA 28 (17.9)	76	NA 5 (6.6)	2.79 [1.08; 7.23]; 0.027

a. Estimated using the Kaplan-Meier method.
b. Cox proportional hazards model with the covariate 'treatment', stratified by the presence of an MCyR (MCyR vs. no MCyR) according to IRT.
c. Two-sided p-value from the log-rank test, stratified by the presence of an MCyR (MCyR vs. no MCyR) according to IRT.
d. Institute's calculation from data in years (years x 12).
e. Median time [95% CI] until the event cannot be meaningfully interpreted.
f. Achieving a scale value of 5, 6 or 7 is considered a clinically relevant deterioration (scale range: 1 to 7).
g. A score increase by ≥ 1.5 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 10 points).
h. A decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
i. Relevant outcomes in this category were not recorded. The company classifies the WPAI-CML instrument under the category of health-related quality of life (see Section 2.2.1).
j. Operationalized as CTCAE grade ≥ 3.

Table 7: Results (mortality, morbidity, side effects) – RCT, direct comparison: asciminib vs. bosutinib (multipage table)

Study Outcome category (data cut-off) Outcome	asciminib		bosutinib		asciminib vs. bosutinib
	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95% CI][b]; p-value[c]
AE: adverse event; CI: confidence interval; CML: chronic myeloid leukaemia; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; IRT: interactive response technology; MCyR: major cytogenetic response; MDASI: MD Anderson Symptom Inventory; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PGIC: Patient Global Impression of Change; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; SAE: serious adverse event; VAS: visual analogue scale					

No statistically significant differences were shown between the treatment arms for the outcomes of overall survival, progression to blast crisis, symptoms recorded using the PGIC, and health status recorded using the EQ-5D VAS. Relevant outcomes on health-related quality of life were not recorded in the study.

A statistically significant difference in favour of asciminib versus bosutinib was shown for the following: for the outcomes of symptom severity and the impact of symptoms on daily functioning, each recorded using the MDASI-CML; and for the outcomes of SAEs, severe AEs, discontinuation due to AEs, respiratory, thoracic and mediastinal disorders (severe AEs), gastrointestinal disorders (severe AEs), skin and subcutaneous tissue disorders (severe AEs), alanine aminotransferase increased (severe AEs) and aspartate aminotransferase increased (severe AEs). However, for the outcome impact of symptoms on daily functioning, there was an effect modification by the characteristic of sex; a statistically significant difference in favour of asciminib was only shown for women (see Section 2.2.4).

Statistically significant differences to the disadvantage of asciminib versus bosutinib were shown for the outcome thrombocytopenia (severe AEs).

2.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for the present addendum:

- Age (< 65 years versus ≥ 65 years)
- Sex (female versus male)

The characteristics listed were prespecified for the study's primary outcome (good molecular response). According to the study protocol, the category ≥ 75 years was also to be included

for the age characteristic. However, as only 6 patients were aged 75 or over at baseline, this subgroup was not included in the analysis. No suitable characteristic for disease severity was available.

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.

The results are presented in Table 8. The Kaplan-Meier curves on the subgroup results are presented in Appendix B.

Table 8: Subgroups (morbidity) – RCT, direct comparison: asciminib versus bosutinib

Study	**asciminib**		**bosutinib**		**asciminib vs. bosutinib**	
Outcome **Characteristic** **Subgroup**	**N**	**Median time to event in months [95% CI][a]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI][a]** **Patients with event n (%)**	**HR [95% CI][b]**	**p-value[b]**
ASCEMBL (data cut-off 22 March 2023)						
Impact of symptoms on daily functioning (MDASI-CML symptom interference – time to first deterioration[c])						
Sex						
Male	78	NA 20 (25.6)	27	NA [8.31; NC] 7 (25.9)	1.11 [0.46; 2.71]	0.814
Female	74	NA [22.14; NC] 16 (21.6)	43	22.11 [2.83; NC] 17 (39.5)	0.30 [0.14; 0.64]	0.002
					Interaction:	0.049[d]

a. Estimated using the Kaplan-Meier method; calculation of the 2-sided 95% CI using the Brookmeyer and Crowley method (log-log transformation).
b. HR, 95% CI and p-value from a stratified Cox proportional hazards model with the stratification factors of presence of an MCyR at screening (MCyR vs. no MCyR) according to IRT and age group (18–65 vs. ≥ 65 years), and the covariates of treatment and baseline questionnaire score.
c. A score increase by ≥ 1.5 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 10 points).
d. p-value from a stratified Cox proportional hazards model with the stratification factors of presence of an MCyR at screening (MCyR vs. no MCyR) according to IRT and age group (18–65 vs. ≥ 65 years), and the covariates of treatment and baseline questionnaire score, subgroup and treatment*subgroup.

CI: confidence interval; CML: chronic myeloid leukaemia; HR: hazard ratio; IRT: interactive response technology; MCyR: major cytogenetic response; MDASI: MD Anderson Symptom Inventory; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial

Impact of symptoms on daily functioning (MDASI-CML symptom interference)

There was an effect modification by sex for the outcome 'impact of symptoms on daily functioning'. For female patients, a statistically significant difference in favour of asciminib compared with bosutinib was shown. For male patients, there was no statistically significant difference between the treatment arms.

2.2.5 Summary of the results

Overall, the ASCEMBL study showed the following results for asciminib versus bosutinib in the total population:

- Statistically significant difference in favour of asciminib:
  - Symptom severity (MDASI-CML total symptom severity)
  - Impact of symptoms on daily functioning (MDASI-CML symptom interference; sex [women])
  - Overall SAE rate
  - Overall rate of severe AEs, including:
    - Respiratory, thoracic and mediastinal disorders
    - Gastrointestinal disorders
    - Skin and subcutaneous tissue disorders
    - Alanine aminotransferase increased
    - Aspartate aminotransferase increased
  - Discontinuation due to AEs
- Statistically significant difference to the disadvantage of asciminib:
  - Thrombocytopenia (severe AEs)

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Asciminib (chronische myeloische Leukämie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2025 [Accessed: 20.10.2025]. URL: https://doi.org/10.60584/A25-70.

2. Novartis. Stellungnahme zum IQWiG-Bericht Nr. 2077: Asciminib (chronische myeloische Leukämie); Nutzenbewertung gemäß § 35a SGB V. 2025: [soon available at: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1225/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Novartis Pharma. Asciminib (Scemblix); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2025 [Accessed: 07.10.2025]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1225/#dossier.

4. Hochhaus A, Rea D, Boquimpani C et al. Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. Leukemia 2023; 37: 617-626. https://doi.org/10.1038/s41375-023-01829-9.

5. Rea D, Boquimpani C, Mauro MJ et al. Health-related quality of life of patients with resistant/intolerant chronic phase chronic myeloid leukemia treated with asciminib or bosutinib in the phase 3 ASCEMBL trial. Leukemia 2023; 37: 1060-1067. https://doi.org/10.1038/s41375-023-01888-y.

6. Rea D, Mauro MJ, Boquimpani C et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood 2021; 138(21): 2031-2041. https://doi.org/10.1182/blood.2020009984.

7. Novartis. A Phase III, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with chronic myelogenous leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors; study CABL001A2301; Clinical Study Report; Preliminary endpoint analysis at Week 24 [unpublished]. 2021.

8. Novartis. A Phase III, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with chronic myelogenous leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors; study CABL001A2301; Supplementary Clinical Study Report to support the 30-day efficacy and safety update [unpublished]. 2021.

9. Novartis. A Phase III, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with chronic myelogenous leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors; study CABL001A2301; Clinical Study Report; Key secondary endpoint analysis at Week 96 [unpublished]. 2022.

10. Novartis. A Phase III, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with chronic myelogenous leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors; study CABL001A2301; Clinical Study Report (End of Treatment) [unpublished]. 2023.

11. Novartis. A Phase III, multi-center, open-label, randomized study of oral ABL001 (asciminib) versus bosutinib in patients with chronic myelogenous leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors; study CABL001A2301; Clinical Study Report (End of Study) [unpublished]. 2025.

12. Gemeinsamer Bundesausschuss. Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Bewertung von Arzneimitteln für seltene Leiden nach § 35a Absatz 1 Satz 11 i. V. m. Kapitel 5 § 12 Nr. 1 Satz 2 VerfO; Wirkstoff: Asciminib [online]. 2023 [Accessed: 03.07.2025]. URL: https://www.g-ba.de/downloads/92-975-6103/2022-10-01_Nutzenbewertung-G-BA_Asciminb_D-865.pdf.

13. Novartis Pharma. A phase 3, multi-center, open-label, randomized study of oral ABL001 versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors [online]. [Accessed: 16.06.2025]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-002461-66.

14. Novartis Pharmaceuticals. Study of Efficacy of CML-CP Patients Treated With ABL001 Versus Bosutinib, Previously Treated With 2 or More TKIs [online]. 2025 [Accessed: 16.06.2025]. URL: https://clinicaltrials.gov/study/NCT03106779.

15. Mulas O, Abruzzese E, Luciano L et al. The new Systematic Coronary Risk Evaluation (SCORE2 and SCORE2-OP) estimates the risk of arterial occlusive events in chronic myeloid leukemia patients treated with nilotinib or ponatinib. Ann Hematol 2024; 103(2): 427-436. https://doi.org/10.1007/s00277-023-05556-0.

16. Novartis. Subpopulation for Written Statement; Asciminib HTA Analysis [unpublished]. 2025.

17. Apperley JF, Milojkovic D, Cross NCP et al. 2025 European LeukemiaNet recommendations for the management of chronic myeloid leukemia. Leukemia 2025; 39. https://doi.org/10.1038/s41375-025-02664-w.

18. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993; 4(5): 353-365. https://doi.org/10.2165/00019053-199304050-00006.

Appendix A Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (CTCAE grade ≥ 3), the following tables present events for System Organ Classes (SOCs) and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Overall rates of severe AEs (CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 9: Common AEs[a] – RCT, direct comparison: asciminib vs. bosutinib (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**asciminib** **N = 156**	**bosutinib** **N = 76**
ASCEMBL		
Overall rate of AEs (data cut-off 22 March 2023)	142 (91.0)	74 (97.4)
Blood and lymphatic system disorders	54 (34.6)	24 (31.6)
Thrombocytopenia	36 (23.1)	11 (14.5)
Neutropenia	30 (19.2)	13 (17.1)
Anaemia	16 (10.3)	6 (7.9)
Cardiac disorders	17 (10.9)	7 (9.2)
Eye disorders	16 (10.3)	6 (7.9)
Gastrointestinal disorders	69 (44.2)	61 (80.3)
Diarrhoea	20 (12.8)	55 (72.4)
Nausea	18 (11.5)	35 (46.1)
Abdominal pain	14 (9.0)	12 (15.8)
Vomiting	12 (7.7)	20 (26.3)
Dyspepsia	11 (7.1)	3 (3.9)

Table 9: Common AEs[a] – RCT, direct comparison: asciminib vs. bosutinib (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**asciminib** **N = 156**	**bosutinib** **N = 76**
General disorders and administration site conditions	52 (33.3)	25 (32.9)
Fatigue	24 (15.4)	8 (10.5)
Asthenia	14 (9.0)	1 (1.3)
Oedema peripheral	12 (7.7)	2 (2.6)
Infections and infestations	76 (48.7)	22 (28.9)
Nasopharyngitis	18 (11.5)	3 (3.9)
COVID-19	17 (10.9)	5 (6.6)
Upper respiratory tract infection	14 (9.0)	4 (5.3)
Injury, poisoning and procedural complications	30 (19.2)	6 (7.9)
Investigations	56 (35.9)	40 (52.6)
Platelet count decreased	11 (7.1)	5 (6.6)
Aspartate aminotransferase increased	9 (5.8)	16 (21.1)
Alanine aminotransferase increased	8 (5.1)	23 (30.3)
Metabolism and nutrition disorders	32 (20.5)	14 (18.4)
Musculoskeletal and connective tissue disorders	56 (35.9)	18 (23.7)
Arthralgia	23 (14.7)	2 (2.6)
Pain in extremity	15 (9.6)	5 (6.6)
Back pain	12 (7.7)	3 (3.9)
Myalgia	10 (6.4)	3 (3.9)
Nervous system disorders	56 (35.9)	17 (22.4)
Headache	30 (19.2)	12 (15.8)
Dizziness	14 (9.0)	2 (2.6)
Psychiatric disorders	22 (14.1)	4 (5.3)
Insomnia	11 (7.1)	1 (1.3)
Renal and urinary disorders	11 (7.1)	5 (6.6)
Reproductive system and breast disorders	17 (10.9)	5 (6.6)
Respiratory, thoracic and mediastinal disorders	36 (23.1)	15 (19.7)
Cough	14 (9.0)	5 (6.6)
Skin and subcutaneous tissue disorders	58 (37.2)	33 (43.4)
Rash	15 (9.6)	18 (23.7)
Vascular disorders	32 (20.5)	6 (7.9)
Hypertension	23 (14.7)	4 (5.3)

a. Events that occurred in ≥ 10 patients in the intervention arm, or in ≥ 10% of patients in the control arm.
b. MedDRA version 26.0; SOC and PT notation taken from Module 4 without adaptation.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 10: Common SAEs[a] – RCT, direct comparison: asciminib vs. bosutinib

Study	Patients with event n (%)	
SOC[b] PT[b]	asciminib N = 156	bosutinib N = 76
ASCEMBL		
Overall rate of SAEs (data cut-off 22 March 2023)	34 (21.8)	20 (26.3)
Infections and infestations	9 (5.8)	2 (2.6)
Respiratory, thoracic and mediastinal disorders	0 (0)	4 (5.3)
Skin and subcutaneous tissue disorders	0 (0)	4 (5.3)

a. Events that occurred in at least one study arm in ≥ 5% of patients.
b. MedDRA version 26.0; SOC and PT notation taken from Module 4 without adaptation.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 11: Common severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: asciminib vs. bosutinib

Study	Patients with event n (%)	
SOC[b] PT[b]	asciminib N = 156	bosutinib N = 76
ASCEMBL		
Overall rate of severe AEs (CTCAE grade ≥ 3) (data cut-off 22 March 2023)	93 (59.6)	52 (68.4)
Blood and lymphatic system disorders	36 (23.1)	14 (18.4)
Neutropenia	24 (15.4)	9 (11.8)
Gastrointestinal disorders	8 (5.1)	12 (15.8)
Diarrhoea	0 (0)	8 (10.5)
General disorders and administration site conditions	9 (5.8)	2 (2.6)
Investigations	28 (17.9)	24 (31.6)
Thrombocytopenia	28 (17.9)	5 (6.6)
Lipase increased	6 (3.8)	4 (5.3)
Aspartate aminotransferase increased	3 (1.9)	5 (6.6)
Alanine aminotransferase increased	1 (0.6)	11 (14.5)
Metabolism and nutrition disorders	11 (7.1)	4 (5.3)
Respiratory, thoracic and mediastinal disorders	1 (0.6)	5 (6.6)
Skin and subcutaneous tissue disorders	1 (0.6)	8 (10.5)
Vascular disorders	16 (10.3)	3 (3.9)
Hypertension	12 (7.7)	3 (3.9)

a. Events that occurred in at least one study arm in ≥ 5% of patients.
b. MedDRA version 26.0; SOC and PT notation taken from Module 4 without adaptation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 12: Discontinuations due to AEs – RCT, direct comparison: asciminib vs. bosutinib (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**asciminib** **N = 156**	**bosutinib** **N = 76**
ASCEMBL		
Overall rate of discontinuation due to AEs (data cut-off 22 March 2023)	13 (8.3)	23 (30.3)
Investigations	6 (3.8)	5 (6.6)
Blood and lymphatic system disorders	4 (2.6)	5 (6.6)[b]
Nervous system disorders	2 (1.3)	0 (0)
Pregnancy, puerperium and perinatal conditions	1 (0.6)	0 (0)
Gastrointestinal disorders	0 (0)	3 (3.9)
General disorders and administration site conditions	0 (0)	1 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	3 (3.9)[b]
Respiratory, thoracic and mediastinal disorders	0 (0)	4 (5.3)
Skin and subcutaneous tissue disorders	0 (0)	2 (2.6)
Lipase increased	3 (1.9)	0 (0)
Thrombocytopenia	3 (1.9)	2 (2.6)[b]
Neutropenia	2 (1.3)	3 (3.9)
Neutrophil count decreased	2 (1.3)	0 (0)
Platelet count decreased	2 (1.3)	0 (0)
Amylase increased	1 (0.6)	0 (0)
Cerebral disorder	1 (0.6)	0 (0)
Ejection fraction decreased	1 (0.6)	0 (0)
Ischaemic stroke	1 (0.6)	0 (0)
Pregnancy	1 (0.6)	0 (0)
Acute myeloid leukaemia	0 (0)	1 (1.3)[b]
Alanine aminotransferase increased	0 (0)	4 (5.3)
Aspartate aminotransferase increased	0 (0)	2 (2.6)
Blood creatinine increased	0 (0)	1 (1.3)
Diarrhoea	0 (0)	3 (3.9)
Diffuse large cell B-cell lymphoma	0 (0)	1 (1.3)
Drug rash	0 (0)	1 (1.3)
Hydrothorax	0 (0)	1 (1.3)
Pleural effusion	0 (0)	3 (3.9)
Pyrexia	0 (0)	1 (1.3)
Rash	0 (0)	1 (1.3)
Squamous cell carcinoma	0 (0)	1 (1.3)

Table 12: Discontinuations due to AEs – RCT, direct comparison: asciminib vs. bosutinib (multipage table)

Study	**Patients with event n (%)**	
SOC[a]	**asciminib**	**bosutinib**
PT[a]	**N = 156**	**N = 76**

a. MedDRA version 26.0; SOC and PT notation taken without adaptation from Module 4 A.
b. In each case, one patient discontinued treatment due to an AE after having switched from bosutinib to asciminib.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Appendix B Kaplan-Meier curves

B.1 Mortality

Overall survival outcome

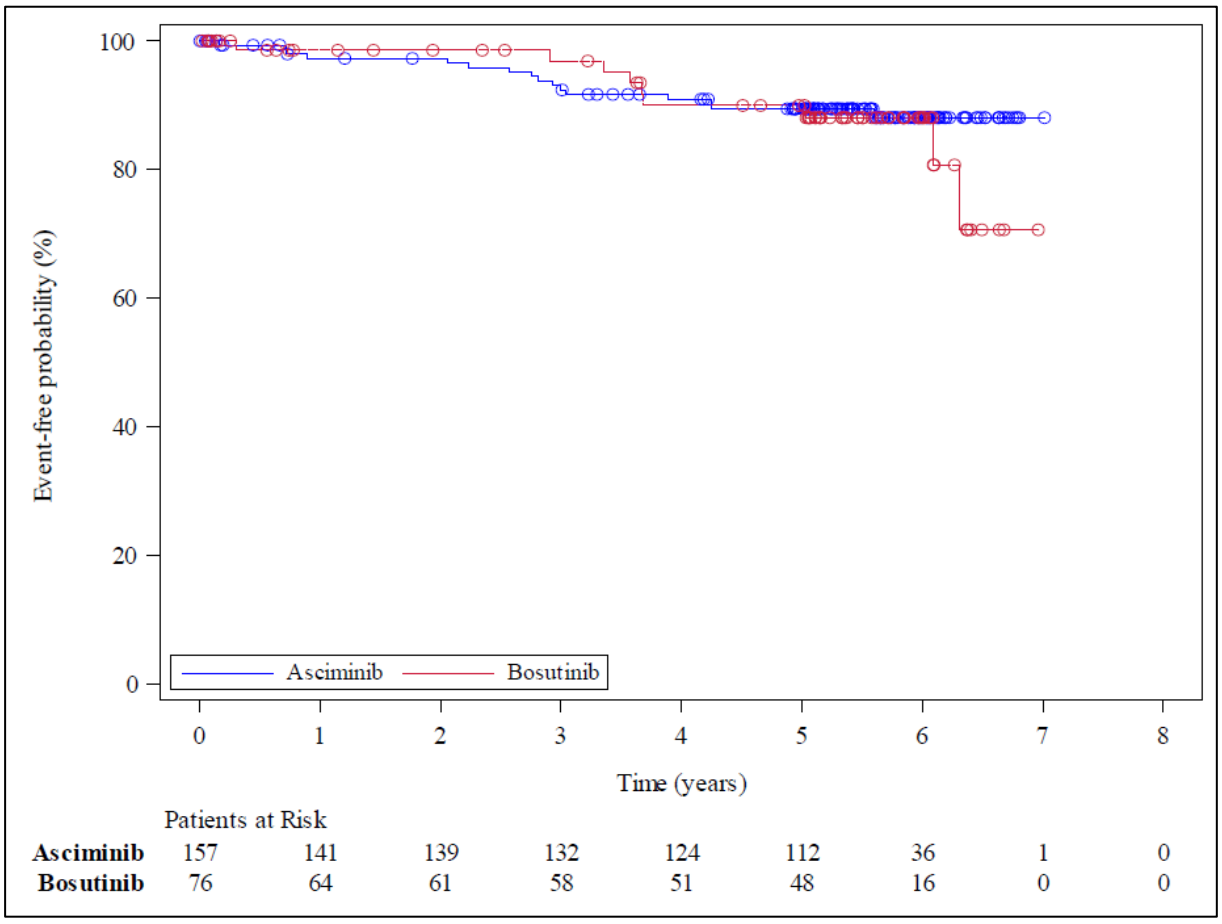

Figure 1: Kaplan-Meier curve for the outcome overall survival – (data cut-off 4 December 2024)

B.2 Morbidity

Progression to blast crisis outcome

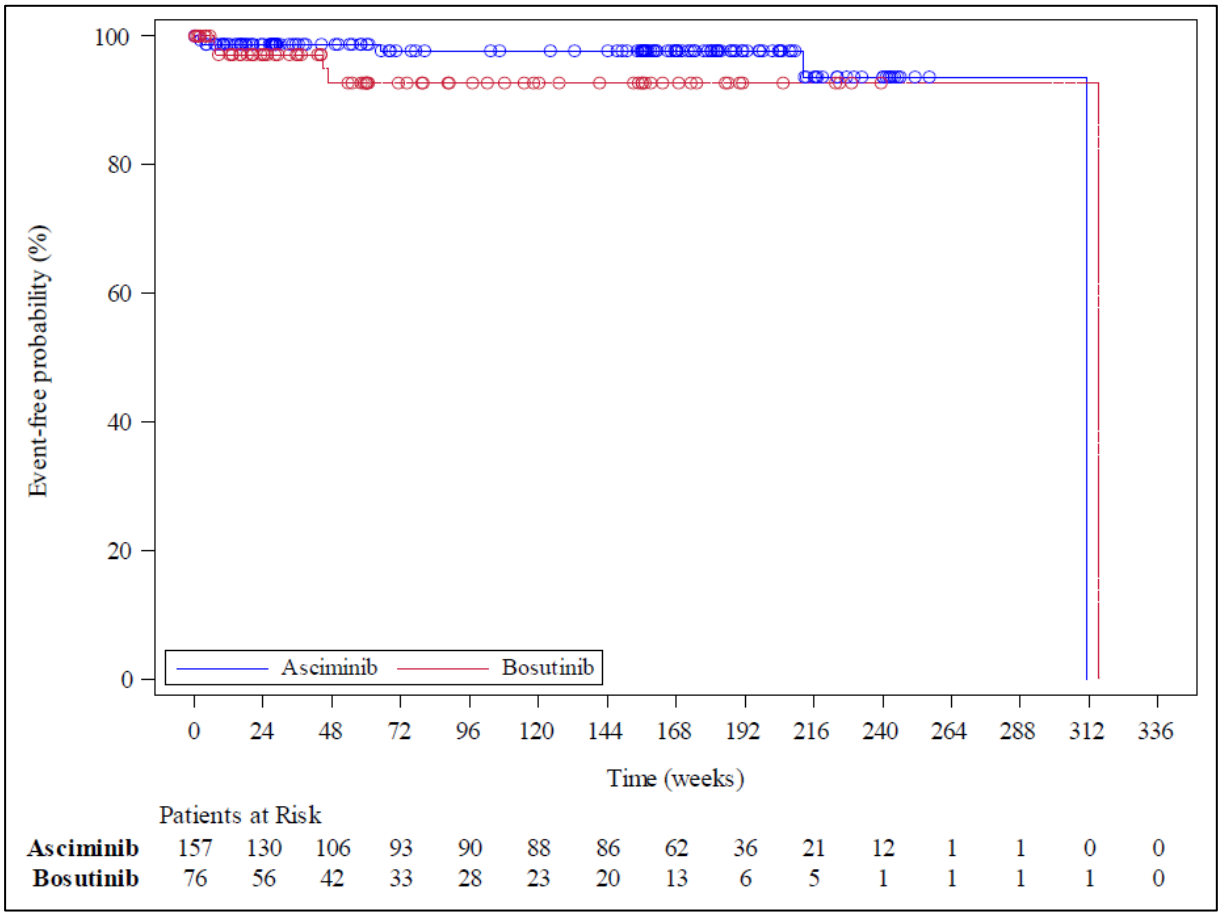

Figure 2: Kaplan-Meier curve for the outcome progression to blast crisis (data cut-off 4 December 2024)

Symptom severity outcome (MDASI-CML)

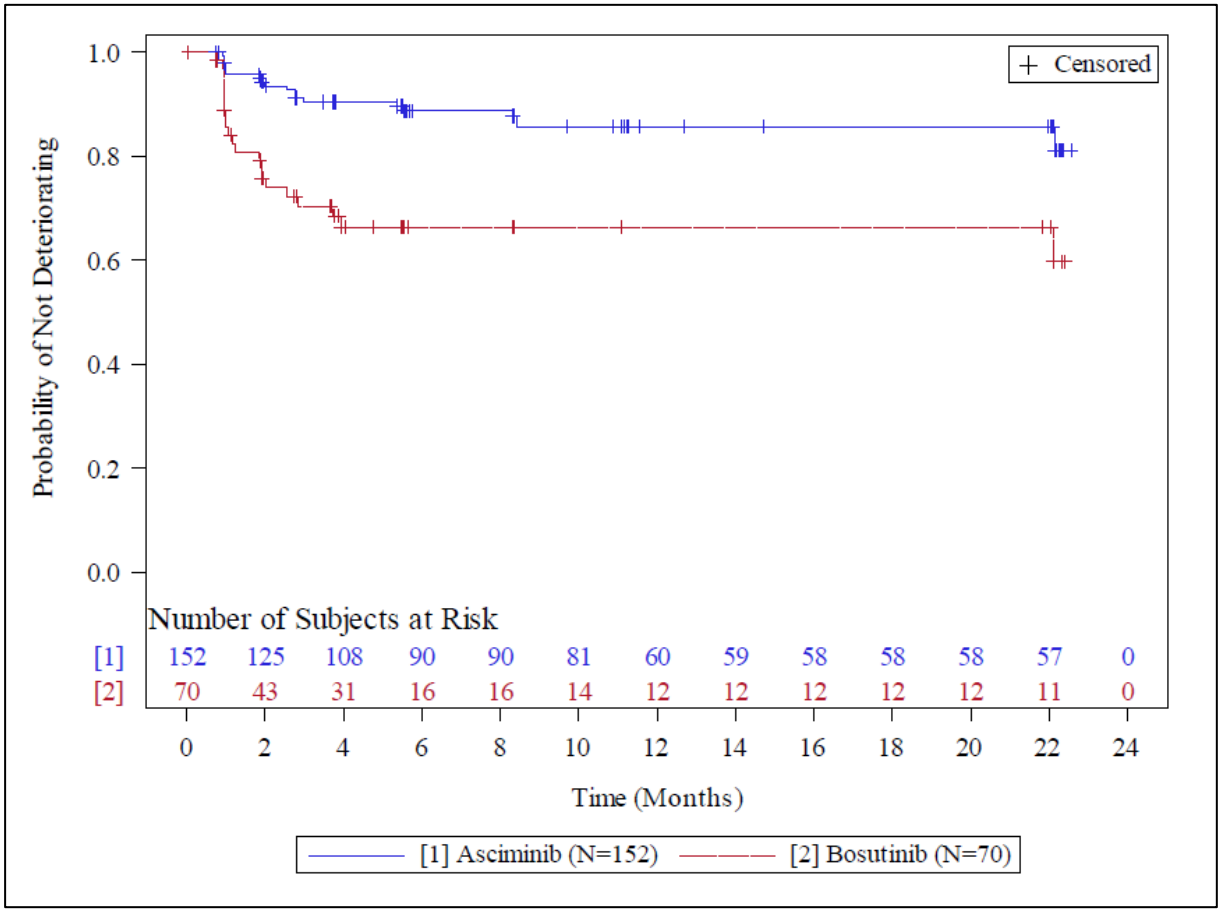

Figure 3: Kaplan-Meier curve for the outcome symptom severity (MDASI-CML total symptom severity – time to first deterioration [data cut-off 22 March 2023])

Impact of symptoms on daily functioning outcome (MDASI-CML)

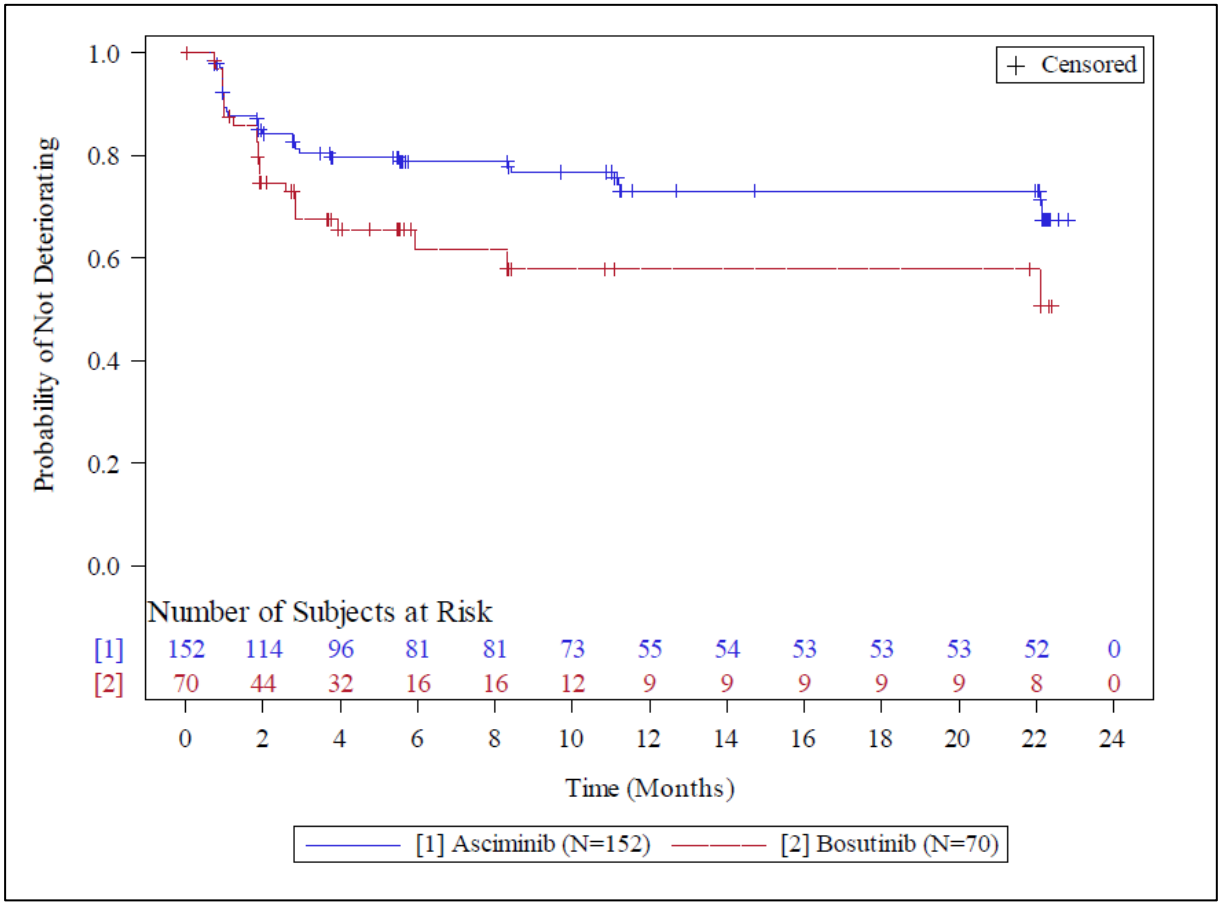

Figure 4: Kaplan-Meier curve for the outcome impact of symptoms on daily functioning (MDASI-CML symptom interference – time to first deterioration [data cut-off 22 March 2023])

Impact of symptoms on daily functioning outcome (MDASI-CML) – split by the characteristic sex

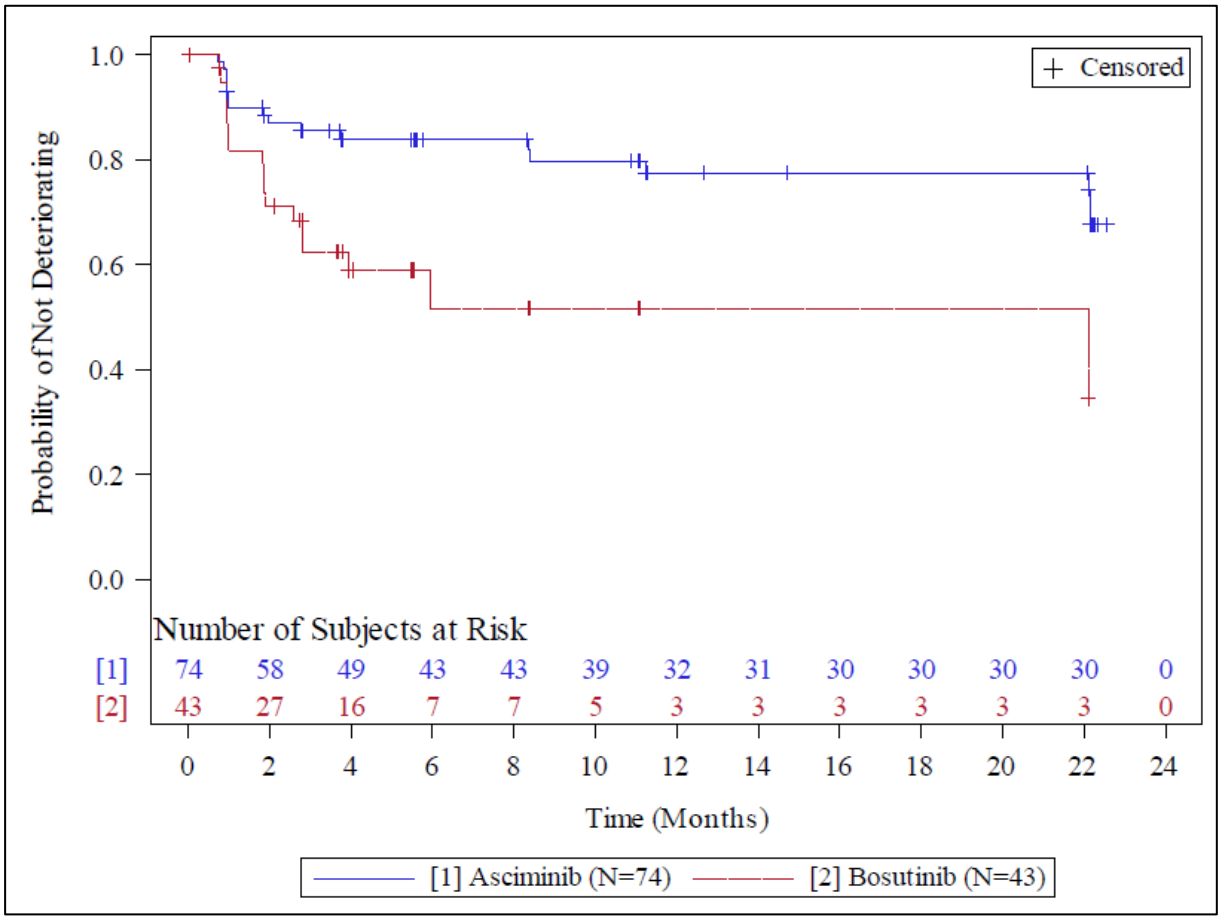

Figure 5: Kaplan-Meier curve for the outcome impact of symptoms on daily functioning (MDASI-CML symptom interference – time to first deterioration [data cut-off 22 March 2023]); sex: female

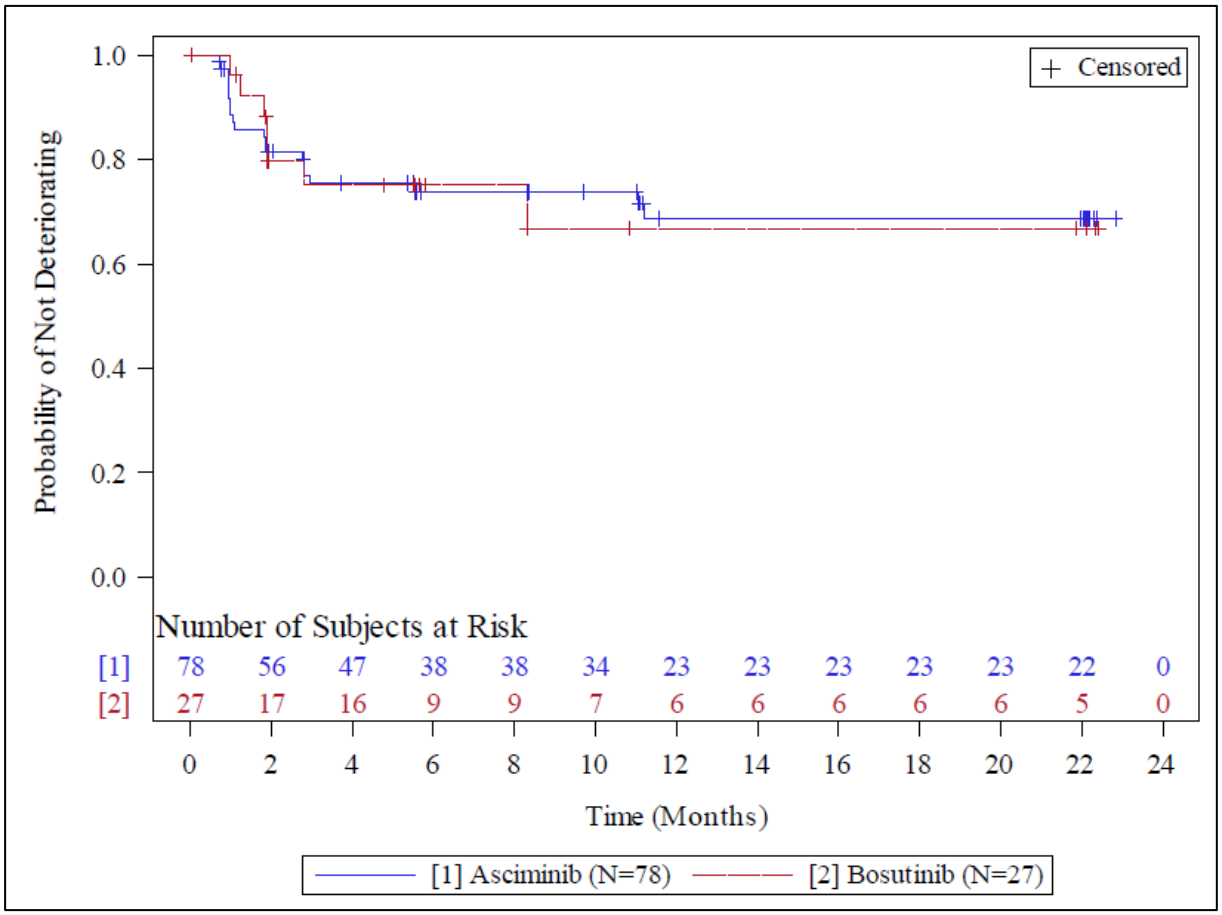

Figure 6: Kaplan-Meier curve for the outcome impact of symptoms on daily functioning (MDASI-CML symptom interference – time to first deterioration [data cut-off 22 March 2023]); sex: male

Symptoms outcome (PGIC)

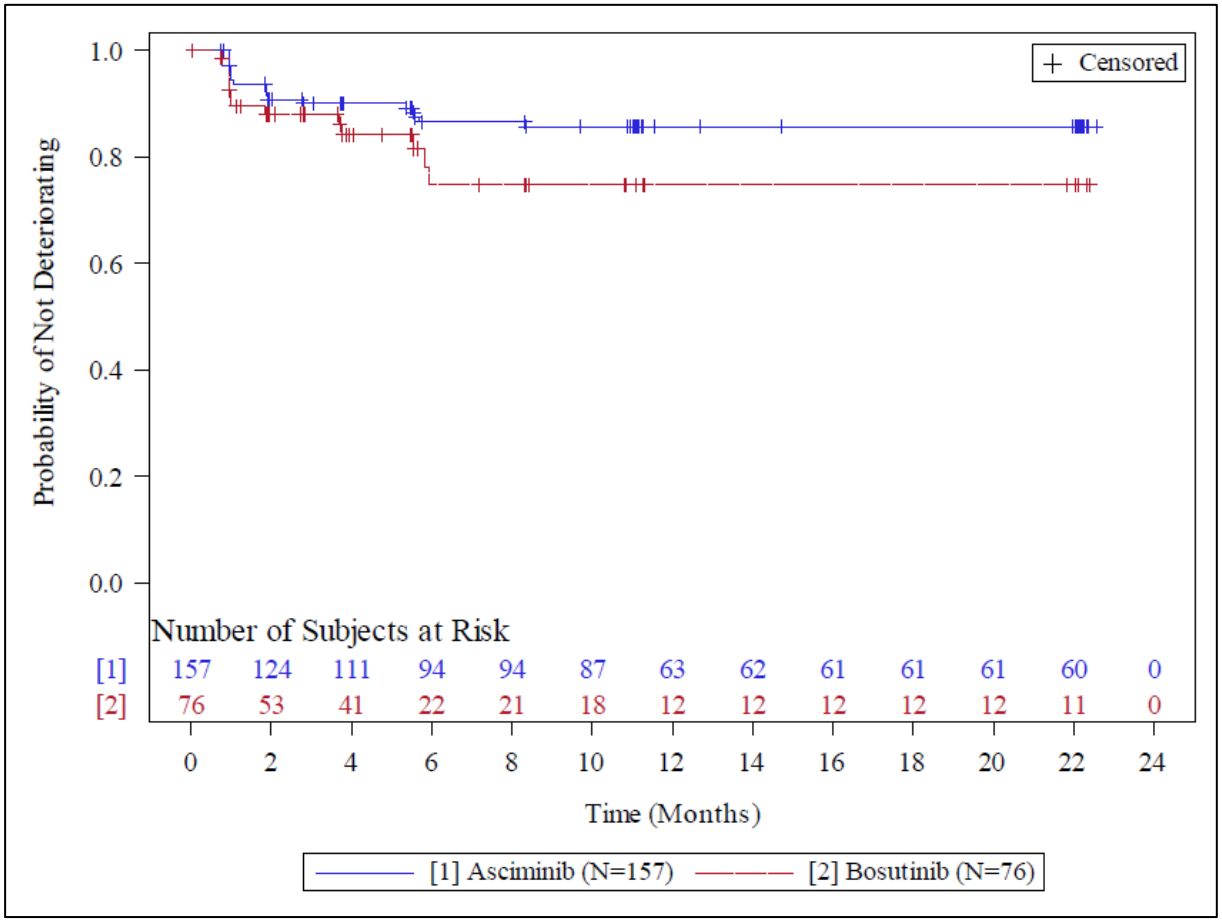

Figure 7: Kaplan-Meier curve for the outcome symptoms (PGIC – time to first deterioration [data cut-off 22 March 2023])

Health status outcome (EQ-5D)

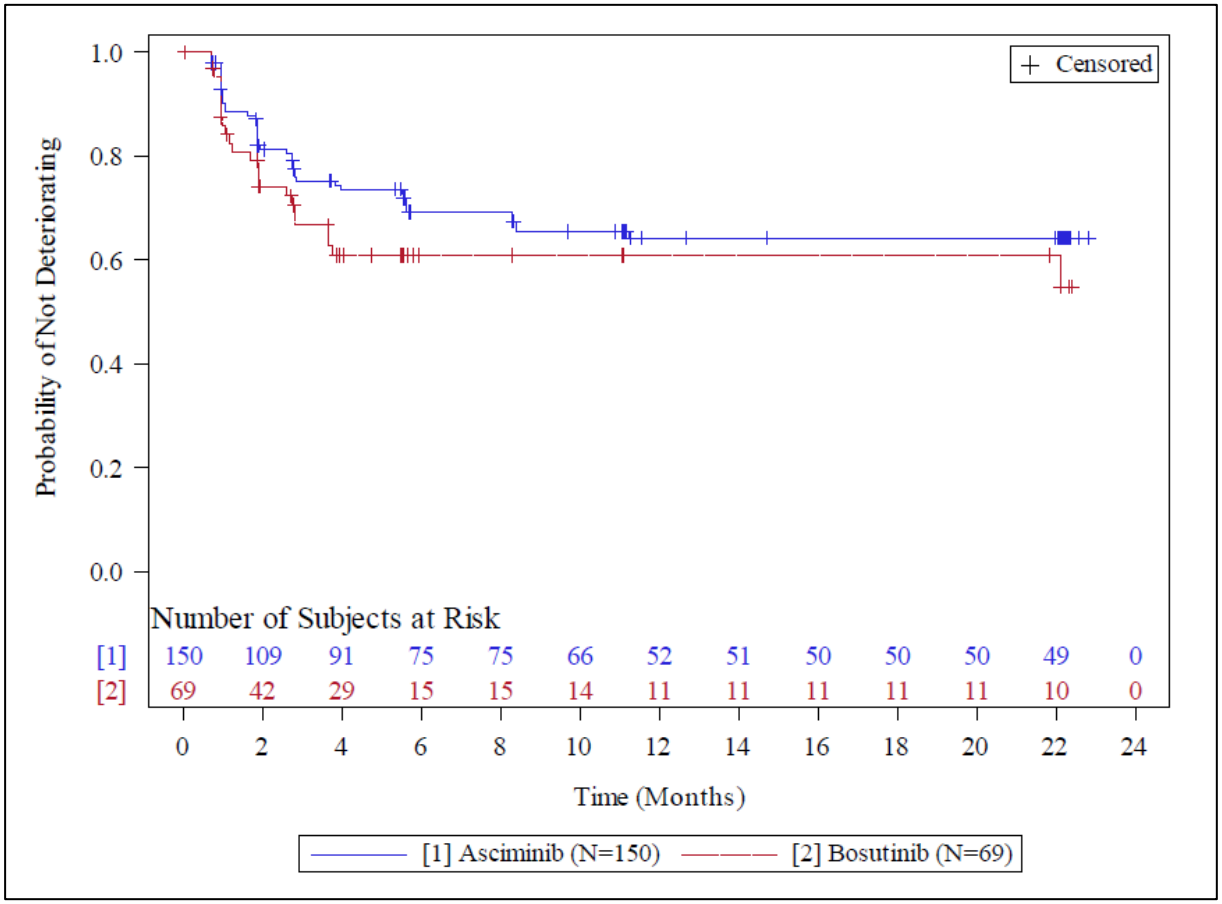

Figure 8: Kaplan-Meier curve for the outcome health status (EQ-5D VAS – time to first deterioration [data cut-off 22 March 2023])

B.3 Side effects

SAEs outcome

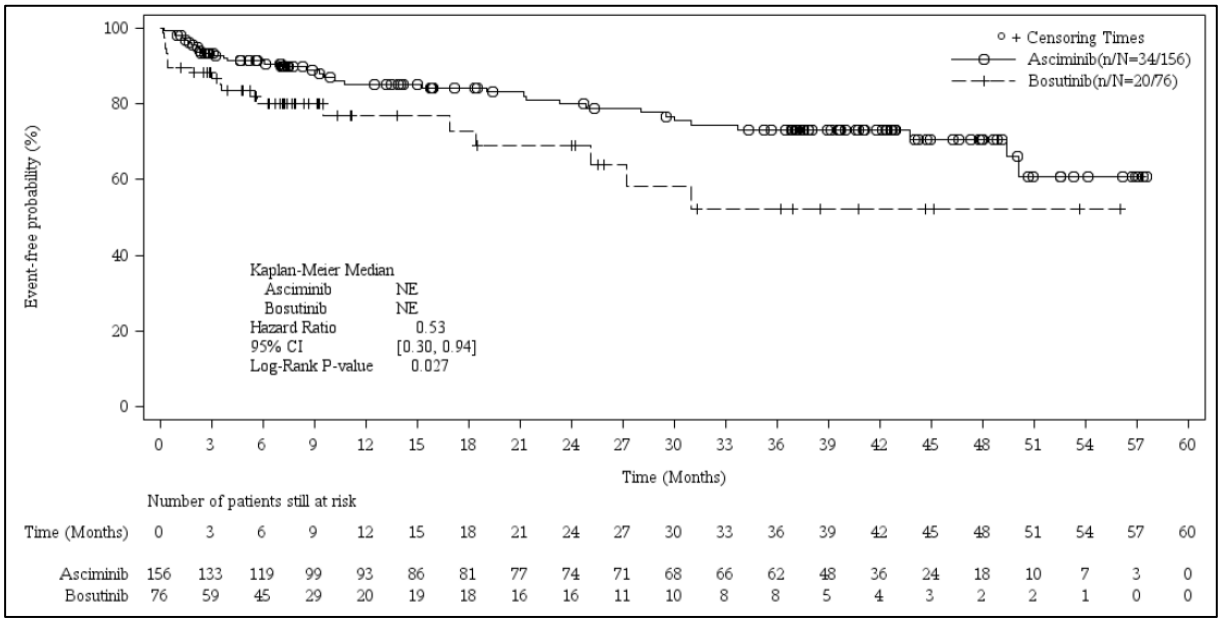

Figure 9: Kaplan-Meier curve for the outcome SAEs (data cut-off 22 March 2023)

Severe AEs outcome (CTCAE grade ≥ 3)

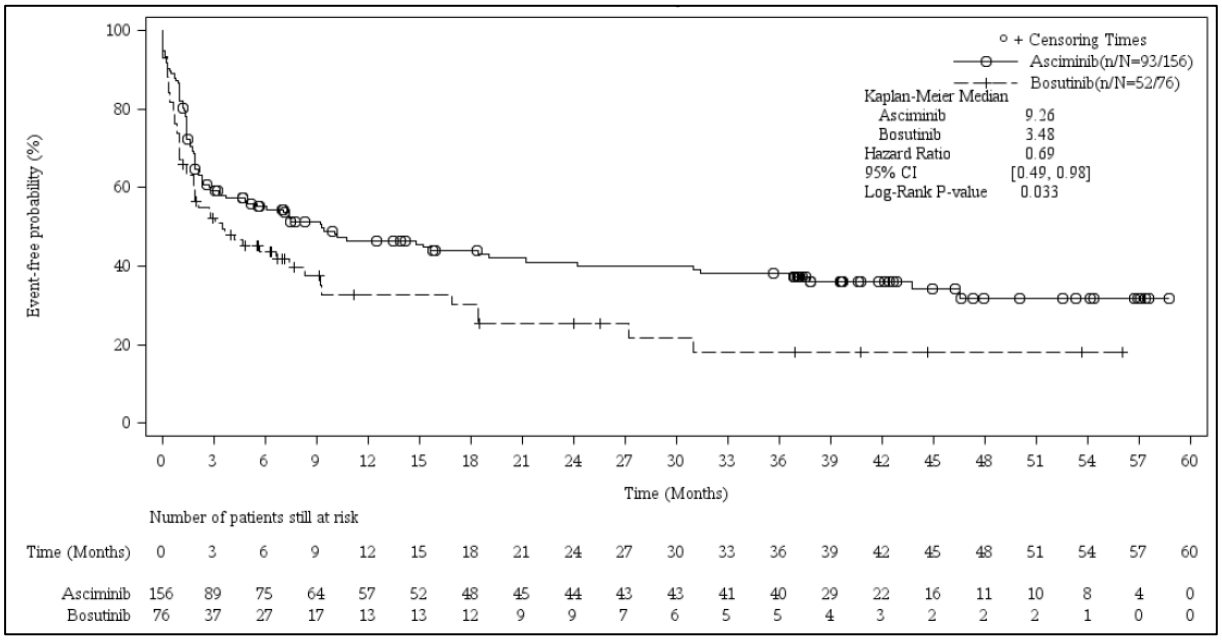

Figure 10: Kaplan-Meier curve for the outcome severe AEs (CTCAE grade ≥ 3 [data cut-off 22 March 2023])

Discontinuation due to AEs outcome

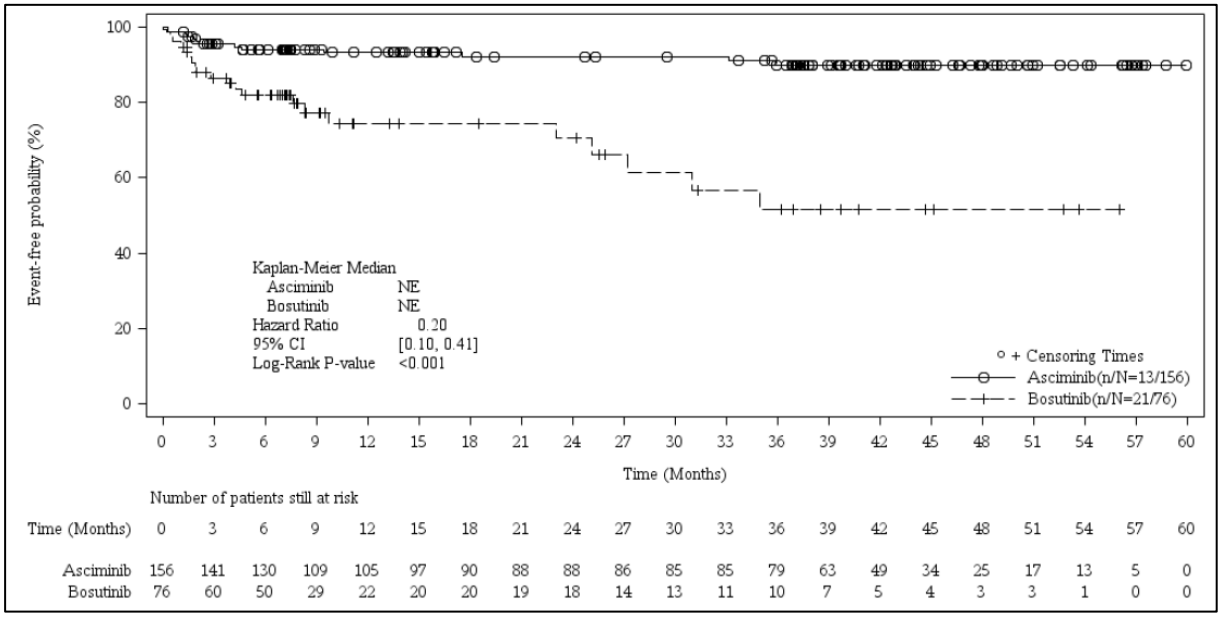

Figure 11: Kaplan-Meier curve for the outcome discontinuation due to AEs (data cut-off 22 March 2023)

Specific AEs

Respiratory, thoracic and mediastinal disorders outcome (SOC, severe AEs)

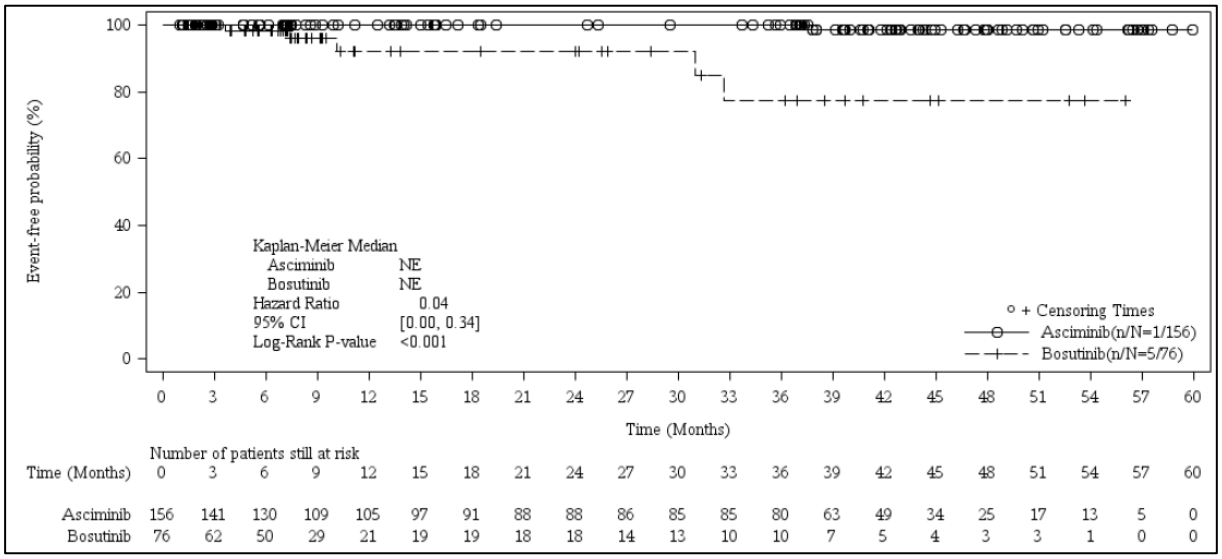

Figure 12: Kaplan-Meier curve for the outcome respiratory, thoracic and mediastinal disorders (SOC, severe AEs [data cut-off 22 March 2023])

Gastrointestinal disorders outcome (SOC, severe AEs)

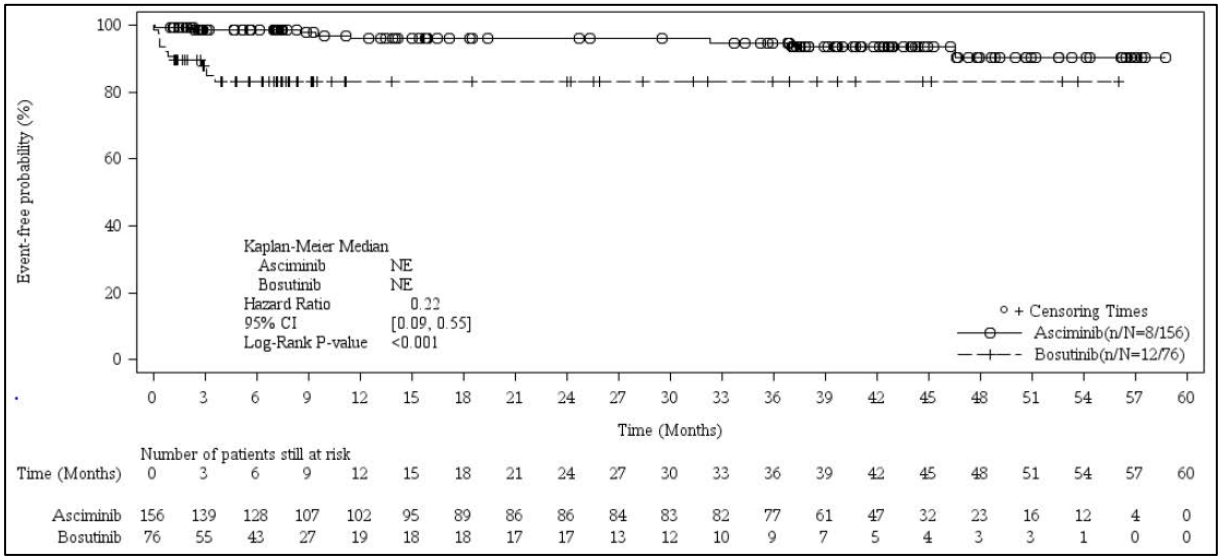

Figure 13: Kaplan-Meier curve for the outcome gastrointestinal disorders (SOC, severe AEs [data cut-off 22 March 2023])

Skin and subcutaneous tissue disorders outcome (SOC, severe AEs)

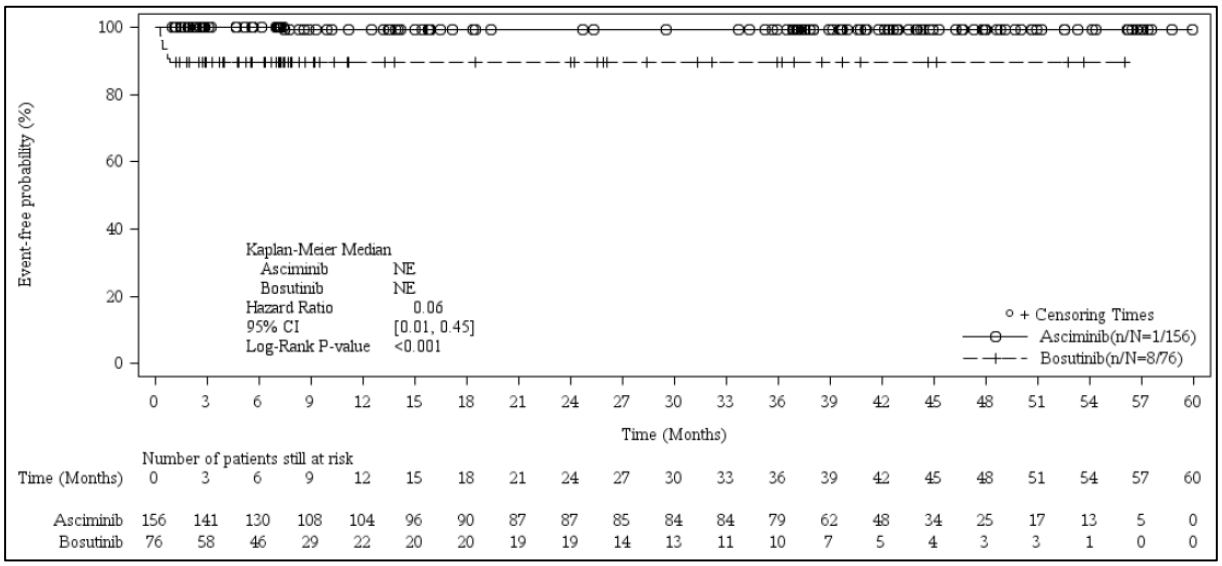

Figure 14: Kaplan-Meier curve for the outcome skin and subcutaneous tissue disorders (SOC, severe AEs [data cut-off 22 March 2023])

Alanine aminotransferase increased outcome (PT, severe AEs)

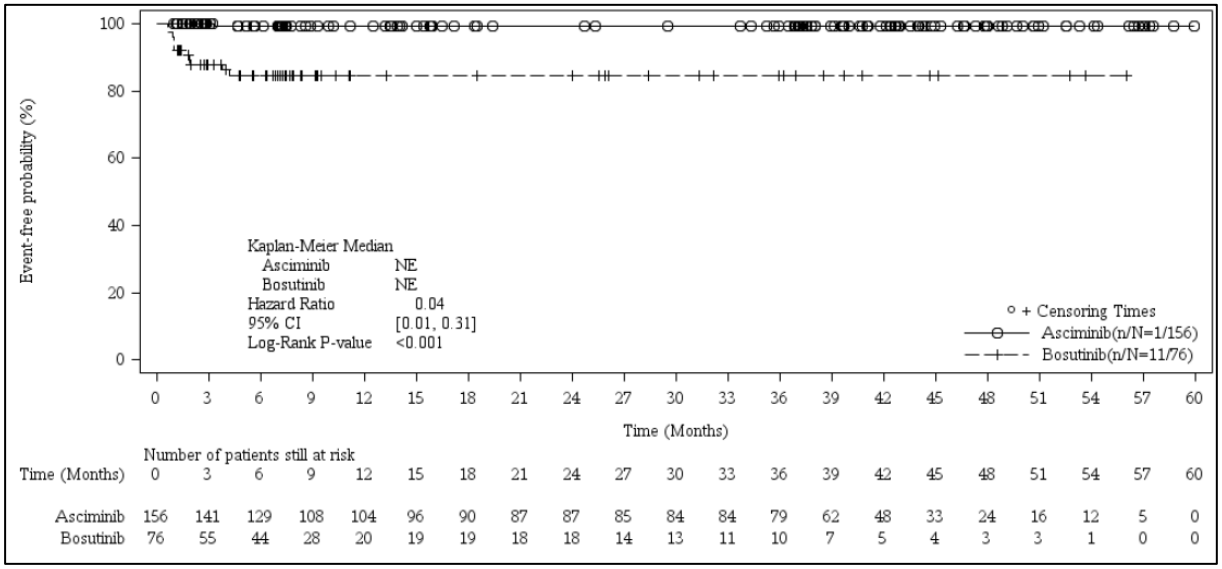

Figure 15: Kaplan-Meier curve for the outcome alanine aminotransferase increased (PT, severe AEs [data cut-off 22 March 2023])

Aspartate aminotransferase increased outcome (PT, severe AEs)

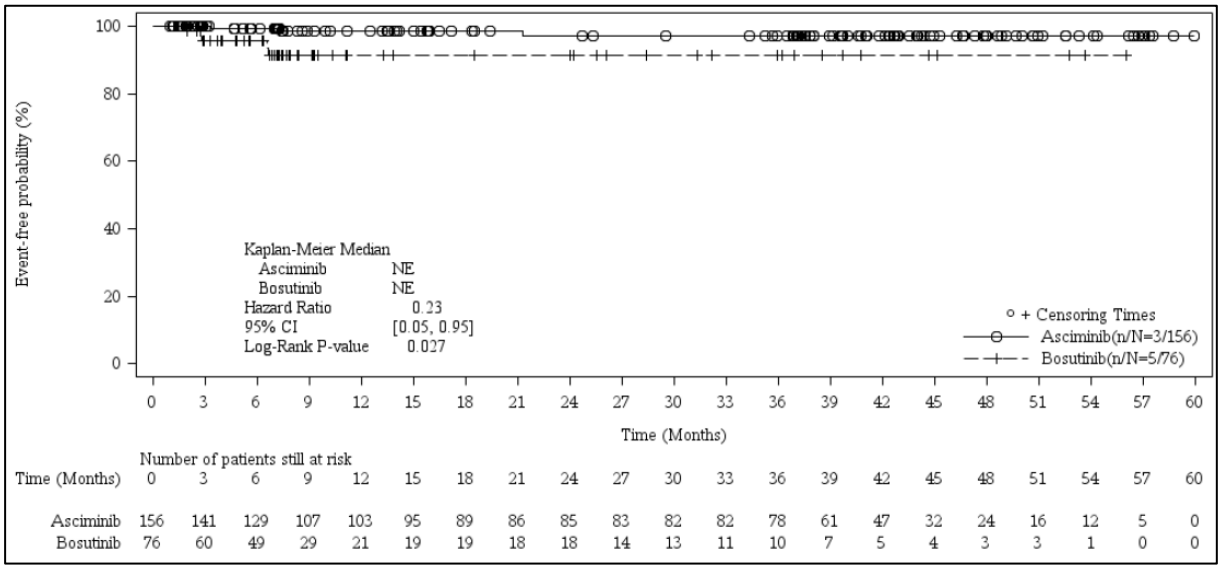

Figure 16: Kaplan-Meier curve for the outcome aspartate aminotransferase increased (PT, severe AEs [data cut-off 22 March 2023])

Thrombocytopenia outcome (PT, severe AEs)

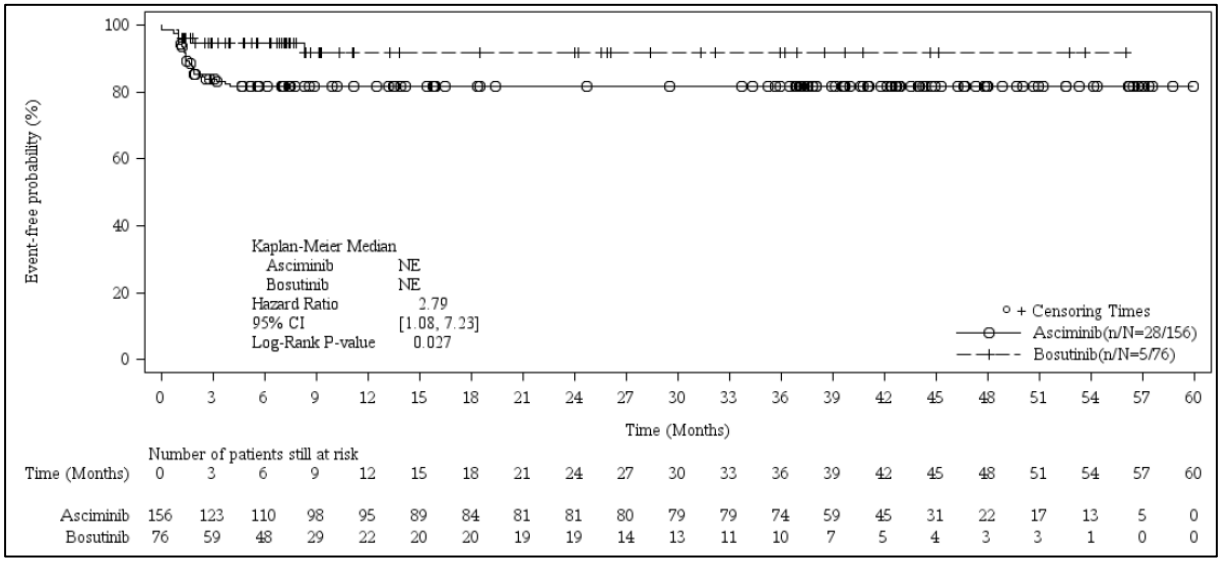

Figure 17: Kaplan-Meier curve for the outcome thrombocytopenia (PT, severe AEs [data cut-off 22 March 2023])

Appendix C Characterization of the study population by country-specific risk based on ESC SCORE2

Table 13: Characterization of the study population by country-specific risk based on ESC SCORE2[a] – RCT, direct comparison: asciminib vs. bosutinib

Study **Availability of risk evaluation** **Risk category** **Recruitment country**	**asciminib** **N = 157**	**bosutinib** **N = 76**
ASCEMBL		
Recruitment country with risk evaluation (ESC SCORE2[a]), n (%)	95 (60.5)	45 (59.2)
Low risk, n (%)		
France	10 (6.4)	7 (9.2)
Israel	2 (1.3)	0 (0)
Netherlands	6 (3.8)	1 (1.3)
Spain	7 (4.5)	4 (5.3)
Switzerland	1 (< 1)	1 (1.3)
Great Britain	11 (7.0)	4 (5.3)
Moderate risk, n (%)		
Germany	11 (7.0)	7 (9.2)
Italy	3 (1.9)	4 (5.3)
High risk, n (%)		
Czech Republic	1 (< 1)	1 (1.3)
Hungary	3 (1.9)	0 (0)
Turkey	9 (5.7)	1 (1.3)
Very high risk, n (%)		
Bulgaria	2 (1.3)	1 (1.3)
Lebanon	3 (1.9)	0 (0)
Romania	3 (1.9)	1 (1.3)
Russia	20 (12.7)	13 (17.1)
Serbia	3 (1.9)	0 (0)
Recruitment country without risk evaluation (ESC SCORE2[a]), n (%)	62 (39.5)	31 (40.8)
Argentina	3 (1.9)	4 (5.3)
Australia	6 (3.8)	1 (1.3)
Brazil	12 (7.6)	7 (9.2)
Canada	3 (1.9)	2 (2.6)
Japan	13 (8.3)	3 (3.9)
Korea	6 (3.8)	5 (6.6)
Mexico	1 (< 1)	0 (0)
Saudi Arabia	5 (3.2)	0 (0)
United States	13 (8.3)	9 (11.8)

a. Country-specific risk evaluation to evaluate individual cardiovascular risk.

ESC: European Society of Cardiology; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SCORE2: Systematic Coronary Risk Evaluation 2