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

Addendum to Project A25-150
(dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

Project: A26-40 Version: 1.0 Status: 30 Apr 2026 DOI: 10.60584/A26-40_en

[1] Translation of the addendum *Asciminib (CML, Erst- und Zweitlinientherapie) – Addendum zum Projekt A25-150 (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 (CML, first-line and second-line treatment) – Addendum to Project A25-150

Commissioning agency

Federal Joint Committee

Commission awarded on

08 April 2026

Internal Project No.

A26-40

https://doi.org/10.60584/A26-40_en

Address of publisher

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Recommended citation

Institute for Quality and Efficiency in Health Care. Asciminib (CML, first-line and second-line treatment); Addendum to Project A25-150 (dossier assessment) [online]. 2026 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A26-40_en.

Keywords

Asciminib, Leukemia – Myelogenous – Chronic – BCR-ABL Positive, Benefit Assessment, NCT04971226, NCT05456191

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Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ELTS	European Treatment and Outcome Study Long-Term Survival
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-CML24	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Myeloid Leukaemia (24 items)
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRT	interactive response technology
Ph+ CML-CP	Philadelphia chromosome-positive chronic myeloid leukaemia in the chronic phase
PRO	patient-reported outcome
PRO-CTCAE	patient-reported outcomes - CTCAE
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
TKI	tyrosine kinase inhibitor

1 Background

On 8 April 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-150 (Asciminib – Benefit assessment according to §35a Social Code Book V) [1].

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

- all analyses submitted subsequently, taking into account patients treated with bosutinib in the comparator arm of the ASC4FIRST study
- a systematic literature search on patients who have undergone exactly one previous treatment, and a comparison of data from studies on newly diagnosed individuals, those who have undergone exactly one previous treatment, and those who have undergone at least two previous treatments

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

In the dossier assessment for Asciminib (A25-150), the G-BA determined two research questions. During the commenting procedure, the company subsequently submitted data for both research question 1 (first-line treatment) and research question 2 (second-line treatment). The data to be assessed for research question 1 are addressed in Section 2.1, and those for research question 2 are addressed in Section 2.2.

2.1 Assessment of the data subsequently for research question 1: adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia in the chronic phase (Ph^+ CML-CP); first-line treatment

The randomized controlled trials (RCTs) ASC4FIRST [4-9] and ASC4START [10-14] were included and the meta-analysis of both studies presented by the company was used for the benefit assessment of asciminib as first-line treatment for adult patients with Ph+ CML-CP (see dossier assessment A25-150 [1]). The ASC4FIRST study compared asciminib with several tyrosine kinase inhibitors (TKIs) (imatinib or nilotinib or dasatinib or bosutinib), whilst ASC4START compared asciminib with nilotinib.

For the benefit assessment, the company presented a subpopulation for the ASC4FIRST study that did not include patients who had been assigned to treatment with bosutinib prior to randomization in Module 4A of its dossier. In doing so, it made reference to the appropriate comparator therapy (ACT) specified by the G-BA in the consultation of 15 February 2024 [15]. Following the submission of the dossier, the G-BA adjusted the ACT and specified imatinib or nilotinib or dasatinib or bosutinib for patients receiving first-line treatment. As only 3.7% of patients in the total population of the ASC4FIRST study were randomized to treatment with bosutinib (4 versus 11 patients in the intervention arm versus the comparator arm), the subpopulation presented by the company, excluding patients allocated to treatment with bosutinib, was used as a sufficient approximation to the total population relevant to the research question for benefit assessment A25-150. As part of the commenting procedure [2], the company submitted analyses for the total population for the ASC4FIRST study and recalculated the meta-analysis accordingly. These analyses were used for the benefit assessment.

Furthermore, the company presented responder analyses for the proportion of patients with a deterioration by ≥ 15 points in Module 4A of its dossier for the disease-specific additional module European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Chronic Myeloid Leukaemia (24 Items) (QLQ-CML24). These were not used in the benefit assessment, as the benefit assessment procedure requires that analyses relating to the response criterion 10 points be presented in the dossier for the validated disease-

specific additional modules of the EORTC QLQ-C30 [16]. The company presented these data as part of the commenting procedure.

The data submitted subsequently by the company regarding the total population of the ASC4FIRST study and the meta-analysis were used for the benefit assessment and assessed below, taking into account the information contained in the dossier.

2.1.1 Study characteristics

A detailed description of ASC4FIRST and ASC4START, including information on study design, characteristics of the intervention and planned duration of follow-up can be found in dossier assessment A25-150 [1].

Dossier assessment A25-150 did not provide any information on the use of bosutinib in ASC4FIRST. The use of bosutinib is therefore described below. In the ASC4FIRST study, bosutinib was administered at a daily dose of 400 mg (orally). The dose could be increased in increments of 100 mg up to a maximum of 600 mg per day. Dose reductions for bosutinib were permitted in accordance with the relevant local marketing authorizations. 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. The approach in the study largely corresponds to the specifications of the SmPC [17].

Information on patient characteristics, the course of the study and subsequent antineoplastic therapies

Dossier assessment A25-150 provides information on patient characteristics, the course of the study (with the exception of data on the EORTC QLQ-CML24) and subsequent antineoplastic therapies for the subpopulation of the ASC4FIRST study presented by the company in Module 4A, and for the ASC4START study. The analyses of the total study population of ASC4FIRST include 4 additional patients in the intervention arm and 11 in the comparator arm (N = 405), compared with the subpopulation presented in Module 4A (N = 390). As the data on the subpopulation presented by company differ only slightly from those for the total population, these tables will not be reproduced here.

The dossier assessment provided no details on the observation period for the patient-reported outcomes recorded using the EORTC QLQ-CML24, as no suitable data were available for this outcome at that time. As suitable analyses are now available, the observation period for these outcomes is set out below for the studies ASC4FIRST and ASC4START. In the ASC4FIRST study, the median follow-up duration for the patient-reported outcomes, assessed using the EORTC QLQ-CML24, was 22.0 [min: 0.0; max: 24.9] months in the intervention arm and thus almost twice as long as in the comparator arm (11.1 months) [Min: 0.0; Max: 24.9]. In the ASC4START study, the median follow-up duration for patient-reported outcomes, as

assessed using the EORTC QLQ-CML24, was 11.1 [min: 0.0; max: 22.6] months in the intervention arm and 11.1 [min: 0.0; max: 26.4] months in the comparator arm.

2.1.2 Results on added benefit

2.1.2.1 Outcomes included

The included outcomes correspond to those in benefit assessment A25-150 [1]:

- Mortality
  - overall survival
- Morbidity
  - progression to blast crisis
  - symptoms, recorded using the EORTC QLQ-C30 and the EORTC QLQ-CML24
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30 and the EORTC QLQ-CML24
- Side effects
  - serious adverse events (SAEs)
  - severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - patient-reported outcomes - CTCAE (PRO-CTCAE)
  - other specific AEs, if any

Notes on selected outcomes

Patient-reported outcomes – dealing with the high proportion of missing values at the time of randomization

As already described in the dossier assessment, a high proportion of patients were not considered in the analysis for the outcomes on symptoms, health status and health-related quality of life due to a lack of baseline values at the time of randomization (see dossier assessment A25-150 [1]). 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. 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. In this situation, 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.

2.1.2.2 Risk of bias

The risk of bias across outcomes and the outcome-specific risk of bias as well as the summarizing assessment of the certainty of conclusions are presented in dossier assessment A25-150 for the subpopulation of the ASC4FIRST study and for the ASC4START study. The data on the risk of bias and the assessment of the certainty of conclusions for the total population of ASC4FIRST do not differ from the data for the subpopulation. Therefore, the tables on the risk of bias will not be re-presented.

For the patient-reported outcomes, recorded using the EORTC QLQ-CML24, the risk of bias was not assessed in dossier assessment A25-150, as no suitable data were available at that time. The risk of bias in the results of these outcomes is assessed below for the studies ASC4FIRST and ASC4START. For each of the results on the outcomes symptoms and health-related quality of life, recorded using the EORTC QLQ-CML24, there is a high risk of bias in line with the assessment for the other patient-reported outcomes. 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 (> 10%) 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 56%) would be too small to allow the results to be used. As described in dossier assessment A25-150 [1] and in the previous section, an added benefit can nevertheless be derived under certain conditions in the present data situation. 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. Thus, there were differences in response rates between the study arms as early as at Week 24. The response rates for the EORTC QLQ-CML24 were 70% versus 56% (ASC4FIRST) and 74% versus 66% (ASC4START), respectively.

2.1.2.3 Results

Table 1 and Table 2 summarize the results of the comparison of asciminib with the ACT for first-line treatment of adults with Ph^+ CML-CP. Where necessary, data from the company's dossier as well as the data subsequently submitted are supplemented by the Institute's calculation.

A comparison of the results of the main and sensitivity analyses for the patient-reported outcomes on symptoms and health-related quality of life can be found in Appendix A.2.

The Kaplan-Meier curves for all outcomes in ASC4FIRST, and the Kaplan-Meier curves for outcomes recorded with the EORTC QLQ-CML24 in the ASC4START study are presented in Appendix A.1. Kaplan-Meier curves for further outcomes of the ASC4START study used in this addendum can be found in dossier assessment A25-150 [1]. The forest plots for the meta-analyses calculated by the Institute on the outcomes in the side effects category are presented in Appendix A.2.

A list of common AEs can be found in Appendix A.4 for the total population of the ASC4FIRST study, and in dossier assessment A25-150 for ASC4START [1].

Table 1: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: asciminib versus TKI[a] (multipage table)

Outcome category outcome study	Asciminib Nb	Asciminib median time to event in months [95% CI] patients with event n (%)	TKI[a] Nb	TKI[a] 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	201	NA 2 (1.0)	204	NA 4 (2.0)	0.49 [0.09; 2.67]; 0.398
ASC4START	284	NA 2 (0.7)	284	NA 1 (0.4)	1.98 [0.18; 21.89]; 0.568
Total					0.79 [0.21; 2.93]; 0.719[d]
Morbidity					
Progression to blast crisis					
ASC4FIRST	201	NA 1 (0.5)	204	NA 2 (1.0)	0.44 [0.04; 4.92]; 0.494
ASC4START	284	NA 3 (1.1)	284	NA 0 (0)	6.99 [0.23; 214.0]; 0.083
Total					1.89 [0.35; 10.37]; 0.455[d]
Symptoms (EORTC QLQ-C30 – time to first deterioration[e])					
Fatigue					
ASC4FIRST	201	22.1 [5.5; NC] 52 (25.9)	204	2.8 [1.8; 11.1] 65 (31.9)	0.65 [0.45; 0.95]; 0.021
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					0.70 [0.54; 0.91]; 0.012[d]
Nausea and vomiting					
ASC4FIRST	201	NA 24 (11.9)	204	22.1 [10.9; NC] 46 (22.5)	0.41 [0.25; 0.68]; < 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					0.58 [0.42; 0.80]; < 0.001[d]
Pain					
ASC4FIRST	201	NA [22.1; NC] 38 (18.9)	204	5.6 [2.7; NC] 59 (28.9)	0.49 [0.32; 0.74]; < 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 = 0.025

Table 1: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: asciminib versus TKI[a] (multipage table)

Outcome category outcome study	Asciminib Nb	Asciminib median time to event in months [95% CI] patients with event n (%)	TKI[a] Nb	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	201	22.2 [22.2; NC] 26 (12.9)	204	NA [22.1; NC] 37 (18.1)	0.58 [0.34; 0.97]; 0.033
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					0.74 [0.54; 1.01]; 0.067[d]
Insomnia					
ASC4FIRST	201	NA 33 (16.4)	204	NA [11.1; NC] 43 (21.1)	0.61 [0.39; 0.96]; 0.072
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	201	NA [22.2; NC] 20 (10.0)	204	NA [22.1; NC] 38 (18.6)	0.36 [0.21; 0.64]; < 0.001
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				Heterogeneity:	p-value = 0.045
Constipation					
ASC4FIRST	201	NA 36 (17.9)	204	NA [11.1; NC] 38 (18.6)	0.76 [0.47; 1.22]; 0.396
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					0.68 [0.50; 0.92]; 0.024[d]
Diarrhoea					
ASC4FIRST	201	NA 29 (14.4)	204	22.0 [5.6; NC] 49 (24.0)	0.44 [0.27; 0.71]; < 0.001
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					0.57 [0.42; 0.79]; < 0.001[d]

Table 1: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: asciminib versus TKI[a] (multipage table)

Outcome category outcome study	Asciminib Nb	Asciminib median time to event in months [95% CI] patients with event n (%)	TKI[a] Nb	TKI[a] median time to event in months [95% CI] patients with event n (%)	Asciminib vs. TKI[a] HR [95% CI]; p-value[c]
Symptoms (EORTC QLQ-CML24 – time to first deterioration[e])					
ASC4FIRST	201	NA 24 (11.9)	204	11.0 [5.5; NA] 53 (26.0)	0.34 [0.21; 0.56]; < 0.001
ASC4START	284	NA [22.1; NC] 27 (9.5)	284	NA 44 (15.5)	0.55 [0.34; 0.89]; 0.023
Total					0.44 [0.31; 0.61]; < 0.001[d]
Health status (EQ-5D VAS – time to first deterioration)					
ASC4FIRST	201	NA [22.2; NC] 20 (10.0)	204	NA [22.1; NC] 34 (16.7)	0.47 [0.27; 0.83]; 0.007
ASC4START			Outcome not recorded		
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration[g]					
Global health status					
ASC4FIRST	201	22.2 [22.0; NC] 40 (19.9)	204	22.0 [5.4; NC] 53 (26.0)	0.67 [0.44; 1.02]; 0.029
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					0.79 [0.60; 1.04]; 0.058[d]
Physical functioning					
ASC4FIRST	201	NA 25 (12.4)	204	22.1 [22.1; NC] 41 (20.1)	0.50 [0.30; 0.83]; 0.006
ASC4START	284	NA [11.2; NC] 49 (17.3)	284	NA 50 (17.6)	0.91 [0.61; 1.35]; 0.616
Total					0.72 [0.53; 0.98]; 0.036[d]
Role functioning					
ASC4FIRST	201	NA [22.2; NC] 35 (17.4)	204	NA [6.7; NC] 45 (22.1)	0.57 [0.36; 0.90]; 0.018
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 = 0.029

Table 1: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: asciminib versus TKI[a] (multipage table)

Outcome category outcome study	Asciminib Nb	Asciminib median time to event in months [95% CI] patients with event n (%)	TKI[a] Nb	TKI[a] median time to event in months [95% CI] patients with event n (%)	Asciminib vs. TKI[a] HR [95% CI]; p-value[c]
Emotional functioning					
ASC4FIRST	201	NA 29 (14.4)	204	NA [22.1; NC] 38 (18.6)	0.71 [0.43; 1.15]; 0.149
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					0.69 [0.51; 0.94]; 0.035[d]
Cognitive functioning					
ASC4FIRST	201	NA [22.1; NC] 40 (20.9)	204	11.1 [10.9; 22.1] 54 (26.5)	0.75 [0.49; 1.13]; 0.151
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 [0.66; 1.09]; 0.205[d]
Social functioning					
ASC4FIRST	201	NA 35 (17.4)	204	22.1 [2.9; NC] 50 (24.5)	0.62 [0.40; 0.97]; 0.027
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					0.71 [0.54; 0.94]; 0.017[d]
EORTC QLQ-CML24 – time to first deterioration[h]					
Effect on worries/mood					
ASC4FIRST	201	22.2 [22.2; NC] 28 (13.9)	204	NA [22.0; NC] 36 (17.6)	0.64 [0.38; 1.06]; 0.087
ASC4START	284	NA 45 (15.8)	284	NA 44 (15.5)	0.92 [0.60; 1.39]; 0.904
Total					0.79 [0.57; 1.09]; 0.235[d]
Effects on everyday life					
ASC4FIRST	201	NA [11.1; NC] 41 (20.4)	204	5.6 [2.8; NA] 56 (27.5)	0.64 [0.43; 0.97]; 0.021
ASC4START	284	NA 42 (14.8)	284	NA [11.3; NC] 54 (19.0)	0.67 [0.44; 1.00]; 0.106
Total					0.65 [0.49; 0.87]; 0.006[d]

Table 1: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: asciminib versus TKI[a] (multipage table)

Outcome category outcome study	Asciminib Nb	Asciminib median time to event in months [95% CI] patients with event n (%)	TKI[a] Nb	TKI[a] median time to event in months [95% CI] patients with event n (%)	Asciminib vs. TKI[a] HR [95% CI]; p-value[c]
Problems with body image					
ASC4FIRST	201	22.2 [22.2; NC] 33 (16.4)	204	NA [11.1; NC] 42 (20.6)	0.65 [0.41; 1.04]; 0.045
ASC4START	284	NA [11.1; NC] 62 (21.8)	284	22.1 [11.1; NC] 57 (20.1)	1.03 [0.72; 1.48]; 0.874
Total					0.87 [0.65; 1.15]; 0.267[d]
Satisfaction with care/information					
ASC4FIRST	201	11.0 [2.8; NC] 54 (26.9)	204	NA [11.1; NC] 38 (18.6)	1.06 [0.68; 1.65]; 0.079
ASC4START	284	11.1 [8.3; 22.1] 76 (26.8)	284	NA [5.7; NC] 63 (22.2)	1.07 [0.76; 1.49]; 0.505
Total					1.08 [0.83; 1.41]; 0.105[d]
Satisfaction with social life					
ASC4FIRST	201	NA [21.9; NC] 41 (20.4)	204	25.7 [22.1; NC] 36 (17.6)	1.10 [0.68; 1.76]; 0.717
ASC4START	284	11.1 [5.6; NC] 79 (27.8)	284	11.3 [3.0; NC] 70 (24.6)	1.10 [0.80; 1.52]; 0.599
Total					1.10 [0.84; 1.44]; 0.523[d]

Table 1: 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]
	Nb	median time to event in months [95% CI] patients with event n (%)	Nb	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[c]

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, 112 (55.7%) in the intervention arm vs. 115 (56.4%) in the control arm (for the EORTC QLQ-C30), 109 (54.2%) in the intervention arm vs. 110 (53.9%) in the control arm (EORTC QLQ-CML24), and 108 (53,7%) in the intervention arm vs. 109 (53.4%) in the control arm (EQ-5D VAS) had a baseline value at randomization. In ASC4START, 168 (59.2%) in the intervention arm versus 165 (58.1%) in the control arm (for the EORTC QLQ-C30) and 161 (56.7%) in the intervention arm vs. 157 (55.3%) in the control arm (for the EORTC QLQ-CML24) 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. A score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).

g. A score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).

h. A score increase by ≥ 10 points from baseline for the scales effect on worries/mood, effects on everyday life and problems with body image, as well as a score decrease by ≥ 10 points from baseline for the scales satisfaction with care/information and satisfaction with social life, is considered a clinically relevant deterioration (scale range: 0 to 100).

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 2: 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	200	191 (95.5)	201	197 (98.0)	–
ASC4START	284	249 (87.7)	282	257 (91.1)	–
SAEs					
ASC4FIRST	200	29 (14.5)	201	41 (20.4)	0.71 [0.46; 1.10]; 0.127
ASC4START	284	47 (16.5)	282	42 (14.9)	1.11 [0.76; 1.63]; 0.683
Total[c]					0.91 [0.69; 1.22]; 0.536
Severe AEs[d]					
ASC4FIRST	200	89 (44.5)	201	110 (54.7)	0.81 [0.67; 0.99]; 0.044
ASC4START	284	102 (35.9)	282	114 (40.4)	0.89 [0.72; 1.10]; 0.289
Total[c]					0.85 [0.74; 0.98]; 0.030
Discontinuation due to AEs					
ASC4FIRST	200	10 (5.0)	201	26 (12.9)	0.39 [0.19; 0.78]; 0.006
ASC4START	284	23 (8.1)	282	44 (15.6)	0.52 [0.32; 0.84]; 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	200	14 (7.0)	201	7 (3.5)	2.01 [0.83; 4.87]; 0.127
ASC4START	284	17 (6.0)	282	6 (2.1)	2.81 [1.13; 7.03]; 0.021
Total[c]					2.38 [1.26; 4.50]; 0.007

a. ASC4FIRST study: with a choice of imatinib, nilotinib, dasatinib or bosutinib prior to randomization; ASC4START study: nilotinib.
b. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [18]).
c. Institute's calculation, meta-analysis with fixed effect according to Mantel and Haenszel.
d. Operationalized as CTCAE grade ≥ 3.
e. For justification see dossier assessment A25-150 [1].

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 determined 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 the sections on the included outcomes and on the risk of bias in dossier assessment A25-150 [1]).

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, in the main analysis, 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.

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 6). This results in a hint of added benefit of asciminib in comparison with the ACT.

Pain and appetite loss

For the outcomes pain and appetite loss, 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 main 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.

Diarrhoea

For the outcome diarrhoea, 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, the company's sensitivity analysis with multiple imputation showed no statistically significant difference between the treatment arms for patients without a baseline value at the time of randomization (see Table 6). 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)

For the outcome symptoms, recorded with the EORTC QLQ-CML24, 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 6). This results in a hint of added benefit of asciminib in comparison with the ACT.

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 VAS; however, the sensitivity analysis with multiple imputation presented by the company showed no statistically significant difference for patients without baseline value at the time of randomization (see Table 7). 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, role functioning and cognitive functioning

For the outcomes global health status, role functioning and cognitive functioning, recorded with the EORTC QLQ-C30, the meta-analysis of the studies ASC4FIRST and ASC4START show, even in the main analysis, that there was 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.

Physical functioning and emotional functioning

For the outcomes physical functioning and 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 presented by the company for patients without a baseline value at the time of randomization (see Table 6). 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 6). This results in a hint of added benefit of asciminib in comparison with the ACT.

EORTC QLQ-CML24

Effects on worries/mood, problems with the body image, satisfaction with care/information, and satisfaction with social life

For the outcomes effects on worries/mood, problems with the body image, satisfaction with care/information, and satisfaction with social life, recorded with the EORTC QLQ-CML24 – 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. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

Effects on everyday life

For the outcome effects on everyday life, recorded with the EORTC QLQ-CML24, 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 6). This results in a hint of added benefit of asciminib in comparison with the ACT.

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 ASC4START showed a statistically significant difference in favour of asciminib. There is proof of lesser harm from asciminib in comparison with the ACT.

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 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.

2.1.2.4 Subgroups and other effect modifiers

For a description of the potential effect modifiers considered and the underlying methods, please see the explanations in dossier assessment A25-150 [1].

For the outcomes for which suitable data were available, no relevant effect modification by the characteristics age, sex or the European Treatment and Outcome Study Long-Term Survival (ELTS) score according to the Interactive Response Technology (IRT), was identified in accordance with the methods described in dossier assessment A25-150.

2.1.3 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 [19].

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.

2.1.3.1 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 2.1.2 (Table 3).

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.

EORTC QLQ-C30 (fatigue, nausea and vomiting, insomnia and constipation) and EORTC QLQ-CML24 (symptoms)

For the outcomes fatigue, nausea and vomiting, insomnia, and constipation, recorded with the EORTC QLQ-C30 as well as for the outcomes on symptoms, recorded with the EORTC QLQ-CML24, there is insufficient information 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 4A and in its comments, the company presents additional analyses on discontinuations 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 3: Extent of added benefit at outcome level: asciminib versus ACT (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: 0.79 [0.21; 2.93]; p = 0.719	Lesser benefit not proven/added benefit not proven
Morbidity		
Progression to blast crisis	Median: NA vs. NA HR: 1.89 [0.35; 10.37]; p = 0.455	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: 0.70 [0.54; 0.91]; p = 0.012	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: 0.58 [0.42; 0.80]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"[f]
Pain	Heterogeneous results[g]	Lesser benefit not proven/added benefit not proven
Dyspnoea	Median: 22.1-22.2 vs. NA HR: 0.74 [0.54; 1.01]; p = 0.067	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	Heterogeneous results[g]	Lesser benefit not proven/added benefit not proven
Constipation	Median: NA or 22.1 vs. NA HR: 0.68 [0.50; 0.92]; p = 0.024	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: 0.57 [0.42; 0.79]; p < 0.001	Lesser benefit not proven/added benefit not proven[h]

Table 3: Extent of added benefit at outcome level: asciminib versus ACT (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]**
Symptoms (EORTC QLQ-CML24 – time to first deterioration)[d]	Median: NA vs 11.0 or NA HR: 0.44 [0.31; 0.61]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit, extent: considerable
Health status (EQ-5D VAS – time to first deterioration[d, i])	Median: NA vs. NA HR: 0.47 [0.27; 0.83]; p = 0.007	Lesser benefit not proven/added benefit not proven[h]
Health-related quality of life		
EORTC QLQ-C30 – time to first deterioration[d]		
Global health status	Median: 22.1-22.2 vs 22.0 or NA HR: 0.79 [0.60; 1.04]; p = 0.058	Lesser benefit not proven/added benefit not proven
Physical functioning	Median: NA vs 22.1 or NA HR: 0.72 [0.53; 0.98]; p = 0.036	Lesser benefit not proven/added benefit not provenh
Role functioning	Heterogeneous results[g]	Lesser benefit not proven/added benefit not proven
Emotional functioning	Median: NA vs. NA HR: 0.69 [0.51; 0.94]; p = 0.035	Lesser benefit not proven/added benefit not proven[h]
Cognitive functioning	Median: NA or 11.1 vs. 11.1 HR: 0.85 [0.66; 1.09]; p = 0.205	Lesser benefit not proven/added benefit not proven
Social functioning	Median: NA or 22.1 vs. 22.1 or NA HR: 0.71 [0.54; 0.94]; p = 0.017 probability: hint	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"[f]
EORTC QLQ-CML24 – time to first deterioration)[d]		
Effect on worries/mood	Median: 22.2 or NA vs. NA HR: 0.79 [0.57; 1.09]; p = 0.235	Lesser benefit not proven/added benefit not proven
Effects on everyday life	Median: NA vs 5.6 or NA HR: 0.65 [0.49; 0.87]; p = 0.006 probability: hint	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"[f]
Problems with body image	Median: 22.2 or NA vs. NA or 22.1 HR: 0.87 [0.65; 1.15]; p = 0.267	Lesser benefit not proven/added benefit not proven

Table 3: Extent of added benefit at outcome level: asciminib versus ACT (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]
Satisfaction with care/information	Median: 11.0-11.1 vs. NA HR: 1.08 [0.83; 1.41]; p = 0.105	Lesser benefit not proven/added benefit not proven
Satisfaction with social life	Median: NA or 11.1 vs. 11.3-25.7 HR: 1.10 [0.84; 1.44]; p = 0.523	Lesser benefit not proven/added benefit not proven
Side effects		
SAEs	14.5 %–16.5 % vs. 14.9 %–20.4 % RR: 0.91 [0.69; 1.22]; p = 0.536	Greater/lesser harm not proven
Severe AEs	35.9 %–44.5 % vs. 40.4 %–54.7 % RR: 0.85 [0.74; 0.98]; p = 0.030 probability: "proof"	Outcome category: serious/severe side effects $0.9 \leq CI_u < 1.0$ lesser harm, extent: minor
Discontinuation due to AEs	5.0 %–8.1 % vs. 12.9 %–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	Greater/lesser harm not proven
Vascular disorders (severe AEs)	6.0 %–7.0 % vs. 2.1 %–3.5 % RR: 2.38 [1.26; 4.50]; RR: 0.42 [0.22; 0.79][j] p = 0.007 probability: "proof"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.9$ greater harm, extent: considerable

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 and relevant effects 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. Quantification is not possible, as the extent varies between the main analysis and the sensitivity analyses (Table 6).
g. No common effect estimation and no conclusive effects can be provided due to heterogeneous data.
h. At least one sensitivity analysis shows no statistically significant difference between the treatment arms (Table 6 and Table 7).
i. Recorded only in the ASC4FIRST study.
j. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

Table 3: Extent of added benefit at outcome level: asciminib versus ACT (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]
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		

2.1.3.2 Overall conclusion on added benefit

Table 4 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 4: 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: “non quantifiable” ▪ symptoms: hint of an added benefit – extent: “considerable”	–
Health-related quality of life ▪ social functioning: hint of added benefit – extent: “non quantifiable” ▪ effects on everyday life: hint of added benefit – extent: “non quantifiable”	–
Serious/severe side effects ▪ severe AEs: proof of lesser harm – extent: "minor" ▪ 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 are available for the outcome PRO-CTCAE.	
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; PRO-CTCAE: Patient-reported Outcome – CTCAE	

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

On the side of the positive effects, there is a hint of added benefit with non-quantifiable extent in the category morbidity for nausea and vomiting, and for the outcome symptoms there is a hint of added benefit with considerable extent.

In the category health-related quality of life, there is a hint of added benefit with non-quantifiable extent for both the outcome social functioning and the outcome effects on everyday life.

In the side effects category, there is a positive effect in the severe AEs, with proof of lesser harm, with the extent minor, and for discontinuation 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 an indication of minor added benefit of asciminib over the ACT for patients with Ph^+ CML-CP.

2.2 Assessment of the data subsequently submitted for research question 2: adult patients with Ph^+ CML-CP; first-line treatment

Concurring with the company, no relevant RCT was identified in the dossier assessment for research question 2 (second line). Therefore, the company expanded its information retrieval and identified the ASCEMBL study [20], which compared asciminib with bosutinib and included adults 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.

Dossier assessment A25-150 [1] described that the data submitted by the company were not suitable for deriving conclusions on the added benefit for research question 2. This is chiefly due to the fact that the company did not conduct an adequate 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. Moreover, the company did not perform any adequate analysis or comparison of data relating to the baseline population (more than two prior treatments) and the target population (second-line treatment).

As part of the commenting procedure, the company addressed some of the mentioned points of criticism. In its comments, the company thus presents a search for further studies with asciminib for patients with Ph^+ CML-CP who have received exactly one prior treatment, in

which it identifies the single-arm study ASC2ESCALATE [21], to which it has already referred to selectively in Module 4 A. However, the company has still not conducted a search for further studies with the ACT. In its comments, the company presents a comparison of data from studies on newly diagnosed patients (first line, ASC4FIRST and ASC4START), patients with exactly one prior treatment (second line, ASC2ESCALATE) and patients with at least two prior treatments (ASCEMBL). This comparison relates to data on patient characteristics, the duration of exposure to asciminib, and the results of selected outcomes.

The data presented by the company in Module 4A in connection with the data subsequently submitted in the commenting procedure are still insufficient to draw conclusions regarding the added benefit of asciminib over individualized treatment choosing from nilotinib, dasatinib, bosutinib and ponatinib for research question 2. However, it did not conduct an information retrieval to identify all potentially relevant studies on the ACT in the target population which support the transfer of the results. Consequently, there is no analysis of the information on the basis of which the company assesses the course of the disease under the ACT. It was also pointed out in the dossier assessment that it is clear from the consultation held on 15 February 2024 [15] 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 in Module 4A, nor does it present any data that would refute the G-BA's assessment in its dossier. In its comments, it refers to the compared data and states that the patient characteristics in the asciminib studies presented are very similar across the treatment lines. However, the data presented by the company do not allow an adequate assessment of the comparability of patient characteristics across the various lines of treatment, as they do not include any further details on clinical characteristics apart from information on the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) and any extramedullary involvement.

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

2.2.1 Results on added benefit L

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 versus the ACT based on the information provided in the dossier and in the comments. There is no hint of an added benefit of asciminib in comparison with the ACT; an added benefit is therefore not proven.

2.2.2 Probability and extent of added benefit

In its dossier and the commenting procedure, 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.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit of asciminib set out in dossier assessment A25-150 for research question 1: instead of a hint of minor added benefit, an indication of minor added benefit of asciminib over the ACT was derived from the data subsequently submitted by the company.

For research question 2, there is no change from dossier assessment A25-150.

The following Table 5 shows the result of the benefit assessment of asciminib, taking into account dossier assessment A25-150 and this addendum.

Table 5: 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	Indication 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; GBA-: Federal Joint Committee; TKI: tyrosine kinase inhibitor

The G-BA decides on the added benefit.

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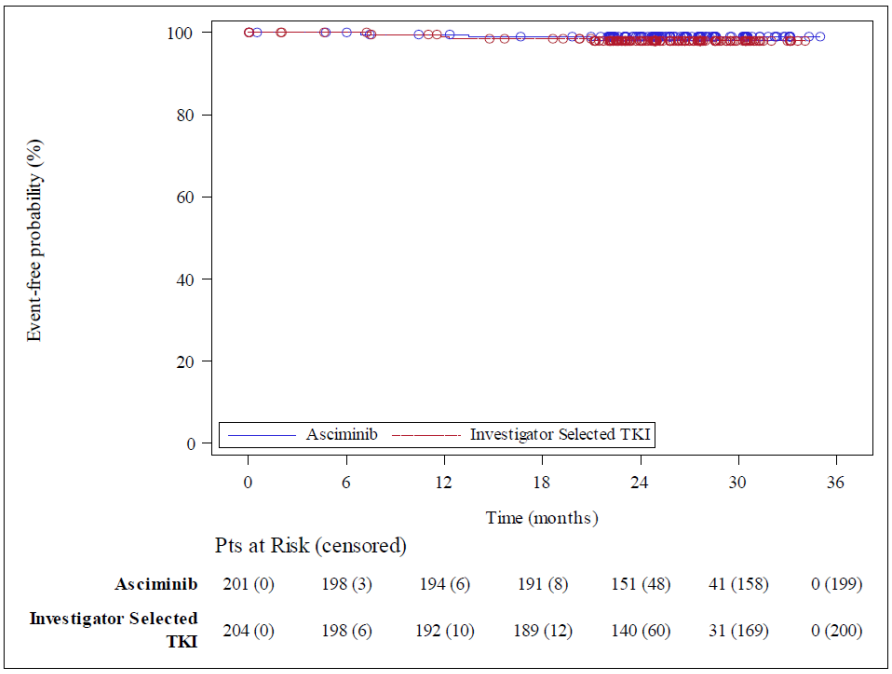
A.1 Kaplan-Meier curves

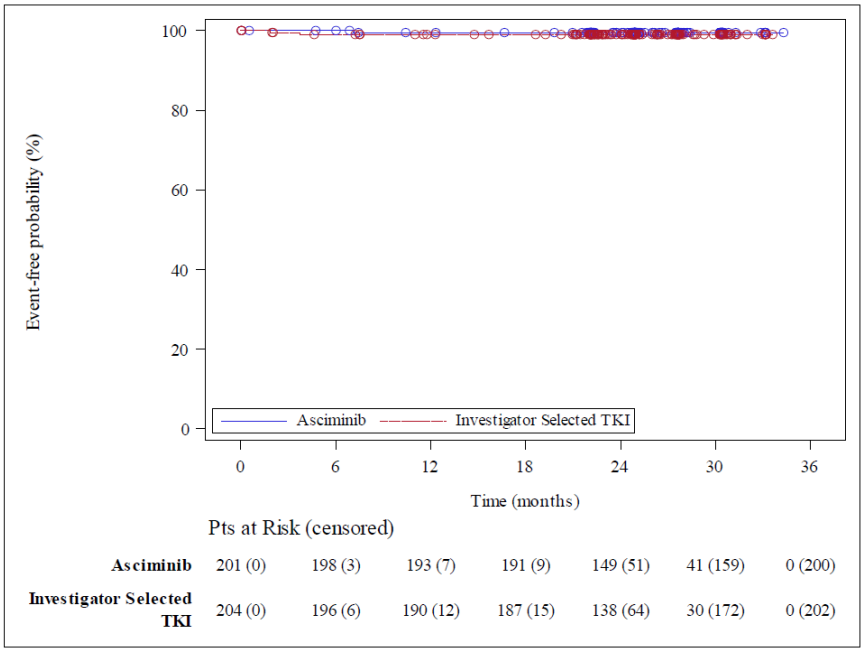
A.1.1 Mortality



Note: o = Censored observations
Data Cut/22OCT2024

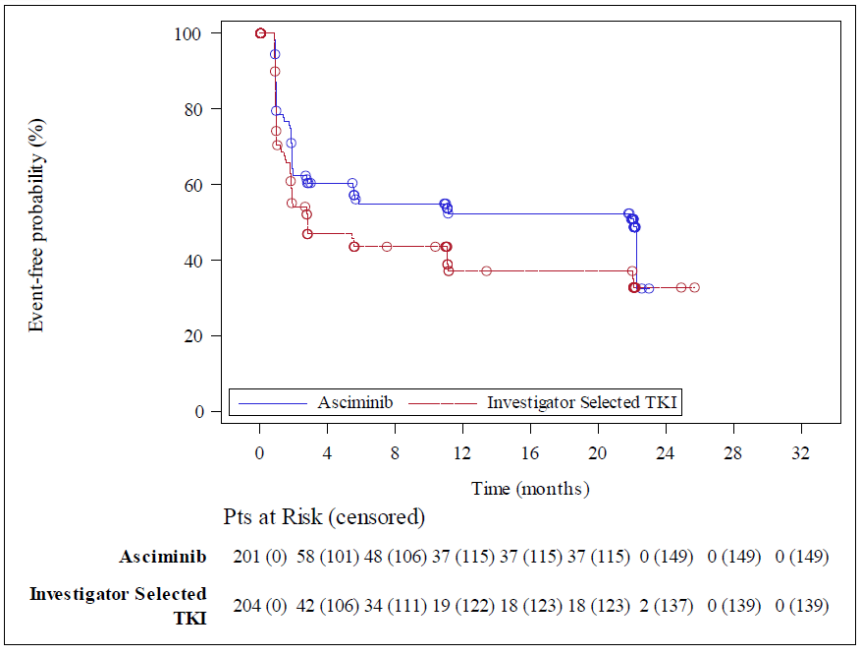
Figure 1: Kaplan-Meier curves for the outcome overall survival, ASC4FIRST study (total population), data cut of 22 October 2024

A.1.2 Morbidity



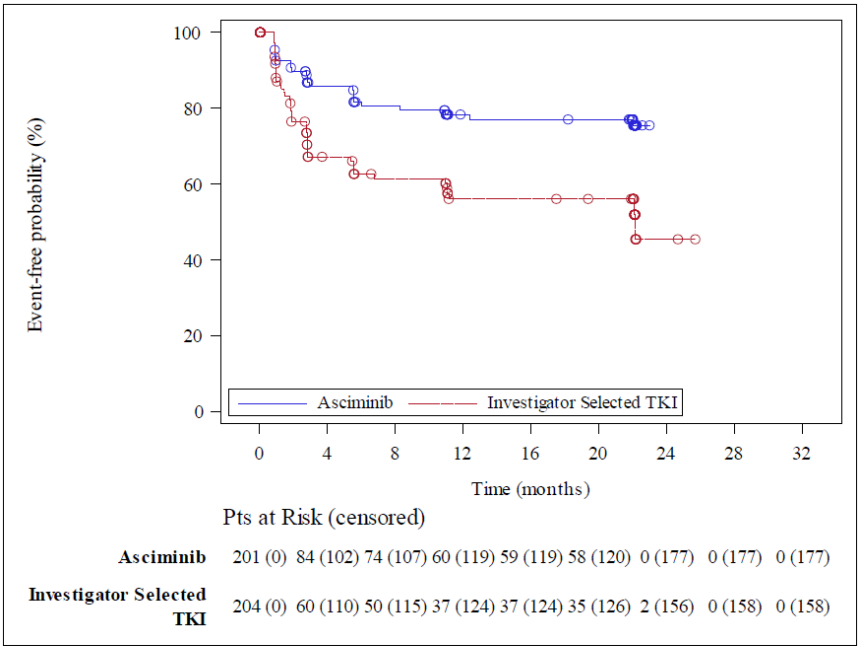
Note: o = Censored observations
Data Cut/22OCT2024

Figure 2: Kaplan-Meier curve for the outcome progression to blast crisis, ASC4FIRST study (total population), data cut of 22 October 2024



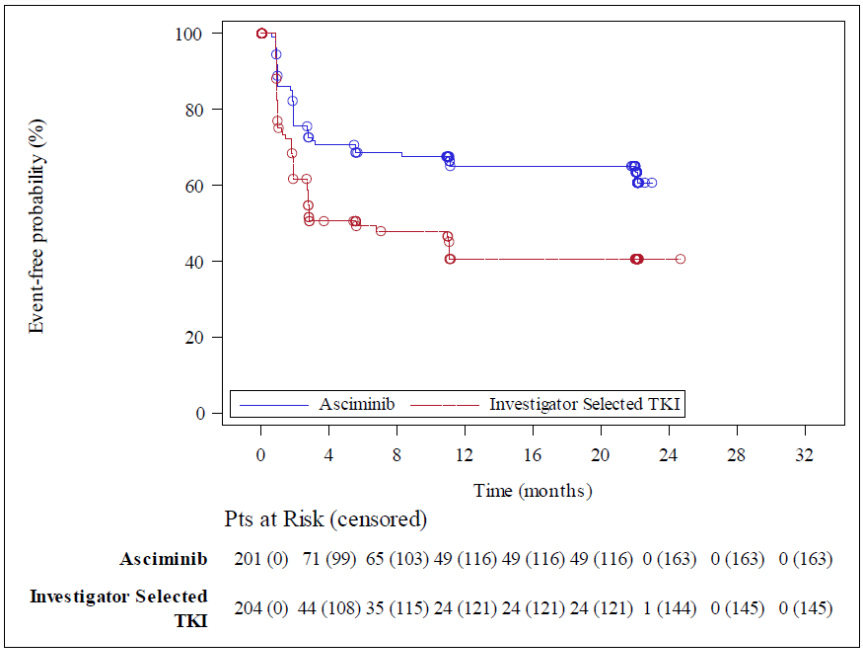
Note: o = Censored observations
Data Cut/22OCT2024

Figure 3: Kaplan-Meier curve for the outcome fatigue (EORTC QLQ C30 – time to first deterioration), ASC4FIRST (total population), data cut of 22 October 2024



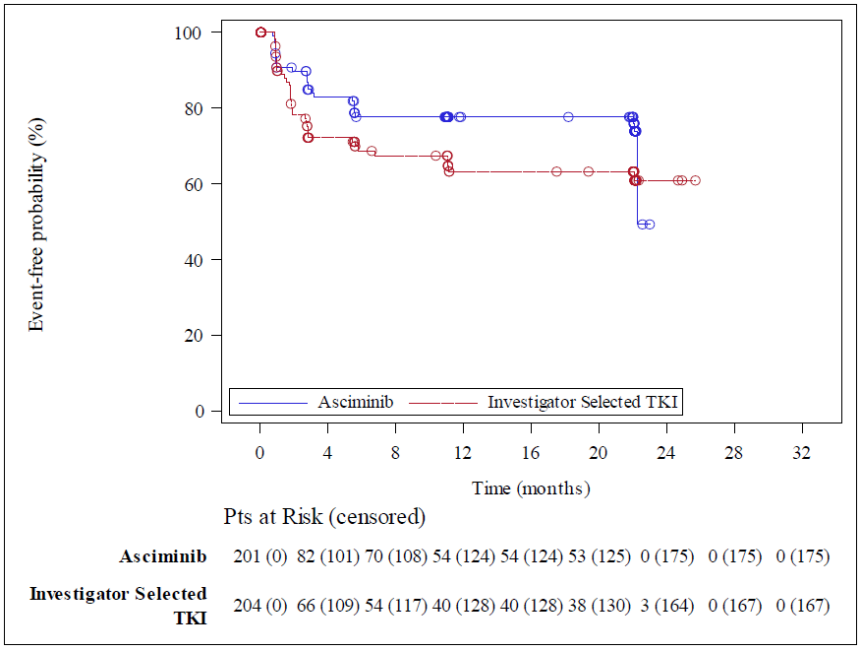
Note: o = Censored observations
Data Cut/22OCT2024

Figure 4: Kaplan-Meier curve for the outcome nausea and vomiting (EORTC QLQ C30 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024 study



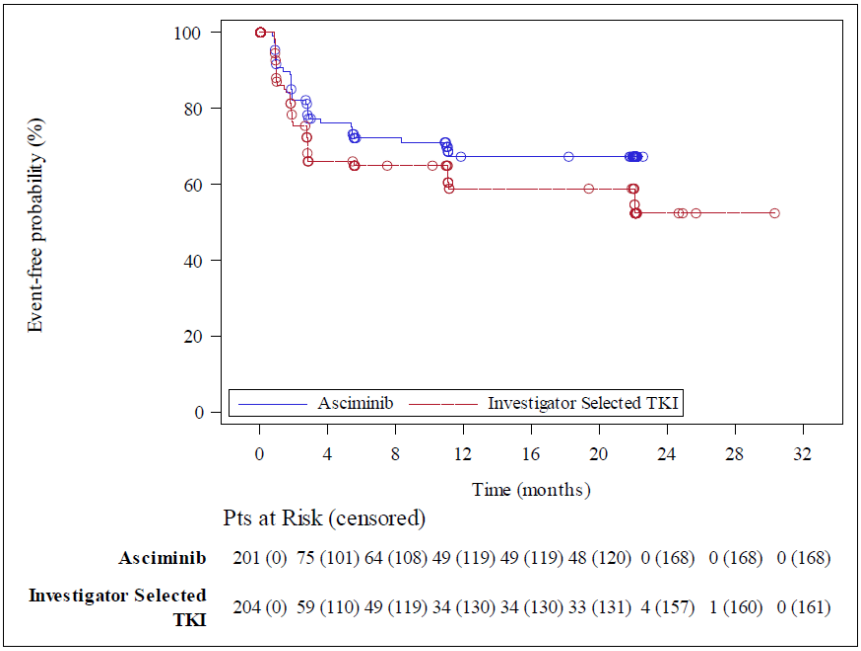
Note: o = Censored observations
Data Cut/22OCT2024

Figure 5: Kaplan-Meier curve for the outcome pain (EORTC QLQ C30 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



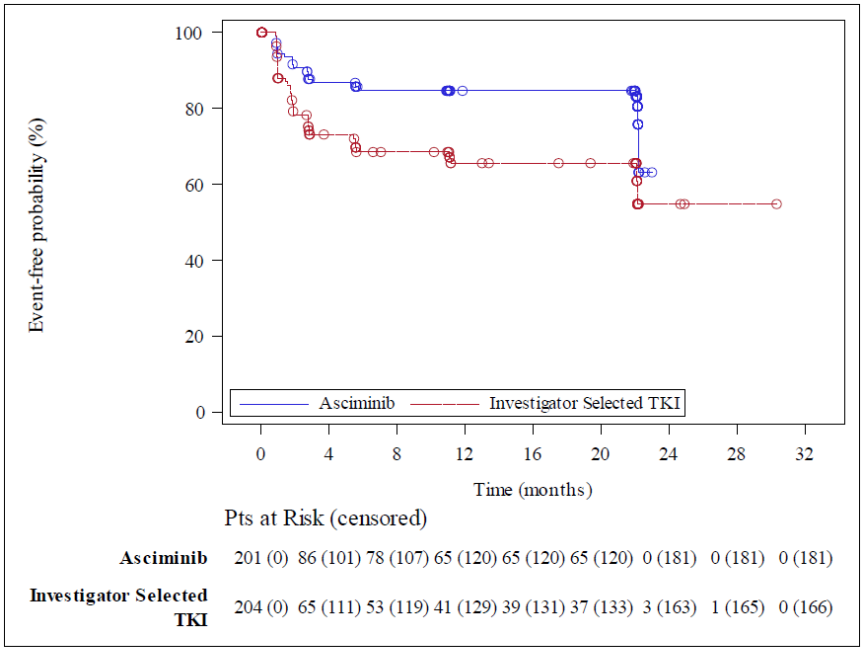
Note: o = Censored observations
Data Cut/22OCT2024

Figure 6: Kaplan-Meier curve for the outcome dyspnoea (EORTC QLQ C30 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



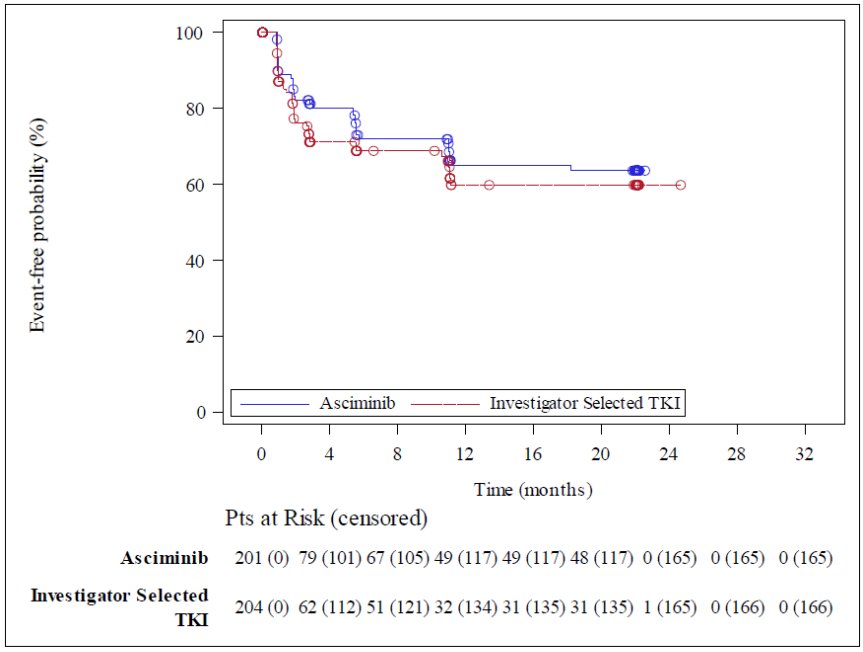
Note: o = Censored observations
Data Cut/22OCT2024

Figure 7: Kaplan-Meier curve for the outcome insomnia (EORTC QLQ C30 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



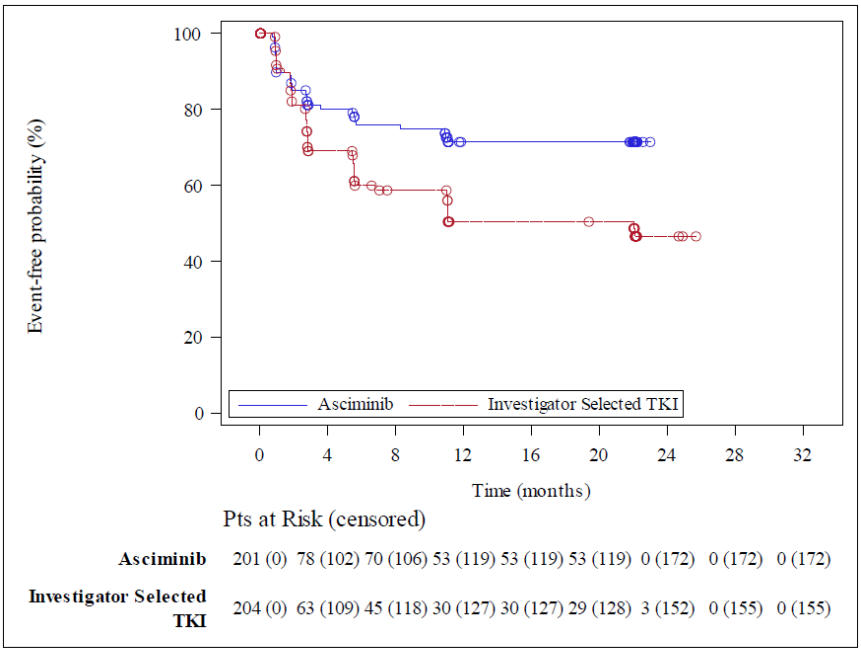
Note: o = Censored observations
Data Cut/22OCT2024

Figure 8: Kaplan-Meier curve for the outcome appetite loss (EORTC QLQ C30 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



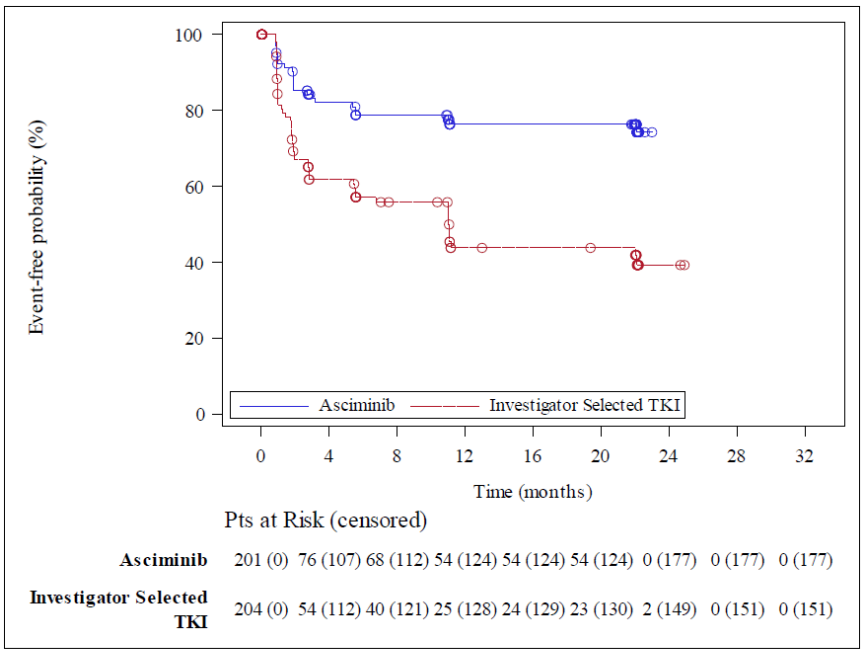
Note: o = Censored observations
Data Cut/22OCT2024

Figure 9: Kaplan-Meier curve for the outcome constipation (EORTC QLQ C30 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



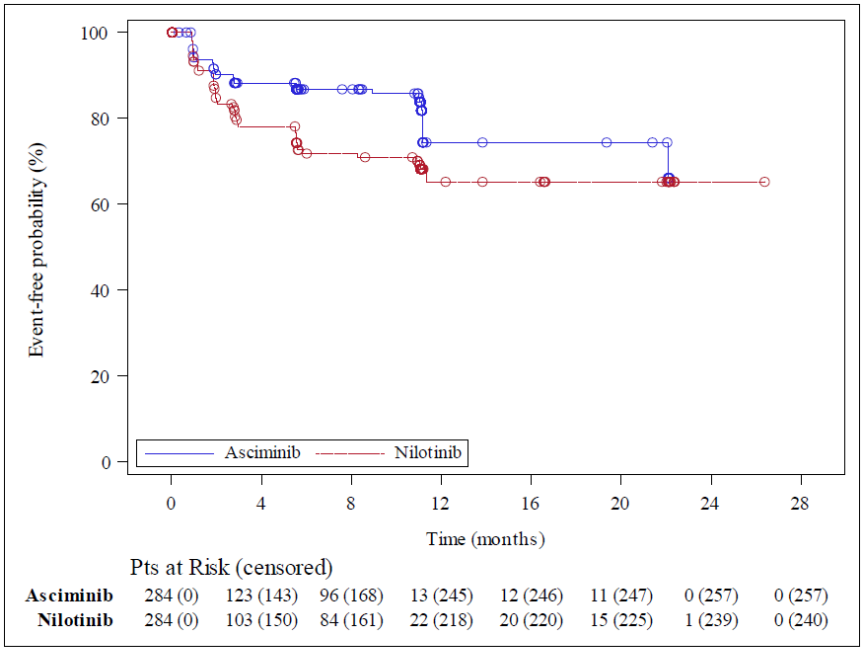
Note: o = Censored observations
Data Cut/22OCT2024

Figure 10: Kaplan-Meier curve for the outcome diarrhoea (EORTC QLQ C30 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



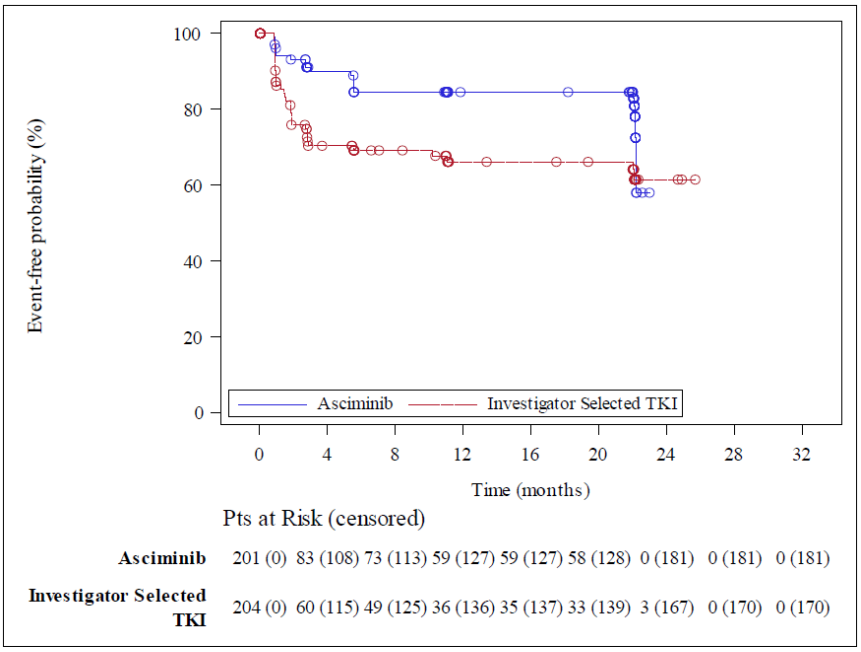
Note: o = Censored observations
Data Cut/22OCT2024

Figure 11: Kaplan-Meier curve for the outcome symptoms (EORTC QLQ CML24 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



Note: o = Censored observations
Data Cut/15MAY2025

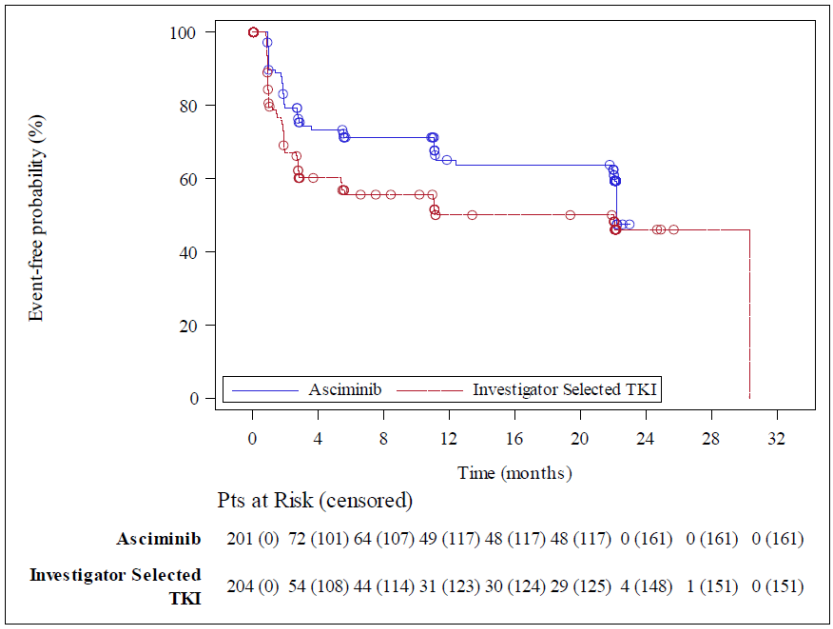
Figure 12: Kaplan-Meier curve for the outcome symptoms (EORTC QLQ CML24 – time to first deterioration), ASC4START study (total population), data cut of 15 May 2025



Note: o = Censored observations
Data Cut/22OCT2024

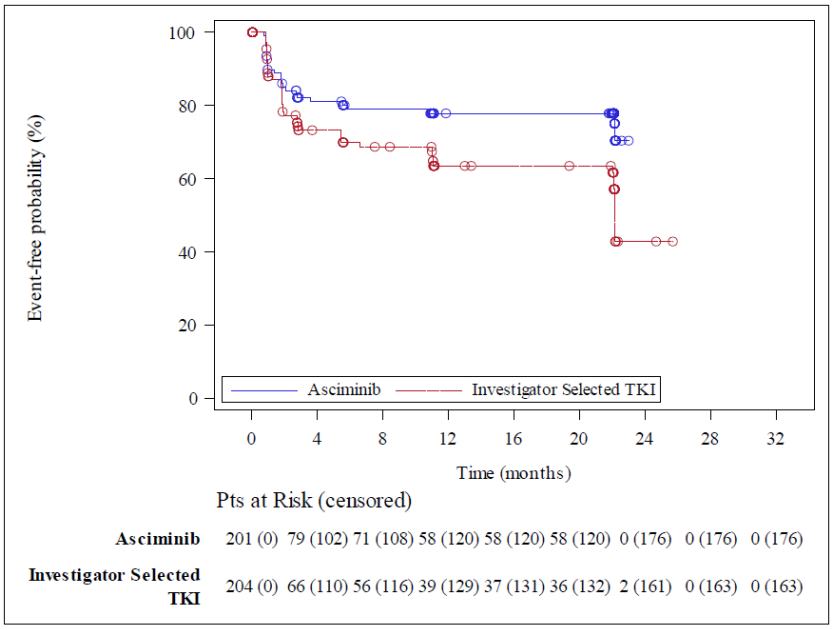
Figure 13: Kaplan-Meier curve for the outcome health status (EQ-5D VAS – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024

A.1.3 Health-related quality of life



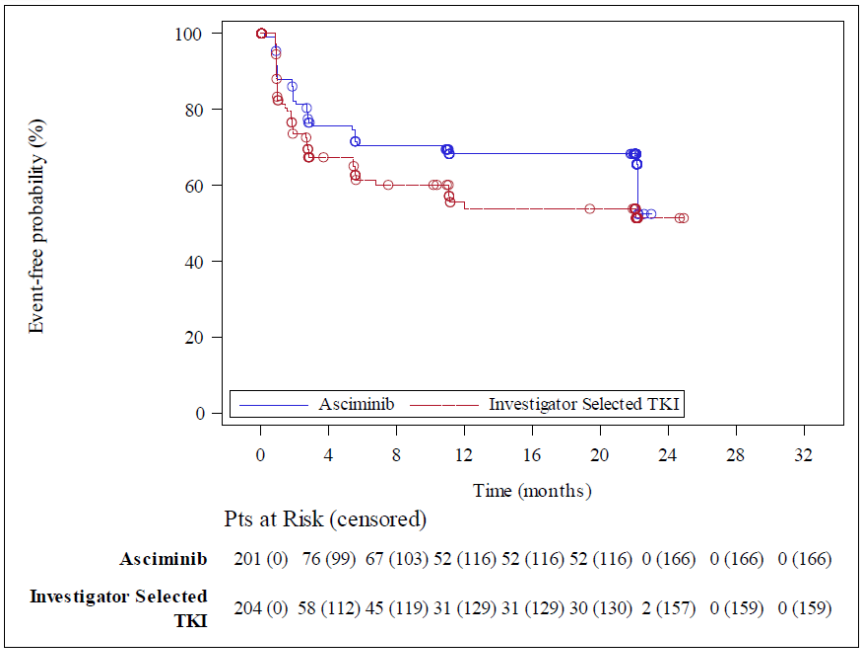
Note: o = Censored observations
Data Cut/22OCT2024

Figure 14: Kaplan-Meier curve for the outcome global health status (EORTC QLQ C30 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



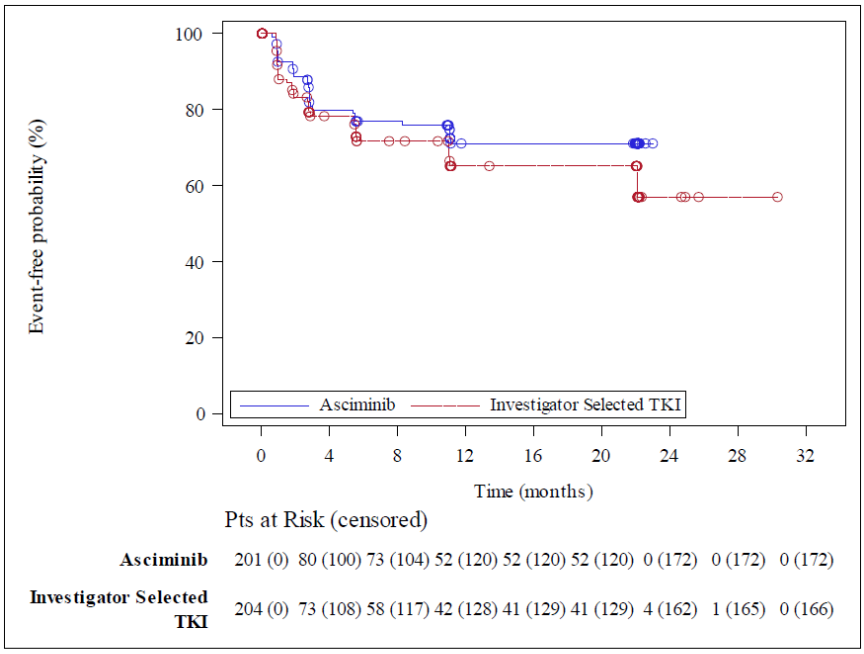
Note: o = Censored observations
Data Cut/22OCT2024

Figure 15: Kaplan-Meier curve for the outcome physical functioning (EORTC QLQ C30 – time to first deterioration), ASC4FIRST study (subpopulation), data cut of 22 October 2024



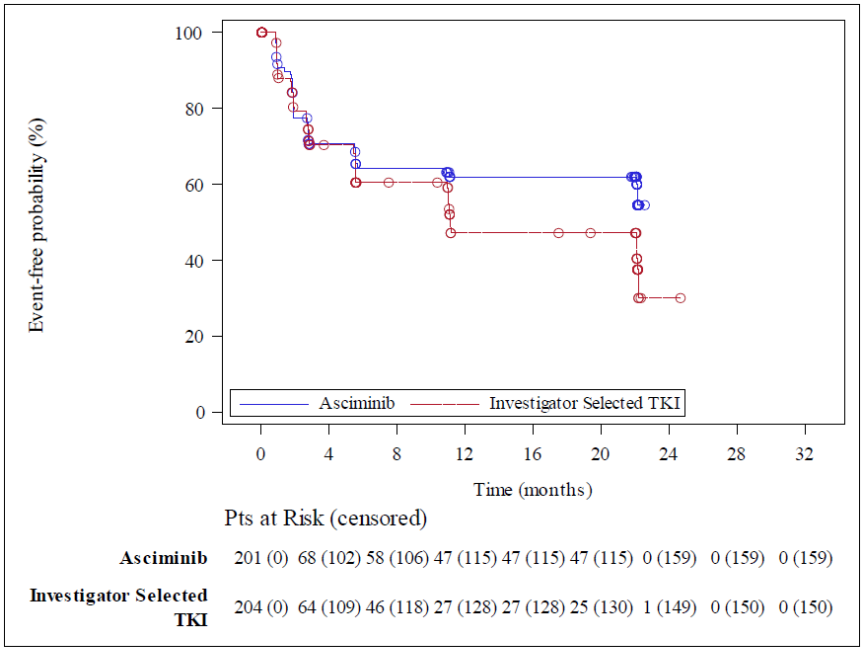
Note: o = Censored observations
Data Cut/22OCT2024

Figure 16: Kaplan-Meier curve for the outcome role functioning (EORTC QLQ C30 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



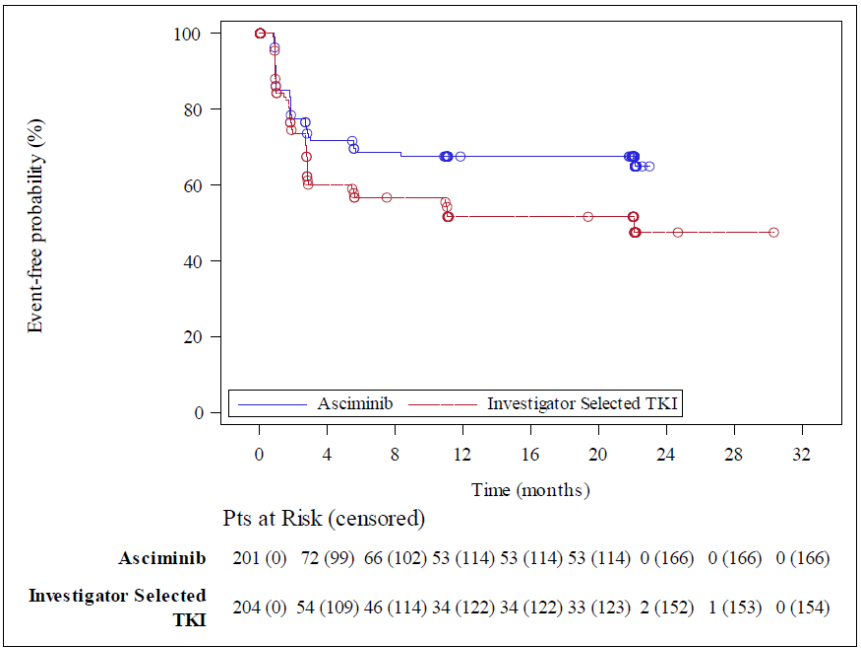
Note: o = Censored observations
Data Cut/22OCT2024

Figure 17: Kaplan-Meier curve for the outcome emotional functioning (EORTC QLQ C30 – time to first deterioration), ASC4FIRST study (subpopulation a), data cut of 22 October 2024



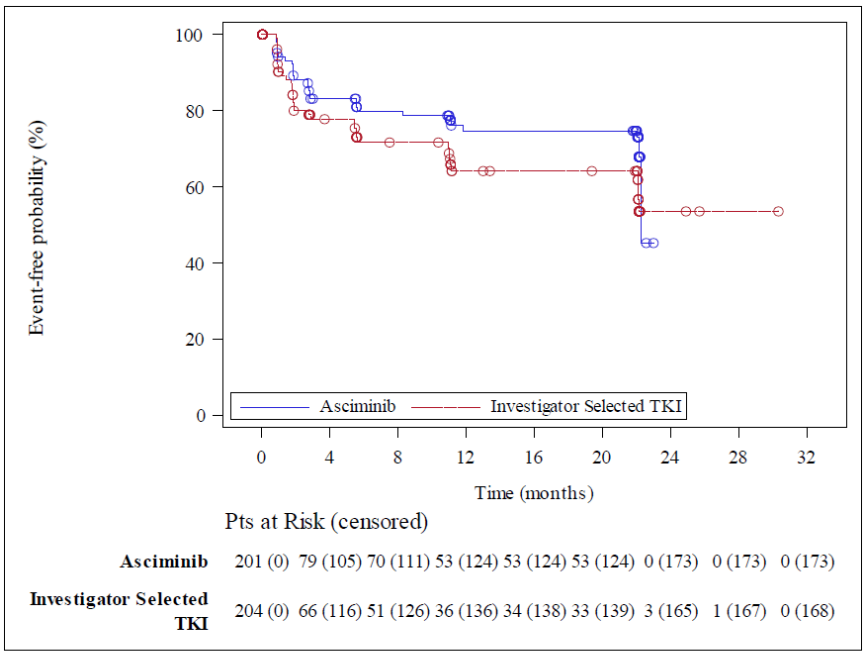
Note: o = Censored observations
Data Cut/22OCT2024

Figure 18: Kaplan-Meier curve for the outcome cognitive functioning (EORTC QLQ C30 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



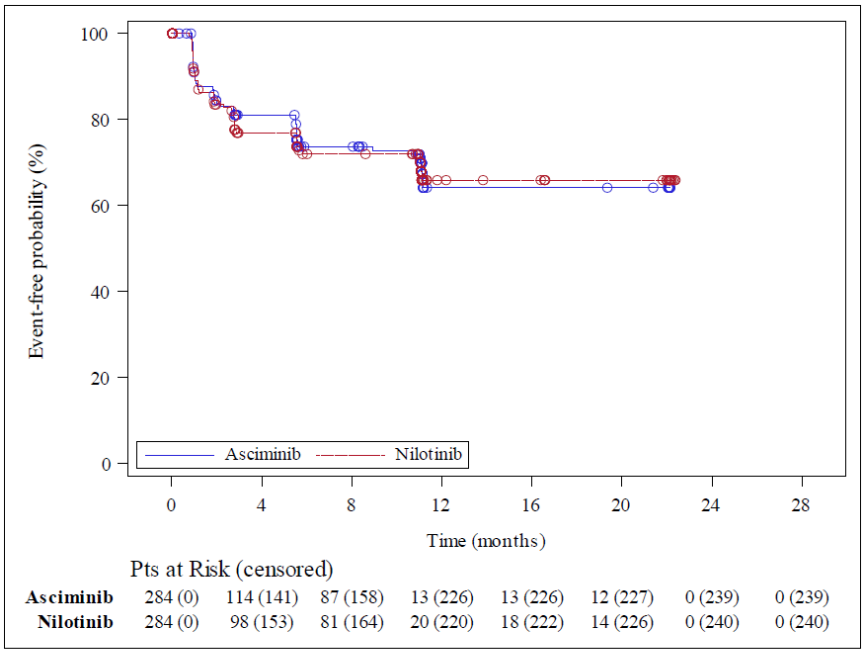
Note: o = Censored observations
Data Cut/22OCT2024

Figure 19: Kaplan-Meier curve for the outcome social functioning (EORTC QLQ C30 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



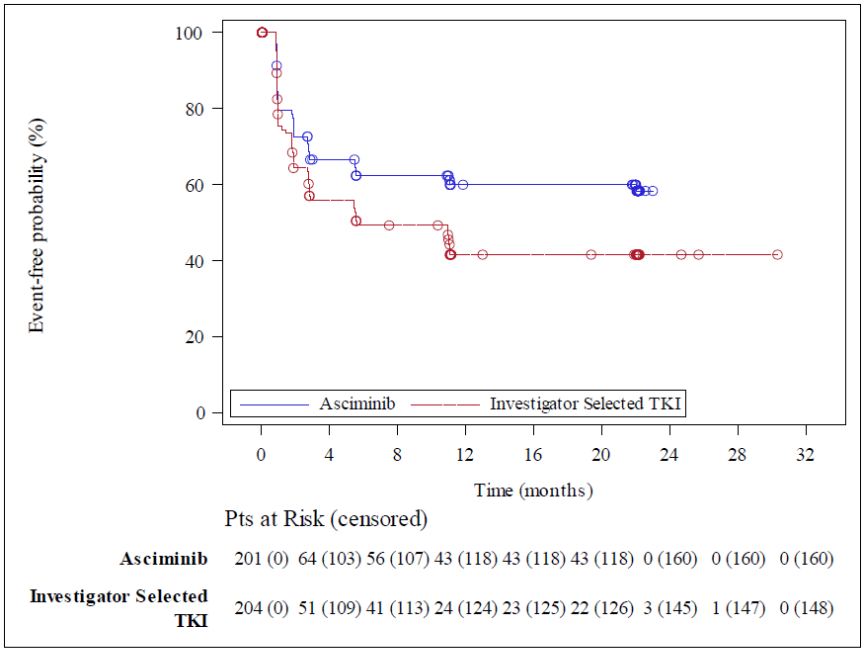
Note: o = Censored observations
Data Cut/22OCT2024

Figure 20: Kaplan-Meier curve for the outcome effects on worries/mood (EORTC QLQ CML24 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



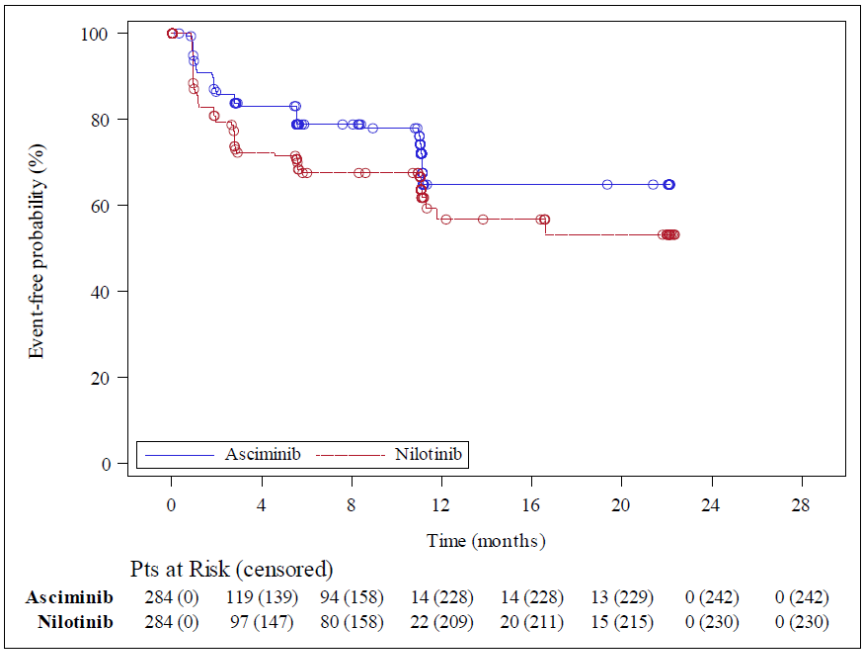
Note: o = Censored observations
Data Cut/15MAY2025

Figure 21: Kaplan-Meier curve for the outcome effect on worries/mood (EORTC QLQ CML24 – time to first deterioration), ASC4START, data cut of 15 May 2025



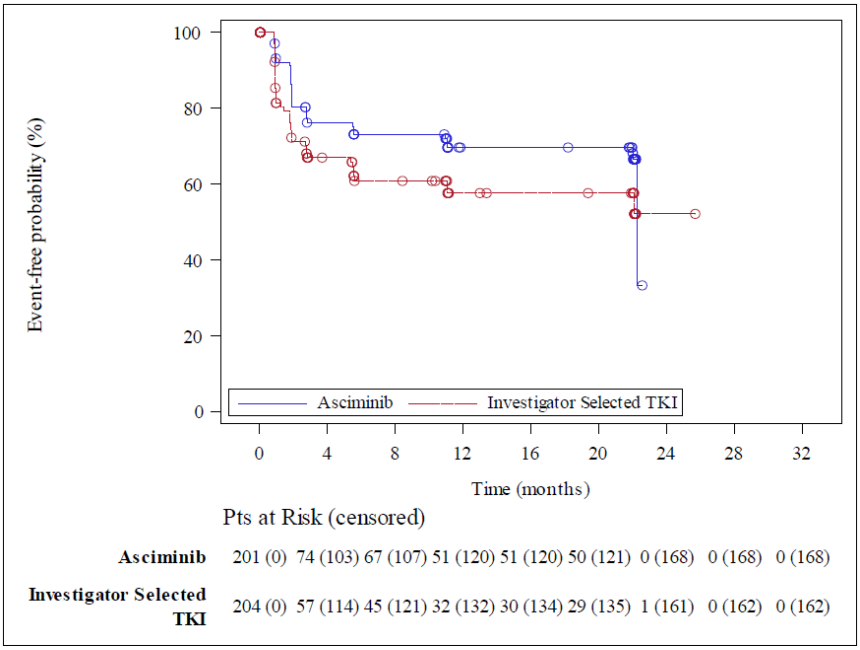
Note: o = Censored observations
Data Cut/22OCT2024

Figure 22: Kaplan-Meier curve for the outcome effects on everyday life (EORTC QLQ CML24 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



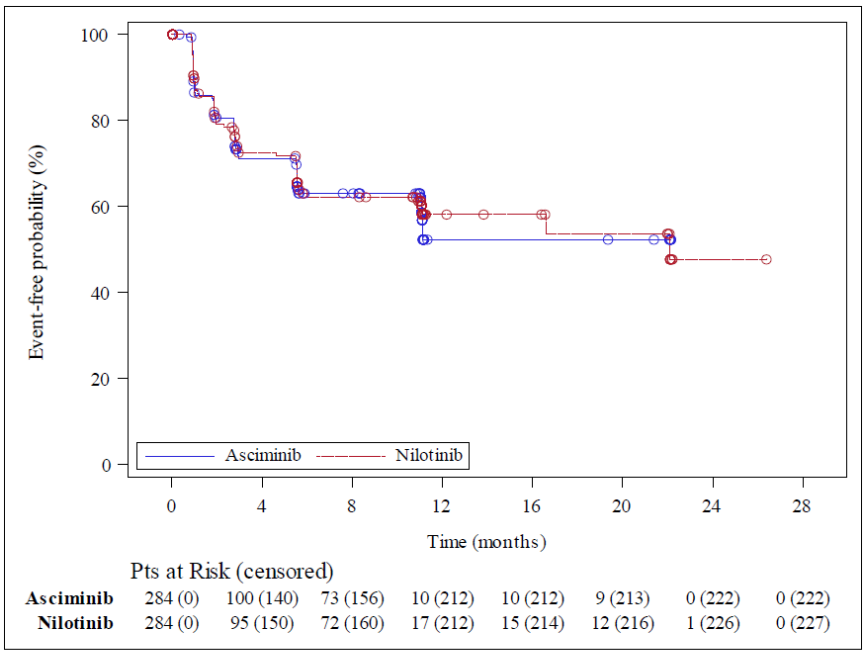
Note: o = Censored observations
Data Cut/15MAY2025

Figure 23: Kaplan-Meier curve for the outcome effects on everyday life (EORTC QLQ CML24 – time to first deterioration), ASC4START, data cut of 15 May 2025



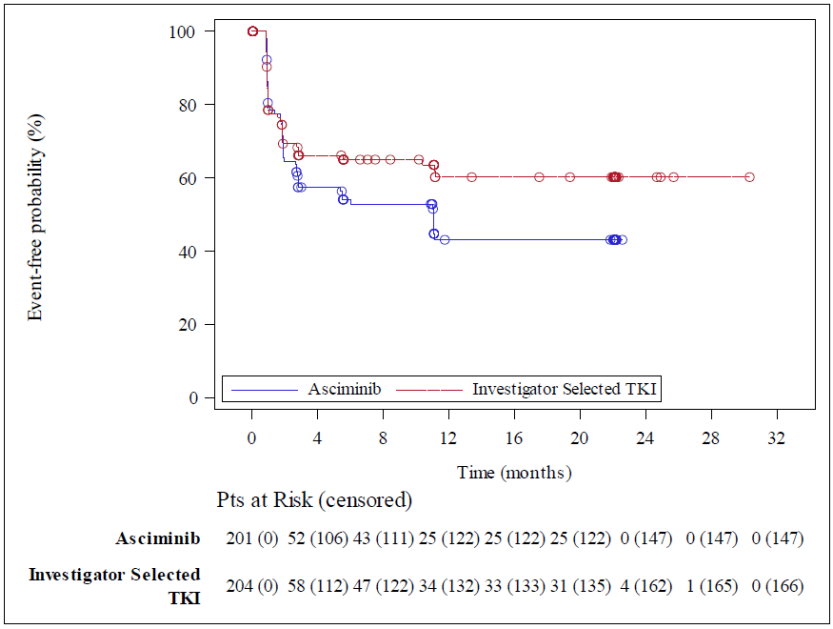
Note: o = Censored observations
Data Cut/22OCT2024

Figure 24: Kaplan-Meier curve for the outcome problems with body image (EORTC QLQ CML24 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



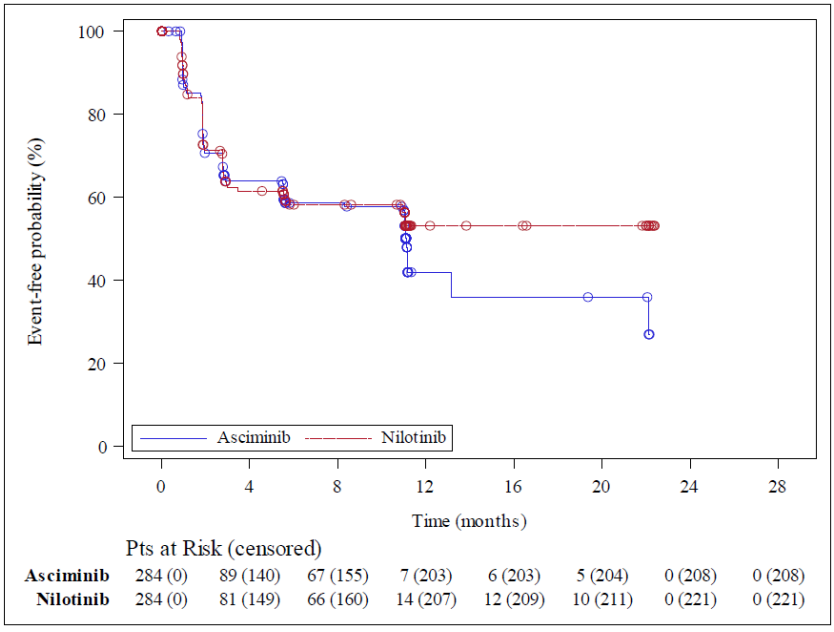
Note: o = Censored observations
Data Cut/15MAY2025

Figure 25: Kaplan-Meier curve for the outcome problems with body image (EORTC QLQ CML24 – time to first deterioration), ASC4START, data cut of 15 May 2025



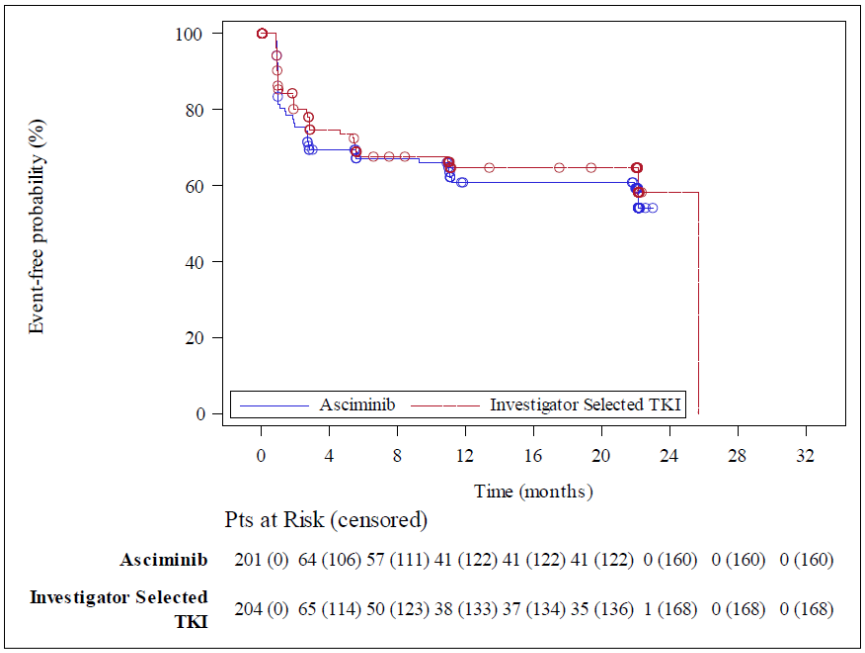
Note: o = Censored observations
Data Cut/22OCT2024

Figure 26: Kaplan-Meier curve for the outcome satisfaction with care/information (EORTC QLQ CML24 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



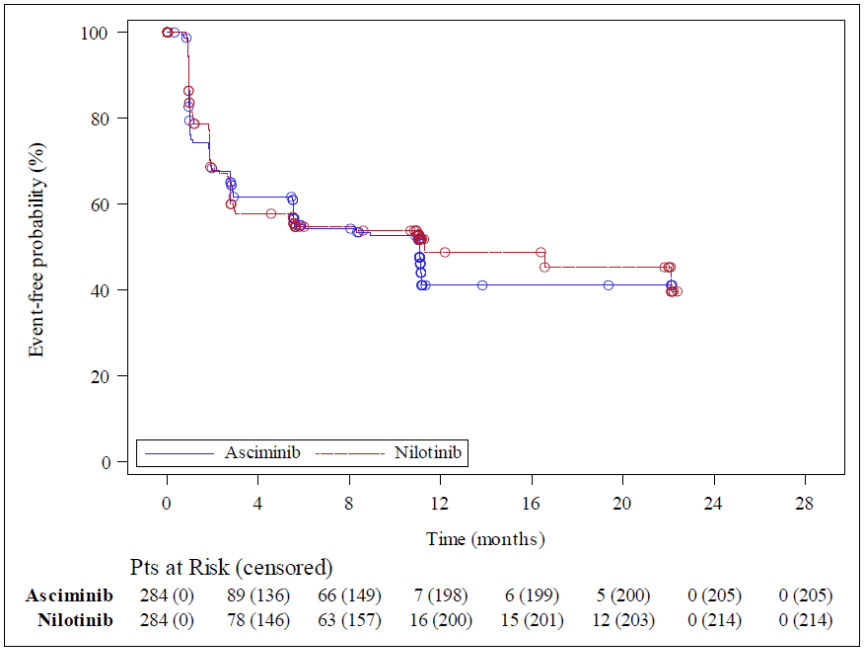
Note: o = Censored observations
Data Cut/15MAY2025

Figure 27: Kaplan-Meier curve for the outcome satisfaction with care/information (EORTC QLQ CML24 – time to first deterioration), ASC4START, data cut of 15 May 2025



Note: o = Censored observations
Data Cut/22OCT2024

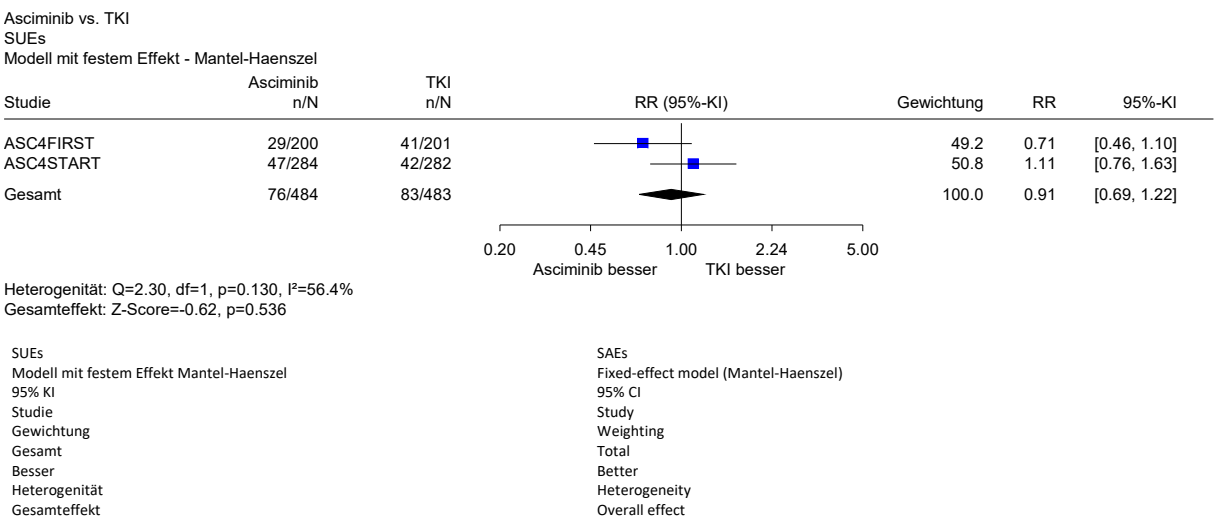
Figure 28: Kaplan-Meier curve for the outcome satisfaction with social life (EORTC QLQ CML24 – time to first deterioration), ASC4FIRST study (total population), data cut of 22 October 2024



Note: o = Censored observations
Data Cut/15MAY2025

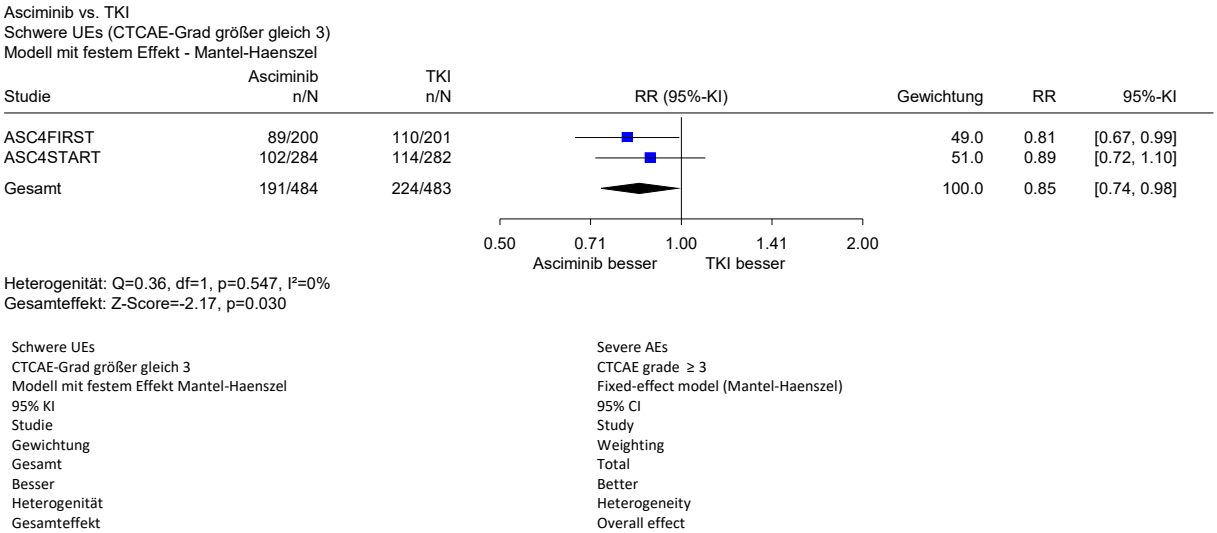
Figure 29: Kaplan-Meier curve for the outcome satisfaction with social life (EORTC QLQ CML24 – time to first deterioration), ASC4START, data cut of 15 May 2025

A.2 Meta-analyses on the outcomes in the side effects category



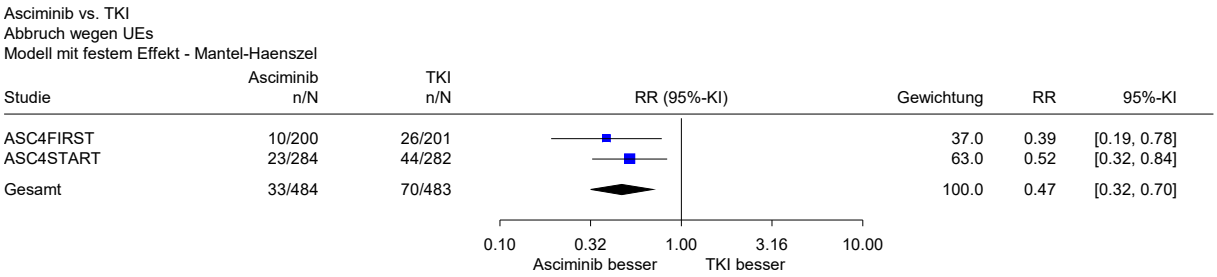
TKI: tyrosine kinase inhibitor. In ASC4FIRST, the comparison with TKI involved a TKI selected by the investigator (imatinib, nilotinib, dasatinib or bosutinib), whilst in ASC4START the TKI was nilotinib

Figure 30: Meta-analysis for the outcome SAEs, ASC4FIRST and ASC4START



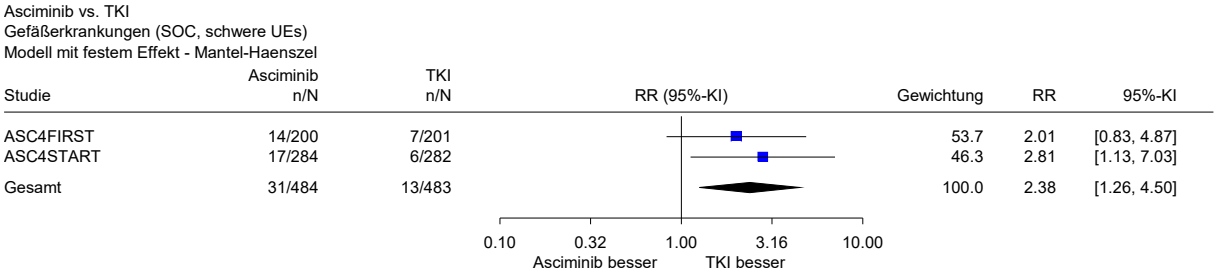
TKI: tyrosine kinase inhibitor. In ASC4FIRST, the comparison with TKI involved a TKI selected by the investigator (imatinib, nilotinib, dasatinib or bosutinib), whilst in ASC4START the TKI was nilotinib

Figure 31: Meta-analysis for the outcome severe AEs, ASC4FIRST and ASC4START



TKI: tyrosine kinase inhibitor. In ASC4FIRST, the comparison with TKI involved a TKI selected by the investigator (imatinib, nilotinib, dasatinib or bosutinib), whilst in ASC4START the TKI was nilotinib

Figure 32: Meta-analysis for the outcome discontinuation due to AEs, ASC4FIRST and ASC4START



TKI: tyrosine kinase inhibitor. In ASC4FIRST, the comparison with TKI involved a TKI selected by the investigator (imatinib, nilotinib, dasatinib or bosutinib), whilst in ASC4START the TKI was nilotinib

Figure 33: Meta-analysis for the outcome vascular disorders (SOC, severe AEs), ASC4FIRST and ASC4START

A.3 Comparison of the main and sensitivity analyses for outcomes on symptoms, health status and health-related quality of life

Table 6: Comparison of the main analysis and the sensitivity analyses for patient-reported outcomes (morbidity, health-related quality of life) – RCT, direct comparison – asciminib vs. TKI[a] (multipage table)

Outcome category outcome	ASC4FIRST	ASC4START	Meta-analysis					
			main analysis[b]		sensitivity analysis 1[c]		sensitivity analysis 2[d]	
	HR [95% CI]; p-value	HR [95% CI]; p-value	HR [95% CI]; p-value[e]	p-value for heterogeneity	HR [95% CI]; p-value[e]	p-value for heterogeneity	HR [95% CI]; p-value[e, f]	p-value for heterogeneity
Morbidity								
Symptoms (EORTC QLQ-C30 – time to first deterioration[g])								
Fatigue	0.65 [0.45; 0.95]; 0.021	0.74 [0.51; 1.09]; 0.214	0.70 [0.54; 0.91]; 0.012	0.609	0.71 [0.55; 0.90]; 0.009	0.704	0.77 [0.62; 0.95]; 0.049	0.727
Nausea and vomiting	0.41 [0.25; 0.68]; < 0.001	0.75 [0.49; 1.16]; 0.176	0.58 [0.42; 0.80]; < 0.001	0.067	0.60 [0.45; 0.80]; < 0.001	0.202	0.62 [0.48; 0.79]; < 0.001	0.584
Pain	0.49 [0.32; 0.74]; < 0.001	0.90 [0.66; 1.23]; 0.453	–[h]	0.025	–[h]	0.048	0.79 [0.65; 0.97]; 0.029	0.323
Dyspnoea	0.58 [0.34; 0.97]; 0.033	0.86 [0.57; 1.29]; 0.524	0.74 [0.54; 1.01]; 0.067	0.238	0.68 [0.51; 0.91]; 0.009	0.109	0.79 [0.63; 1.01]; 0.164	0.392
Insomnia	0.61 [0.39; 0.96]; 0.072	0.74 [0.52; 1.07]; 0.122	0.69 [0.52; 0.92]; 0.020	0.517	0.76 [0.58; 0.98]; 0.064	0.617	0.79 [0.63; 0.99]; 0.226	0.637
Appetite loss	0,36 [0.21; 0.64]; < 0.001	0.78 [0.48; 1.25]; 0.229	–[h]	0.045	–[h]	0.014	0,59 [0.46; 0.78]; < 0.001	0.137
Constipation	0.76 [0.47; 1.22]; 0.396	0.63 [0.42; 0.93]; 0.026	0.68 [0.50; 0.92]; 0.024	0.448	0.66 [0.50; 0.87]; 0.005	0.497	0.66 [0.52; 0.84]; 0.007	0.194
Diarrhoea	0.44 [0.27; 0.71]; < 0.001	0.72 [0.48; 1.09]; 0.055	0,57 [0.42; 0.79]; < 0.001	0.127	0,63 [0.48; 0.83]; < 0.001	0.386	0.86 [0.69; 1.09]; 0.409	0.227
Symptoms (EORTC QLQ-CML24 – time to first deterioration[g])	0.34 [0.21; 0.56]; < 0.001	0.55 [0.34; 0.89]; 0.023	0.44 [0.31; 0.61]; < 0.001	0.160	0.43 [0.31; 0.59]; < 0.001	0.156	0.54 [0.42; 0.70]; < 0.001	0.800

Table 6: Comparison of the main analysis and the sensitivity analyses for patient-reported outcomes (morbidity, health-related quality of life) – RCT, direct comparison – asciminib vs. TKI[a] (multipage table)

Outcome category outcome			Meta-analysis					
	ASC4FIRST	ASC4START	main analysis[b]		sensitivity analysis 1[c]		sensitivity analysis 2[d]	
	HR [95% CI]; p-value	HR [95% CI]; p-value	HR [95% CI]; p-value[e]	p-value for heterogeneity	HR [95% CI]; p-value[e]	p-value for heterogeneity	HR [95% CI]; p-value[e, f]	p-value for heterogeneity
Health-related quality of life								
EORTC-QLQ-C30 – time to first deterioration[i]								
Global health status	0.67 [0.44; 1.02]; 0.029	0.89 [0.62; 1.27]; 0.529	0.79 [0.60; 1.04]; 0.058	0.322	0.79 [0.61; 1.01]; 0.030	0.250	0.83 [0.66; 1.03]; 0.089	0.620
Physical functioning	0.50 [0.30; 0.83]; 0.006	0.91 [0.61; 1.35]; 0.616	0.72 [0.53; 0.98]; 0.036	0.066	0.71 [0.52; 0.95]; 0.018	0.078	0.75 [0.58; 0.96]; 0.053	0.581
Role functioning	0.57 [0.36; 0.90] 0.018	1.08 [0.76; 1.55]; 0.587	–[h]	0.029	–[h]	0.002	0.77 [0.62; 0.95]; 0.071	0.451
Emotional functioning	0.71 [0.43; 1.15]; 0.149	0.65 [0.44; 0.96]; 0.120	0.69 [0.51; 0.94]; 0.035	0.881	0.73 [0.55; 0.97]; 0.028	0.956	0.78 [0.62; 0.98]; 0.210	0.824
Cognitive functioning	0.75 [0.49; 1.13]; 0.151	0.92 [0.67; 1.26]; 0.626	0.85 [0.66; 1.09]; 0.205	0.439	0.81 [0.65; 1.03]; 0.068	0.241	0.82 [0.67; 1.00]; 0.128	0.851
Social functioning	0.62 [0.40; 0.97]; 0.027	0.76 [0.53; 1.09]; 0.203	0.71 [0.54; 0.94]; 0.017	0.482	0.67 [0.52; 0.87]; 0.002	0.297	0.69 [0.56; 0.86]; 0.002	0.857
EORTC QLQ-CML24 – time to first deterioration[j]								
Effect on worries/mood	0.64 [0.38; 1.06]; 0.087	0.92 [0.60; 1.39]; 0.904	0.79 [0.57; 1.09]; 0.235	0.268	0.82 [0.61; 1.10]; 0.197	0.310	0.79 [0.62; 1.02]; 0.412	0.825
Effects on everyday life	0.64 [0.43; 0.97]; 0.021	0.67 [0.44; 1.00]; 0.106	0.65 [0.49; 0.87]; 0.006	0.905	0.72 [0.55; 0.93]; 0.011	0.964	0.70 [0.55; 0.88]; 0.013	0.843
Problems with body image	0.65 [0.41; 1.04]; 0.045	1.03 [0.72; 1.48]; 0.874	0.87 [0.65; 1.15]; 0.267	0.124	0.94 [0.73; 1.23]; 0.558	0.191	0.84 [0.68; 1.04]; 0.312	0.721

Table 6: Comparison of the main analysis and the sensitivity analyses for patient-reported outcomes (morbidity, health-related quality of life) – RCT, direct comparison – asciminib vs. TKI[a] (multipage table)

Outcome category outcome			Meta-analysis					
	ASC4FIRST	ASC4START	main analysis[b]		sensitivity analysis 1[c]		sensitivity analysis 2[d]	
	HR [95% CI]; p-value	HR [95% CI]; p-value	HR [95% CI]; p-value[e]	p-value for heterogeneity	HR [95% CI]; p-value[e]	p-value for heterogeneity	HR [95% CI]; p-value[e, f]	p-value for heterogeneity
Satisfaction with care/information	1.06 [0.68; 1.65]; 0.079	1.07 [0.76; 1.49]; 0.505	1.08 [0.83; 1.41]; 0.105	0.827	1.12 [0.87; 1.44]; 0.037	0.972	1.04 [0.84; 1.30]; 0.550	0.698
Satisfaction with social life	1.10 [0.68; 1.76]; 0.717	1.10 [0.80; 1.52]; 0.599	1.10 [0.84; 1.44]; 0.523	0.960	1.16 [0.90; 1.49]; 0.207	0.740	1.02 [0.82; 1.27]; 0.781	0.689

a. ASC4FIRST study: with a choice of imatinib, nilotinib or dasatinib prior to randomization; ASC4START study: nilotinib.
b. Main analysis: patients without a baseline value at the time of randomization were censored on Day 1.
c. Sensitivity analysis with an extended definition of baseline values: patients whose baseline values were recorded prior to the first administration of the study medication; patients without an extended baseline value were censored on Day 1.
d. Time-to-event analysis with multiple imputation: missing baseline values at randomization were imputed using multiple imputation. Multiple imputation separated by family origin, by consideration in the 'by' argument, with additional demographic and clinical patient characteristics (age, sex, ECOG PS, TKI stratum and ELTS risk group) as variables in the model.
e. HR + 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).
f. The test results were summarized using the Wilson-Hilferty transformation.
g. A score increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range 0 to 100).
h. No common effect estimation due to heterogeneity, and no conclusive effects.
i. A score decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
j. A score increase by ≥ 10 points from baseline for the scales effect on worries/mood, effects on everyday life and problems with body image, as well as a score decrease by ≥ 10 points from baseline for the scales satisfaction with care/information and satisfaction with social life, is considered a clinically relevant deterioration (scale range: 0 to 100).

CI: confidence interval; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; 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; 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

Table 7: Comparison of the main analysis and the sensitivity analyses for the outcome EQ-5D VAS – RCT, direct comparison: – (morbidity) asciminib vs. TKI[a]

Outcome category outcome study	Main analysis[b] HR [95% CI]; p-value[e]	Sensitivity analysis 1[c] HR [95% CI]; p-value[e]	Sensitivity analysis 2[d] HR [95% CI]; p-value[e, f]
Morbidity			
Health status (EQ-5D VAS - time to first deterioration[g])			
ASC4FIRST	0.47 [0.27; 0.83]; 0.007	0.55 [0.35; 0.87]; 0.008	0.77 [0.53; 1.13]; 0.343
ASC4START		Outcome not recorded	

a. ASC4FIRST study: with a choice of imatinib, nilotinib or dasatinib prior to randomization; ASC4START study: nilotinib.
b. Main analysis: patients without a baseline value at the time of randomization were censored on Day 1.
c. Sensitivity analysis with an extended definition of baseline values: patients whose baseline values were recorded prior to the first administration of the study medication; patients without an extended baseline value were censored on Day 1.
d. Time-to-event analysis with multiple imputation: missing baseline values at randomization were imputed using multiple imputation. Multiple imputation separated by family origin, by consideration in the 'by' argument, with additional demographic and clinical patient characteristics (age, sex, ECOG PS, TKI stratum and ELTS risk group) as variables in the model.
e. HR + 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).
f. The test results were summarized using the Wilson-Hilferty transformation.
g. A score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).

CI: confidence interval; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; ELTS: European Treatment and Outcome Study Long-Term Survival; HR: hazard ratio; p_H-value: RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor; VAS: visual analogue scale

A.4 Results on side effects

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

- AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- 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 8: Common AEsa – RCT, direct comparison: asciminib vs. TKIb (ASC4FIRST study) (multipage table)

	Patients with event n (%)	
SOC[c] **PT[c]**	**asciminib N = 200**	**TKI[b] N = 201**
Overall AE rate	191 (95.5)	197 (98.0)
Blood and lymphatic system disorders	63 (31.5)	86 (42.8)
Cardiac disorders	9 (4.5)	20 (10.0)
Ear and labyrinth disorders	5 (2.5)	16 (8.0)
Eye disorders	31 (15.5)	49 (24.4)
Gastrointestinal disorders	91 (45.5)	111 (55.2)
General disorders and administration site conditions	67 (33.5)	87 (43.3)
Hepatobiliary disorders	15 (7.5)	8 (4.0)
Infections and infestations	108 (54.0)	118 (58.7)
Injury, poisoning and procedural complications	20 (10.0)	17 (8.5)
Investigations	94 (47.0)	113 (56.2)
Metabolism and nutrition disorders	57 (28.5)	58 (28.9)
Musculoskeletal and connective tissue disorders	76 (38.0)	91 (45.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (3.0)	15 (7.5)
Nervous system disorders	56 (28.0)	57 (28.4)
Psychiatric disorders	22 (11.0)	18 (9.0)
Renal and urinary disorders	7 (3.5)	14 (7.0)
Reproductive system and breast disorders	19 (9.5)	16 (8.0)
Respiratory, thoracic and mediastinal disorders	36 (18.0)	47 (23.4)
Skin and subcutaneous tissue disorders	79 (39.5)	85 (42.3)
Vascular disorders	33 (16.5)	17 (8.5)
Abdominal pain	22 (11.0)	14 (7.0)
Alanine aminotransferase increased	17 (8.5)	28 (13.9)
Alopecia	5 (2.5)	14 (7.0)
Amylase increased	11 (5.5)	10 (5.0)
Anaemia	25 (12.5)	52 (25.9)
Arthralgia	26 (13.0)	19 (9.5)
Aspartate aminotransferase increased	6 (3.0)	23 (11.4)
Asthenia	8 (4.0)	11 (5.5)
Back pain	12 (6.0)	22 (10.9)
Blood alkaline phosphatase increased	12 (6.0)	19 (9.5)

Table 8: Common AEsa – RCT, direct comparison: asciminib vs. TKIb (ASC4FIRST study) (multipage table)

	Patients with event n (%)	
SOC[c] **PT[c]**	**asciminib N = 200**	**TKI[b] N = 201**
Blood bilirubin increased	8 (4.0)	13 (6.5)
Blood creatine phosphokinase increased	11 (5.5)	15 (7.5)
COVID-19	43 (21.5)	44 (21.9)
Constipation	20 (10.0)	18 (9.0)
Cough	12 (6.0)	20 (10.0)
Decreased appetite	6 (3.0)	11 (5.5)
Diarrhoea	35 (17.5)	56 (27.9)
Dry eye	14 (7.0)	9 (4.5)
Dry skin	12 (6.0)	8 (4.0)
Dyspepsia	9 (4.5)	11 (5.5)
Face oedema	0 (0)	10 (5.0)
Fatigue	30 (15.0)	35 (17.4)
Gamma-glutamyltransferase increased	14 (7.0)	13 (6.5)
Headache	33 (16.5)	33 (16.4)
Hypercholesterolaemia	10 (5.0)	8 (4.0)
Hyperlipidaemia	11 (5.5)	7 (3.5)
Hypertension	21 (10.5)	10 (5.0)
Hypertriglyceridaemia	11 (5.5)	3 (1.5)
Hyperuricaemia	12 (6.0)	9 (4.5)
Hypocalcaemia	6 (3.0)	10 (5.0)
Hypophosphataemia	1 (0.5)	12 (6.0)
Influenza like illness	5 (2.5)	10 (5.0)
Leukopenia	17 (8.5)	20 (10.0)
Lipase increased	27 (13.5)	30 (14.9)
Lymphocyte count decreased	10 (5.0)	16 (8.0)
Muscle spasms	6 (3.0)	24 (11.9)
Myalgia	31 (15.5)	35 (17.4)
Nasopharyngitis	15 (7.5)	15 (7.5)
Nausea	19 (9.5)	40 (19.9)
Neutropenia	21 (10.5)	33 (16.4)
Neutrophil count decreased	30 (15.0)	37 (18.4)
Oedema peripheral	3 (1.5)	13 (6.5)
Pain in extremity	10 (5.0)	11 (5.5)
Periorbital oedema	2 (1.0)	12 (6.0)
Platelet count decreased	29 (14.5)	33 (16.4)

Table 8: Common AEsa – RCT, direct comparison: asciminib vs. TKIb (ASC4FIRST study) (multipage table)

	Patients with event n (%)	
SOC[c] **PT[c]**	**asciminib N = 200**	**TKI[b] N = 201**
Pleural effusion	0 (0)	10 (5.0)
itching	19 (9.5)	9 (4.5)
Pyrexia	12 (6.0)	12 (6.0)
Rash	29 (14.5)	35 (17.4)
Thrombocytopenia	27 (13.5)	31 (15.4)
Upper respiratory tract infection	17 (8.5)	23 (11.4)
Vertigo	2 (1.0)	10 (5.0)
Vomiting	14 (7.0)	20 (10.0)
White blood cell count decreased	22 (11.0)	30 (14.9)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. Choosing from imatinib, nilotinib, dasatinib or bosutinib prior to randomization.
c. MedDRA version 27.1; SOCs and PTs 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; TKI: tyrosine kinase inhibitor

Table 9: Common SAEsa – RCT, direct comparison: asciminib vs. TKIb (ASC4FIRST study)

	Patients with event n (%)	
SOC[c]	**asciminib N = 200**	**TKI[b] N = 201**
Overall SAE rate	29 (14.5)	41 (20.4)
Infections and infestations	5 (2.5)	16 (8.0)

a. Events that occurred in ≥ 10 of the patients in at least one study arm.
b. Choosing from imatinib, nilotinib, dasatinib or bosutinib prior to randomization.
c. MedDRA version 27.1; SOCs 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; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class: TKI: tyrosine kinase inhibitor

Table 10: Common severe AEs (CTCAE grade ≥ 3)a – RCT, direct comparison: asciminib vs. TKIb (ASC4FIRST study)

	Patients with event n (%)	
SOC[c] **PT[c]**	**asciminib** **N = 200**	**TKI[b]** **N = 201**
Overall rate of severe AEs (CTCAE grade ≥ 3)	89 (44.5)	110 (54.7)
Blood and lymphatic system disorders	21 (10.5)	37 (18.4)
Infections and infestations	8 (4.0)	13 (6.5)
Investigations	39 (19.5)	47 (23.4)
Musculoskeletal and connective tissue disorders	10 (5.0)	4 (2.0)
Vascular disorders	14 (7.0)	7 (3.5)
Alanine aminotransferase increased	4 (2.0)	10 (5.0)
Anaemia	4 (2.0)	12 (6.0)
Hypertension	11 (5.5)	7 (3.5)
Neutropenia	9 (4.5)	21 (10.4)
Neutrophil count decreased	12 (6.0)	16 (8.0)
Platelet count decreased	10 (5.0)	9 (4.5)
Thrombocytopenia	16 (8.0)	11 (5.5)

a. Events that occurred in ≥ 10 of the patients in at least one study arm.
b. Choosing from imatinib, nilotinib, dasatinib or bosutinib prior to randomization.
c. MedDRA version 27.1; SOCs and PTs 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; TKI: tyrosine kinase inhibitor

Table 11: Discontinuations due to AEs – RCT, direct comparison: asciminib vs. TKIa (ASC4FIRST study) (multipage table)

	Patients with event n (%)	
SOC[b] **PT[b]**	**asciminib** **N = 200**	**TKI[a]** **N = 201**
Overall rate of discontinuations due to AEs	10 (5.0)	26 (12.9)
Blood and lymphatic system disorders	2 (1.0)	3 (1.5)
Lymphadenopathy	0 (0)	1 (0.5)
Lymphopenia	0 (0)	1 (0.5)
Neutropenia	0 (0)	1 (0.5)
Thrombocytopenia	2 (1.0)	0 (0)
Cardiac disorders	0 (0)	2 (1.0)
Heart failure	0 (0)	1 (0.5)
Pericardial effusion	0 (0)	1 (0.5)
Gastrointestinal disorders	1 (0.5)	5 (2.5)
Colitis	0 (0)	1 (0.5)
Diarrhoea	0 (0)	3 (1.5)
Nausea	0 (0)	1 (0.5)
Pancreatitis	0 (0)	1 (0.5)
Pancreatitis acute	1 (0.5)	0 (0)
General disorders and administration site conditions	0 (0)	5 (2.5)
Asthenia	0 (0)	2 (1.0)
Face oedema	0 (0)	1 (0.5)
Pyrexia	0 (0)	1 (0.5)
Hepatobiliary disorders	1 (0.5)	1 (0.5)
Hepatotoxicity	1 (0.5)	1 (0.5)
Immune system disorders	0 (0)	1 (0.5)
Hypersensitivity	0 (0)	1 (0.5)
Investigations	4 (2.0)	4 (2.0)
Alanine aminotransferase increased	0 (0)	1 (0.5)
Aspartate aminotransferase increased	0 (0)	1 (0.5)
Electrocardiogram QT prolonged	0 (0)	1 (0.5)
Lipase increased	3 (1.5)	0 (0)
Lymphocyte count decreased	0 (0)	1 (0.5)
Neutrophil count decreased	1 (0.5)	0 (0)
Platelet count decreased	0 (0)	1 (0.5)
Metabolism and nutrition disorders	0 (0)	1 (0.5)
Decreased appetite	0 (0)	1 (0.5)

Table 11: Discontinuations due to AEs – RCT, direct comparison: asciminib vs. TKIa (ASC4FIRST study) (multipage table)

	Patients with event n (%)	
SOC[b] **PT[b]**	**asciminib** **N = 200**	**TKI[a]** **N = 201**
Musculoskeletal and connective tissue disorders	0 (0)	2 (1.0)
Muscular weakness	0 (0)	1 (0.5)
Myalgia	0 (0)	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	2 (1.0)
Metastatic gastric cancer	0 (0)	1 (0.5)
Prostate cancer	0 (0)	1 (0.5)
Nervous system disorders	2 (1.0)	0 (0)
Cerebrovascular accident	1 (0.5)	0 (0)
Neuralgia	1 (0.5)	0 (0)
Psychiatric disorders	1 (0.5)	0 (0)
Delirium	1 (0.5)	0 (0)
Respiratory, thoracic and mediastinal disorders	0 (0)	3 (1.5)
Pleural effusion	0 (0)	3 (1.5)
Skin and subcutaneous tissue disorders	0 (0)	2 (1.0)
Rash	0 (0)	1 (0.5)
Rash maculo-papular	0 (0)	1 (0.5)
Vascular disorders	1 (0.5)	0 (0)
Peripheral vascular disease	1 (0.5)	0 (0)

a. Choosing from imatinib, nilotinib, dasatinib or bosutinib prior to randomization.
b. MedDRA version 27.1; 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; TKI: tyrosine kinase inhibitor