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Bosutinib (chronic myeloid leukaemia) – Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Bosutinib (chronische myeloische Leukämie) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 30 August 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CMQ	Customized MedDRA Query
CNL	chronic myeloid leukaemia
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D VAS	European-Quality-of-Life-5-Dimensions questionnaire visual analogue scale
FACT-Leu	Functional Assessment of Cancer Therapy – Leukaemia
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
mITT	modified intention to treat
MMR	major molecular response
Ph^+CML	Philadelphia chromosome-positive chronic myeloid leukaemia
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	system organ class

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug bosutinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 June 2021.

For the drug to be assessed, the company submitted a dossier for early benefit assessment for the first time as per 18 May 2018. With its decision dated 22 November 2018, the G-BA set a time limit for the validity of the decision until 1 June 2021. In accordance with the justification paper on the decision dated 22 November 2018, the reason for imposing the time limit was that the overall survival data available for the assessment from the 12 July 2017 data cut-off of the BFORE study were of little informative value since few events had occurred. To facilitate the reassessment of benefit after expiry, the final study results of all outcomes from the ongoing BFORE study were to be presented in the dossier.

Research question

The aim of this report is to assess the added benefit of bosutinib in comparison with imatinib, nilotinib, or dasatinib as the appropriate comparator therapy (ACT) in adults with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukaemia (Ph^+ CML) in chronic phase.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of bosutinib

Therapeutic indication	**ACT**[a]
Treatment of adults with newly diagnosed Ph^+ CML in chronic phase	**Imatinib** or nilotinib or dasatinib
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; Ph^+ CML: Philadelphia chromosome-positive chronic myeloid leukaemia	

The company followed the G-BA's specification of the ACT and selected imatinib from the presented options.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier.

Study pool and study design

The BFORE study was included in the benefit assessment. The BFORE study is an open-label, randomized controlled trial (RCT) comparing bosutinib versus imatinib in adults with newly diagnosed chronic myeloid leukaemia (CML) in chronic phase.

The study randomized a total of 536 patients (268 to each treatment arm). The Philadelphia chromosome was found in 487 of these patients (246 in the bosutinib arm and 241 in the imatinib arm). These patients represent the relevant subpopulation for this benefit assessment.

In both study arms, the treatment was administered as approved. Treatment was to be discontinued in case of treatment failure, unacceptable toxicity, withdrawal of the declaration of consent, or upon the investigator's discretion. The primary outcome of the BFORE study was major molecular response (MMR) after 12 months. Patient-relevant secondary outcomes were overall survival, morbidity, health-related quality of life, and adverse events (AEs).

Risk of bias

For the BFORE study, the risk of bias on the study level was rated as low. On the outcome level, the risk of bias was rated as low for overall survival and as high for the remaining outcomes.

Results

Mortality – overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of bosutinib in comparison with imatinib; an added benefit is therefore not proven.

Morbidity – transition to blast crisis

For the outcome of transition to blast crisis, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of bosutinib in comparison with imatinib; an added benefit is therefore not proven.

Morbidity – health status (European-Quality-of-Life-5-Dimensions questionnaire visual analogue scale [EQ-5D VAS])

For the outcome of health status, as documented using the EQ-5D VAS, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of bosutinib in comparison with imatinib; an added benefit is therefore not proven.

Health-related quality of life – Functional Assessment of Cancer Therapy – Leukaemia (FACT-Leu)

For health-related quality of life as measured using FACT-Leu, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of bosutinib in comparison with imatinib; an added benefit is therefore not proven.

Side effects – serious adverse events [SAEs]

For the outcome of SAEs, no statistically significant difference between treatment groups was found. Consequently, there is no hint of greater or lesser harm of bosutinib in comparison with imatinib; greater or lesser harm is therefore not proven.

Side effects – severe AEs

For the outcome of severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), a statistically significant difference to the disadvantage of bosutinib in comparison with imatinib was found. For this outcome, there was also an effect modification for the attribute of age. A statistically significant difference to the disadvantage of bosutinib was found both for patients < 65 years of age and for those ≥ 65 years of age. This results in a hint of greater harm of bosutinib in comparison with imatinib for both age groups, with the extent differing between them.

Side effects – discontinuation due to AEs

For the outcome of discontinuation due to AEs, a statistically significant difference to the disadvantage of bosutinib was found. For this outcome, there is therefore a hint of greater harm from bosutinib in comparison with imatinib.

Side effects – specific AEs in favour of bosutinib

Eye disorders (system organ class [SOC], AEs)

For the outcome of eye disorders (SOC, AEs), a statistically significant difference in favour of bosutinib was found. Despite a high risk of bias of results, this outcome is associated with a high certainty of results due to the effect size already observed early in the study. For this outcome, this results in an indication of lesser harm from bosutinib in comparison with imatinib.

Peripheral oedema (PT, AEs), musculoskeletal and connective tissue disorders (SOC, SAEs), neutropenia (PT, severe AEs)

For each of the outcomes of peripheral oedema (PT, AEs), musculoskeletal and connective tissue disorders (SOC, AEs), and neutropenia (PT, severe AEs), a statistically significant difference in favour of bosutinib was found. For each of these outcomes, there is therefore a hint of lesser harm from bosutinib in comparison with imatinib.

Side effects – specific AEs to the disadvantage of bosutinib

Gastrointestinal disorders (SOC, AEs), pruritus (PT, AEs), thrombocytopenia (PT, severe AEs), cardiac disorders (SOC, severe AEs), and elevated lipase (PT, severe AEs)

For each of the outcomes of gastrointestinal disorders (SOC, AEs), pruritus (PT, AEs), thrombocytopenia (PT, severe AEs), cardiac disorders (SOC, severe AEs), and elevated lipase (PT, severe AEs), there is a statistically significant difference to the disadvantage of bosutinib. For each of these outcomes, there is therefore a hint of greater harm from bosutinib in comparison with imatinib.

Diarrhoea (PT, severe AEs), abnormal hepatic function (Customized MedDRA Query [CMQ], severe AEs)

For each of the outcomes of diarrhoea (PT, severe AEs) and abnormal hepatic function (CMQ, severe AEs), a statistically significant difference to the disadvantage of bosutinib was found. Despite a high risk of bias of results, these outcomes are each associated with high certainty of results due to the effect size already observed early in the study. For each of these outcomes, there is therefore an indication of greater harm from bosutinib in comparison with imatinib.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug bosutinib compared with the ACT is assessed as follows:

Overall, the comparison of bosutinib with imatinib showed favourable and unfavourable effects exclusively for the outcome category of side effects.

For the dimension of serious/severe side effects, the total rate of severe AEs is associated with a hint of greater harm of bosutinib in comparison with imatinib, with an extent of minor or major depending on patient age. For the dimension of non-serious/non-severe side effects, there is a hint of greater harm from bosutinib in comparison with imatinib for total rate of discontinuation due to AEs. Further disadvantages of different extents were found for several specific AEs.

These disadvantages are offset by advantages in individual specific AEs, for the dimensions of serious/severe as well as non-serious/non-severe side side effects.

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

In summary, for patients with newly diagnosed Ph^+ CML in chronic phase, there is a hint of lesser benefit of bosutinib in comparison with imatinib. This is in line with the results of the initial assessment.

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

Table 3: Bosutinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Treatment of adults with newly diagnosed Ph^+ CML in chronic phase	**Imatinib** or nilotinib or dasatinib	Hint of lesser benefit[b]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**.
b. Only patients with an ECOG-PS of 0 or 1 were included in the BFORE study. It remains unclear whether the observed effects can be assumed to occur also in patients with an ECOG-PS ≥ 2.

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; Ph^+ CML: Philadelphia chromosome-positive chronic myeloid leukaemia

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

2.2 Research question

The aim of this report is to assess the added benefit of bosutinib in comparison with imatinib, nilotinib, or dasatinib as the ACT in adults with newly diagnosed Ph^+ CML in chronic phase.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of bosutinib

Therapeutic indication	**ACT**[a]
Treatment of adults with newly diagnosed Ph^+ CML in chronic phase	**Imatinib** or nilotinib or dasatinib
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; Ph^+ CML: Philadelphia chromosome-positive chronic myeloid leukaemia	

The company followed the G-BA's specification of the ACT and selected imatinib from the presented options.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier.

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on bosutinib (as of 18 March 2021)
- Bibliographic literature search on bosutinib (most recent search on 18 March 2021)
- Search in trial registries / study results databases on bosutinib (most recent search on 18 March 2021)
- Search on the G-BA website on bosutinib (most recent search on 18 March 2021)

To check the completeness of the study pool:

- Search in trial registries for bosutinib (most recent search on 8 June 2021); see Appendix A of the full dossier assessment for search strategies.

The check did not identify any additional relevant studies.

2.3.1 Included studies

The study listed in the table below was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: bosutinib vs. imatinib

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication and other sources[c] (yes/no [reference])
BFORE[d] study (AV001, B1871053)	Yes	Yes	No	Yes [3,4]	Yes [5-7]	Yes [8-10]

a. Study sponsored by the company.
b. References off trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the tables below, the study will be referred to using this acronym.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool is consistent with that of the company. The BFORE study has already been submitted and assessed in the prior benefit assessment of bosutinib [10]. The present benefit assessment is based on the final study results of the BFORE study.

2.3.2 Study characteristics

Table 6 and Table 7 present the study used in the benefit assessment.

Table 6: Characterization of the included study – RCT, direct comparison: bosutinib vs. imatinib

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
BFORE	RCT, open-label, parallel-group	Adults (≥ 18 years) with newly diagnosed[b] chronic myeloid leukaemia in chronic phase	Bosutinib (N = 268) Imatinib (N = 268) Relevant subpopulation thereof with Philadelphia chromosome: Bosutinib (n = 246) Imatinib (n = 241)	Screening: up to 28 days Treatment: ▪ Treatment phase: up to Week 48 ▪ Extension phase[c]: up to the end of the 5th year after randomization Follow-up observation[d]: ▪ up to 28 days after the last dose of the randomized study drug ▪ In case of treatment discontinuation, by phone up to 5 years after randomization	146 centres in Australia, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Mexico, Netherlands, Norway, Poland, Singapore, Slovakia, South Africa, South Korea, Spain, Sweden, Taiwan, Thailand, Ukraine, United Kingdom, United States 07/2014–04/2020	Primary: major molecular response (MMR) Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. At study inclusion, the diagnosis had to have been established for ≤ 6 months.
c. In the extension phase, treatment with the randomized study drug was continued.
d. Outcome-specific information is provided in Table 8.

AE: adverse event; MMR: major molecular response; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characterization of the intervention – RCT, direct comparison: bosutinib vs. imatinib

Study	Intervention	Comparison	Pretreatment and concomitant treatment
BFORE	Bosutinib orally, 400 mg/day, recommended to be taken in the morning with a meal and 200 mL of water ▪ Dose increases were permitted in case of insufficient response or loss of already achieved response; dose reductions were permitted in case of side effects.	Imatinib orally, 400 mg/day, recommended to be taken in the morning with a meal and 200 mL of water ▪ Dose increases were permitted in case of insufficient response or loss of already achieved response; dose reductions were permitted in case of side effects.	**Prior treatment** Hydroxyurea and/or anagrelide (≤ 6 months prior to study start, up to 21 days after study inclusion) **Permitted concomitant treatment** ▪ Treatment of gastrointestinal symptoms (e.g. diarrhoea) ▪ Growth factors for neutropenia ▪ Systemic steroids against AEs (≤ 10 days and ≤ 60 mg/day) ▪ Inhaled and topical steroids **Non-permitted prior and concomitant treatment** ▪ Chemotherapy, radiotherapy, immunotherapy, or other cancer therapy ▪ Other investigational substances ▪ QT-prolonging drugs ▪ Anticoagulants with warfarin or related oral drugs ▪ Prophylaxis with growth factors ▪ Radiotherapy or major surgery ≤ 14 days before study start

AE: adverse event; RCT: randomized controlled trial

Study design and relevant subpopulation

The BFORE study is an open-label RCT comparing bosutinib versus imatinib. It included adults with newly diagnosed CML in chronic phase, with "newly diagnosed" being defined as "within 6 months before study inclusion". Patients were to have received no prior CML treatment other than hydroxyurea or anagrelide.

The study randomized a total of 536 patients (268 to each treatment arm), stratified by Sokal score and geographic region. This population formed the intention to treat (ITT) population.

The presence of the Philadelphia chromosome was determined after randomization. From among the ITT population, a total of 487 patients (246 in the bosutinib arm and 241 in the imatinib arm) were Philadelphia chromosome positive. These patients represent the population identified by the company as modified ITT (mITT). The mITT population is the relevant subpopulation for the present benefit assessment. Unless indicated otherwise, the data below is based on the mITT population.

The study treatment was administered following the regimens described in Table 7 and corresponds to the specifications of the Summary of Product Characteristics (SPC) for bosutinib [11] and imatinib [12] in the present therapeutic indication. Treatment was to be discontinued in case of treatment failure, unacceptable toxicity, withdrawal of the declaration of consent, or upon the investigator's discretion.

The primary outcome was MMR after 12 months. Patient-relevant secondary outcomes were overall survival, morbidity, health-related quality of life, and adverse events (AEs).

Data cut-off dates

The 1st visit of the BFORE study was on 15 July 2014, and the study came with a total of 7 data cut-offs:

- 1st data cut-off: 14 January 2016 (predefined interim analysis of MMR status)
- 2nd data cut-off: 27 April 2016 (predefined interim analysis of MMR status)
- 3rd data cut-off: 11 August 2016 (predefined interim analysis of MMR status)
- 4th data cut-off: 12 April 2017 (predefined interim analysis of MMR status)
- 5th data cut-off: 12 July 2017 (post hoc analysis requested by the European Medicines Agency [EMA])
- 6th data cut-off: 11 June 2018 (analysis after a follow-up period of ≥ 36 months)
- 7th data cut-off: 12 June 2020: (final analysis at study end after a follow-up period of ≥ 60 months)

The final data cut-off forms the basis for the present benefit assessment.

Planned duration of follow-up observation

Table 8 shows the planned duration of the patients' follow-up observation for the individual outcomes.

Table 8: Planned follow-up observation – RCT, direct comparison: bosutinib vs. imatinib

Study **Outcome category** **Outcome**	**Planned follow-up observation**
BFORE	
Mortality	
All-cause mortality	Up to 5 years after randomization
Morbidity	
Health status	Up to 28 days after the last dose of the study drug
Transition to blast crisis	Up to 5 years after randomization
Health-related quality of life	Up to 28 days after the last dose of the study drug
Side effects	
All outcomes of the side effects category	Up to 28 days after the last dose of the study drug[a]
a. SAEs about which the investigator was notified after the active reporting period closed had to be reported regardless of the specified follow-up duration.	
RCT: randomized controlled trial; SAE: serious adverse event	

The follow-up periods for the outcomes of morbidity (except for transition to blast crisis), health-related quality of life, and side effects are systematically shortened since the outcomes were surveyed only for the period of treatment with the study drug (plus 28 days). To be able to draw a reliable conclusion for the entire study period or until patient death, these outcomes, like survival, would have to be surveyed and analysed over the entire period.

Characterization of the study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characterization of the study population – RCT, direct comparison: bosutinib vs. imatinib

Study **Characteristic** **Category**	**Bosutinib** **N[a] = 246**	**Imatinib** **N[a] = 241**
BFORE		
Age [years], mean (SD)	51 (16)	51 (14)
Sex [f/m], %	42/58	44/56
Disease duration: Period from initial diagnosis to randomization [days], median [min; max]	23 [4; 183]	25 [1; 183]
Geographic region, n (%)		
USA, Canada, and Western Europe	137 (56)	135 (56)
Eastern Europe, Latin America, and South America	74 (30)	73 (30)
Other regions	35 (14)	33 (14)
ECOG Performance Status, n (%)		
0	174 (71)	171 (71)
1	72 (29)	70 (29)
Sokal score, n (%)		
> 1.2 (high risk)	51 (21)	51 (21)
≥ 0.8 to ≤ 1.2 (moderate risk)	101 (41)	95 (39)
< 0.8 (low risk)	94 (38)	95 (39)
Extramedullary disease, n (%)		
Yes	10 (4)	7 (3)
No	235 (96)	231 (96)
Missing	1 (0)	3 (1)
Treatment discontinuation[b], n (%)	98 (40)	96 (40)
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients from the relevant subpopulation. Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. In the bosutinib arm, treatment discontinuation was largely due to AEs (25%), followed by treatment failure (5%), while in the imatinib arm, treatment discontinuation was in most cases due to treatment failure (15%), followed by AEs (14%).

f: female; m: male; max: maximum; min.: minimum; n: number of patients in the category; N: number of randomized (or included) patients with Philadelphia chromosome; ND: no data; RCT: randomized controlled trial; SD: standard deviation

At 487 patients, the relevant subpopulation (mITT population) comprises about 91% of the ITT population. The patient characteristics of the two treatment arms are largely balanced.

The average patient age was about 51 years. Both treatment arms included slightly more men (approx. 57%) than women (43%). At study inclusion, the median treatment duration was 23 and 25 days, respectively. In the BFORE study, the majority (71%) of patients had a Cooperative Oncology Group Performance Status (ECOG-PS) of 0. About 20% of patients had a baseline Sokal score indicating high risk.

While at 40% each, the bosutinib arm and the imatinib arm exhibit the same percentage of treatment discontinuation, the reasons for discontinuation differ markedly. The difference between bosutinib and imatinib was particularly pronounced for treatment discontinuation due to AEs, at 25.2% versus 13.8% of patients, and for treatment discontinuation due to treatment failure or disease progression, at 5.3% versus 15.4% of patients. No data are available for study discontinuation.

Course of the study.

Table 10 shows the mean/median duration of patient treatment as well as the mean/median duration of follow-up observation for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: bosutinib vs. imatinib

Study **Duration of the study phase** **Outcome category**	**Bosutinib** **N = 246**	**Imatinib** **N = 241**
BFORE		
Treatment duration [weeks]		
Median [min; max]	239.6 [1; 256]	239.3 [3; 245]
Mean (SD)	174.8 (91.3)	169.1 (94.4)
Follow-up observation duration [weeks]		
Overall survival		
Median [min; max]	240.1 [1.6; 257.6]	240.1 [7.4; 258.0]
Mean (SD)	226.8 (45.6)	222.6 (51.5)
Morbidity[a] (transition to blast crisis)		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Morbidity (EQ-5D VAS)		
Median [min; max]	239.4 [0.1; 256.1]	239.1 [0.1; 246.0]
Mean (SD)	173.3 (89.4)	166.5 (94.2)
Health-related quality of life (FACT-Leu)		
Median [Q1; Q3]	239.4 [88.6; 240.3]	239.1 [58.4; 240.3]
Mean (SD)	172.7 (89.8)	166.1 (94.0)
Side effects[b]		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND

a. After treatment end, transformation was surveyed by phone every 3 months.
b. AEs were surveyed for up to 28 days after the last treatment. Therefore, their follow-up observation duration is longer than the above-indicated treatment duration.

EQ-5D: European-Quality-of-Life-5-Dimensions questionnaire; FACT-Leu: Functional Assessment of Cancer Therapy – Leukaemia; max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

The treatment and follow-up durations are balanced between both treatment arms. However, the standard deviation is very high in each case. The company's dossier does not contain any data on follow-up duration for the outcome of morbidity (transition to blast crisis) or for side effects.

Subsequent therapies

Table 11 shows which subsequent therapies patients received after discontinuing the study drug. The data in the table are based on the total population of the BFORE study; no data are available on the relevant subpopulation (91% of the total population).

Table 11: Data on antineoplastic subsequent therapies (≥ 1 patient in ≥ 1 treatment arm) – RCT, direct comparison: bosutinib vs. imatinib (BFORE study)

Study Drug	Patients with subsequent therapy n (%)	
	Bosutinib N = 268	Imatinib N = 265
BFORE		
Total[a]	86 (32.1)	97 (36.6)
Dasatinib	30 (11.2)	48 (18.1)
Imatinib	38 (14.2)	14 (5.3)
Nilotinib	14 (5.2)	29 (10.9)
Bosutinib	6 (2.2)	30 (11.3)
Hydroxycarbamide	7 (2.6)	10 (3.8)
Dasatinib monohydrate	6 (2.2)	10 (3.8)
Ponatinib	4 (1.5)	10 (3.8)
Imatinib mesylate	8 (3.0)	3 (1.1)
Nilotinib hydrochloride	3 (1.1)	4 (1.5)
Asciminib	1 (0.4)	2 (0.8)
Cytarabine	1 (0.4)	1 (0.4)
Paclitaxel	2 (0.7)	0
Ponatinib hydrochloride	0	2 (0.8)
Anagrelide	0	1 (0.4)
Anagrelide hydrochloride	1 (0.4)	0
Busulfan	0	1 (0.4)
Cyclophosphamide	0	1 (0.4)
Daunorubicin	1 (0.4)	0
Doxorubicin; vincristine	0	1 (0.4)
Fluorouracil	0	1 (0.4)
Radotinib hydrochloride	1 (0.4)	0
Trastuzumab	1 (0.4)	0
Other antineoplastic agents	0	1 (0.4)

a. All patients with or without Philadelphia chromosome who took at least 1 dose of the randomized study drug (safety population).

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

The BFORE study did not restrict potential subsequent therapies. Up to the present data cut-off, about a third of the BFORE study's total population had received antineoplastic subsequent therapy; in both study arms, most of these involved other tyrosine kinase inhibitors (TKIs) (dasatinib, imatinib, nilotinib). In the comparator arm, 11% of patients received bosutinib as subsequent therapy. This way, an approved treatment option is available at least for patients for whom imatinib, nilotinib, and dasatinib are deemed unsuitable treatment options. No data are available on the extent to which these criteria were met for all patients.

Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: bosutinib vs. imatinib

Study	Adequate random sequence generation	Allocation concealment	Blinding		Results-independent reporting	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
BFORE	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

For the BFORE study, the risk of bias on the study level was rated as low. This concurs with the company's assessment.

Restrictions resulting from the open-label study design are described in Section 2.4 under risk of bias at outcome level.

Transferability of the study results to the German healthcare context

The company bases the transferability of study results to the German context of care on the comparison of BFORE patient characteristics with the data of the European Society for Medical Oncology (ESMO) guideline [13] and studies on the epidemiology of CML [14,15].

The company did not submit any further information on the transferability of the study results to the German healthcare context.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Transition to blast crisis
  - Health status surveyed with the EQ-5D VAS
- Health-related quality of life
  - Health-related quality of life, surveyed with the FACT-Leu
- Side effects
  - SAEs
  - Severe AEs (Common-Terminology-Criteria-for-Adverse-Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4).

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

Table 13: Matrix of outcomes – RCT, direct comparison: bosutinib vs. imatinib

Study	Outcomes							
	Overall survival	Morbidity (transition to blast crisis)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-Leu)	SAEs[a]	Severe AEs[a, b]	Discontinuation due to AEs[a]	Other specific AEs[c]
BFORE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Excluding progression-associated AEs (PT: acute myeloid leukaemia and leukaemic retinopathy).
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events were assessed (MedDRA coding): eye disorders (SOC, AEs), gastrointestinal disorders (SOC, AEs), peripheral oedema (PT, AEs), musculoskeletal and connective tissue disorders (SOC, SAEs), pruritus (PT, AEs), neutropenia (PT, severe AEs), thrombocytopenia (PT, severe AEs), cardiac disease (SOC, severe AEs), diarrhoea (PT, severe AEs), abnormal hepatic function (CMQ, severe AEs), elevated lipase (PT, severe AEs).

AE: adverse event; CMQ: Customized MedDRA Queries; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European-Quality-of-Life-5-Dimensions questionnaire; FACT-Leu: Functional Assessment of Cancer Therapy – Leukaemia; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

- Health status (as measured using EQ-5D VAS): For the EQ-5D VAS, the company's dossier presents responder analyses for the percentage of patients with a change by ≥ 7 or ≥ 10 points as well as by 15% (on a scale of 0 to 100 mm or points). As discussed in IQWiG General Methods [16], a predefined response criterion should cover at least 15% of the range of an instrument's scale (for post hoc analyses, exactly 15% of the range of the scale) in order to reflect with sufficient certainty a change which is perceivable for patients. The 15% responder analyses presented by the company were used for the assessment, while the ≥ 7-point and ≥ 10-point responder analyses are presented as supplementary information in Appendix D of the full dossier assessment.
- Health-related quality of life (surveyed using FACT-Leu): For health-related quality of life as per FACT-Leu total score, the company's dossier presents responder analyses for the percentage of patients with a change by ≥ 6 or ≥ 12 points as well as by 15% (on a scale of 0 to 176 points). As described above, the 15% responder analyses presented by the company were used for the assessment.

2.4.2 Risk of bias

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

Table 14: Risk of bias at study and outcome levels – RCT, direct comparison: bosutinib vs. imatinib

Study	Study level	Outcomes							
		Overall survival	Morbidity (transition to blast crisis)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-Leu)	SAEs[a]	Severe AEs[a, b]	Discontinuation due to AEs[a]	Other specific AEs[c]
BFORE	L	L	H[d]	H[e, f]	H[e, f]	H[d]	H[d]	H[e]	H[d, e]

a. Excluding progression-associated AEs (PT: acute myeloid leukaemia and leukaemic retinopathy).
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events were assessed (MedDRA coding): eye disorders (SOC, AEs), gastrointestinal disorders (SOC, AEs), peripheral oedema (PT, AEs), musculoskeletal and connective tissue disorders (SOC, SAEs), pruritus (PT, AEs), neutropenia (PT, severe AEs), thrombocytopenia (PT, severe AEs), cardiac disease (SOC, severe AEs), diarrhoea (PT, severe AE), abnormal hepatic function (CMQ, severe AEs), elevated lipase (PT, severe AEs).
d. Incomplete observations for potentially informative reasons.
e. Lack of blinding with subjective recording of outcomes; for specific AEs, applies only to those which are neither severe nor serious.
f. High percentage of missing values at study end (37% in both study arms).

AE: adverse event; CMQ: Customized MedDRA Queries; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European-Quality-of-Life-5-Dimensions questionnaire; FACT-Leu: Functional Assessment of Cancer Therapy – Leukaemia; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

The risk of bias of the results for the outcome of overall survival is rated as low. This rating is consistent with that by the company.

The risk of bias of the results for the outcome of transition to blast crisis is deemed high. As per study protocol, this outcome is followed up beyond the end of treatment, but the analyses presented by the company include only events which occurred while taking the study drug. The presented analyses therefore do not allow drawing any conclusions on the complete follow-up period. The risk of bias is therefore deemed high due to incomplete follow-up for potentially informative reasons. It remains unclear why the company has not submitted any corresponding

analyses including all available follow-up periods. The assessment of the risk of bias for this outcome departs from the company's assessment, which rated the risk of bias as low.

For the results on the outcomes of health status (EQ-5D VAS) and health-related quality of life (FACT-Leu), the risk of bias is deemed high due to the high percentage of missing values as well as lack of blinding with subjective recording of outcomes. Due to lack of blinding, the company likewise rated the risk of bias for these outcomes as high.

For the results on the outcomes of SAEs, severe AEs, and specific AEs, the risk of bias is also deemed high, due to incomplete follow-up for potentially informative reasons. Most treatment discontinuations in the BFORE study were due to AEs (25.2% in the bosutinib arm and 13.8% in the imatinib arm) and treatment failure or disease progression (5.3% in the bosutinib arm and 15.4% in the imatinib arm), with the percentages differing strongly between treatment arms. These reasons for discontinuation are potentially informative for the occurrence of events in these outcomes.

For the results on the outcomes of discontinuation due to AEs and non-serious/non-severe AEs, lack of blinding leads to a high risk of bias.

The assessment of risk of bias in part deviates from the company's evaluation, which rated the risk of bias as low for the results of the outcome of serious/severe events and high for the results of the outcome of non-serious/non-severe events.

2.4.3 Results

Table 15 summarizes the results on the comparison of bosutinib with imatinib in patients with newly diagnosed Ph^+ CML in chronic phase. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier.

Kaplan-Meier curves relating to the event-time analyses are found in Appendix B of the full dossier assessment. The results regarding common AEs, SAEs, severe AEs, and discontinuation due to AEs are found in Appendix C of the full dossier assessment.

Table 15: Results (overall survival, morbidity, side effects) – RCT, direct comparison: bosutinib vs. imatinib (multipage table)

Study Outcome category Outcome	Bosutinib N	Bosutinib Median time to event in weeks [95% CI] Patients with event n (%)	Imatinib N	Imatinib Median time to event in weeks [95% CI] Patients with event n (%)	Bosutinib vs. imatinib HR [95% CI]; p-value[a]
BFORE					
Mortality					
Overall survival	246	NR 12 (4.9)	241	NR 14 (5.8)	0.80 [0.37; 1.73]; 0.564
Morbidity					
Transition to blast crisis	246	–[b] 3 (1.2)	241	–[b] 1 (0.4)	2.89 [0.30; 28.03]; 0.336
Health status (EQ-5D VAS)[c]	246	NA [241.0; NC] 72 (29.3)	241	NR 62 (25.7)	1.09 [0.78; 1.54]; 0.608
Health-related quality of life					
FACT-Leu total score[c]	246	NR 51 (20.7)	241	NR 44 (18.3)	1.16 [0.77; 1.73]; 0.477
Physical well-being[c] (PWB)	246	NR [241.0; NC] 86 (35.0)	241	NR 86 (35.7)	0.92 [0.68; 1.25]
Social well-being[c] (SWB)	246	NR [96.1; NC] 103 (41.9)	241	240.9 [144.1; NC] 92 (38.2)	1.13 [0.86; 1.50]
Emotional well-being[c] (EWB)	246	NR [192.0; NC] 92 (37.4)	241	NR 77 (32.0)	1.20 [0.88; 1.62]
Functional well-being[c] (FWB)	246	NA [133.4; NC] 98 (39.8)	241	NR 73 (30.3)	1.38 [1.02; 1.87]
FACT-LeuS[c]	246	NR 48 (19.5)	241	NR 52 (21.6)	0.85 [0.57; 1.26]
Side effects					
AEs[d] (supplementary data)	246	0.4 [0.3; 0.7] 243 (98.8)	239	1.1 [0.9; 1.1] 236 (98.7)	–
SAEs[d]	246	NR [224.1; NC] 91 (37.0)	239	NR 65 (27.2)	1.37 [1.00; 1.89]; 0.051
Severe AEs[d, e]	246	21.1 [12.1; 41.7] 182 (74.0)	239	107.1 [49.9; 168.1] 138 (57.7)	1.55 [1.24, 1.93]; < 0.001
Discontinuation due to AEs[d]	246	NR 62 (25.2)	239	NR 33 (13.8)	1.82 [1.19; 2.77]; 0.005
Eye disorders (SOC, AEs)	246	NR 39 (15.9)	239	135.4 [62.1; NC] 114 (47.7)	0.25 [0.17, 0.36]; < 0.001
Gastrointestinal disorders (SOC, AEs)	246	1.0 [0.6; 1.4] 208 (84.6)	239	9.4 [5.3; 21.3] 162 (67.8)	1.90 [1.54, 2.35]; < 0.001
Peripheral oedema (PT, AEs)	246	NR 18 (7.3)	239	NR 38 (15.9)	0.42 [0.24; 0.73]; 0.002

Table 15: Results (overall survival, morbidity, side effects) – RCT, direct comparison: bosutinib vs. imatinib (multipage table)

Study Outcome category Outcome	Bosutinib N	Bosutinib Median time to event in weeks [95% CI] Patients with event n (%)	Imatinib N	Imatinib Median time to event in weeks [95% CI] Patients with event n (%)	Bosutinib vs. imatinib HR [95% CI]; p-value[a]
Musculoskeletal and connective tissue disorders (SOC, SAEs)	246	NR [166.7; NC] 98 (39.8)	239	19.1 [8.1; 48.4] 145 (60.7)	0.45 [0.35, 0.59]; < 0.001
Pruritus (PT, AEs)	246	NR 27 (11.0)	239	NR 9 (3.8)	3.02 [1.42; 6.43]; 0.003
Neutropenia (PT, severe AEs[e])	246	NR 16 (6.5)	239	NR 28 (11.7)	0.54 [0.29; 1.01]; 0.049
Thrombocytopenia (PT, severe AEs[e])	246	NR 23 (9.3)	239	NR 10 (4.2)	2.31 [1.10; 4.86]; 0.023
Cardiac disorders (SOC, severe AEs[e])	246	NR 15 (6.1)	239	NR 4 (1.7)	3.66 [1.21; 11.04]; 0.014
Diarrhoea (PT, severe AEs[e])	246	NR 22 (8.9)	239	NR 3 (1.3)	7.35 [2.20, 24.56]; < 0.001
Abnormal hepatic function (CMQ, severe AEs[e])	246	NR 66 (26.8)	239	NR 10 (4.2)	7.08 [3.64, 13.77]; < 0.001
Elevated lipase (PT, severe AEs[e])	246	NR 32 (13.0)	239	NR 13 (5.4)	2.44 [1.28; 4.65]; 0.005

a. For all outcomes except transition to blast crisis: Cox proportional hazards model and log rank test, each stratified by Sokal score and geographic region; for transition to blast crisis: proportional subdistribution hazards model, taking into account the competing risks of treatment discontinuation (except due to progression) and death, stratified by Sokal score and geographic region.
b. Given the small number of events, the median reported by the company does not permit a meaningful interpretation.
c. Patients with an initial deterioration by ≥ 15% of the scale range. This corresponds to a deterioration by the following values: EQ-5D VAS: ≥ 15 points, FACT-Leu total score: ≥ 26.4 points; physical well-being (PWB), social well-being (SWB), and functional well-being (FWB): ≥ 4.2 points; emotional well-being (EWB): ≥ 3.6 points; additional leukaemia-specific problems (LeuS): ≥ 10.2 points.
d. Excluding progression-associated AEs (PT: acute myeloid leukaemia; chronic myeloid leukaemia, and leukaemic retinopathy); when considering all AEs, the number of patients with (at least 1) event in the control arm increases by 1 for the outcomes of SAEs, severe AEs, and discontinuation due to AEs, while the number does not change in the intervention arm.
e. Operationalized as CTCAE grade ≥ 3.

CI: confidence interval; CMQ: Customized MedDRA Queries; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European-Quality-of-Life-5-Dimensions questionnaire; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; PT: preferred term; RCT: randomized controlled trial; SOC: system organ class; VAS: visual analogue scale

The available information allows deriving no more than an indication, e.g. of an added benefit, for the outcome of overall survival. The results for the remaining outcomes are each subject to a high risk of bias, and therefore, no more than a hint, e.g. of added benefit, can be derived for

each of them. However, the certainty of results on the specific outcome level has not been downgraded in some cases (see below description of results).

Mortality

For the outcome of overall survival, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of bosutinib in comparison with imatinib; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Transition to blast crisis

For the outcome of transition to blast crisis, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of bosutinib in comparison with imatinib; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health status (EQ-5D VAS)

For health status, as documented using the EQ-5D VAS, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of bosutinib in comparison with imatinib; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

FACT-Leu

For health-related quality of life as measured using FACT-Leu, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit of bosutinib in comparison with imatinib; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

SAEs

For the outcome of SAEs, no statistically significant difference between treatment groups was found. Consequently, there is no hint of greater or lesser harm of bosutinib in comparison with imatinib; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Severe AEs (CTCAE grade ≥ 3)

For the outcome of severe AEs (CTCAE grade ≥ 3), a statistically significant difference to the disadvantage of bosutinib in comparison with imatinib was found. For this outcome, there was also an effect modification for the attribute of age (see Section 2.4.4). A statistically significant difference to the disadvantage of bosutinib was found both for patients < 65 years of age and for those ≥ 65 years of age. This results in a hint of greater harm of bosutinib in comparison with imatinib for both age groups, with the extent differing between them.

This departs from the company's assessment in so far as the company has likewise derived lesser benefit for the outcome of severe AEs, but without differentiating by effect modification using the attribute of age.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, a statistically significant difference to the disadvantage of bosutinib was found. For this outcome, there is therefore a hint of greater harm from bosutinib in comparison with imatinib.

This concurs with the company’s assessment.

Specific AEs in favour of bosutinib

Eye disorders (SOC, AEs)

For the outcome of eye disorders (SOC, AEs), a statistically significant difference in favour of bosutinib was found. Despite a high risk of bias of results, this outcome is associated with a high certainty of results due to the effect size observed already early in the study (see Kaplan-Meier curves in Appendix B.3 of the full dossier assessment). For this outcome, this results in an indication of lesser harm from bosutinib in comparison with imatinib.

Peripheral oedema (PT, AEs), musculoskeletal and connective tissue disorders (SOC, SAEs), neutropenia (PT, severe AEs)

For each of the outcomes of peripheral oedema (PT, AEs), musculoskeletal and connective tissue disorders (SOC, AEs), and neutropenia (PT, severe AEs), a statistically significant difference in favour of bosutinib was found. For each of these outcomes, there is therefore a hint of lesser harm from bosutinib in comparison with imatinib.

Specific AEs to the disadvantage of bosutinib

Gastrointestinal disorders (SOC, AEs), pruritus (PT, AEs), thrombocytopenia (PT, severe AEs), cardiac disorders (SOC, severe AEs), and elevated lipase (PT, severe AEs)

For each of the outcomes of gastrointestinal disorders (SOC, AEs), pruritus (PT, AEs), thrombocytopenia (PT, severe AEs), cardiac disorders (SOC, severe AEs), and elevated lipase (PT, severe AEs), there is a statistically significant difference to the disadvantage of bosutinib. For each of these outcomes, there is therefore a hint of greater harm from bosutinib in comparison with imatinib.

Diarrhoea (PT, severe AEs), abnormal hepatic function (CMQ, severe AEs)

For each of the outcomes of diarrhoea (PT, severe AEs) and abnormal hepatic function (CMQ, severe AEs), a statistically significant difference to the disadvantage of bosutinib was found. Despite a high risk of bias of results, these outcomes are associated with a high certainty of results due to the effect size observed already early in the study (see Kaplan-Meier curves in Appendix B.3 of the full dossier assessment). For each of these outcomes, there is therefore an indication of greater harm from bosutinib in comparison with imatinib.

2.4.4 Subgroups and other effect modifiers

The present assessment accounts for the following potential effect modifiers:

- Age (< 65 vs. ≥ 65 years)
- Sex (female vs. male)
- Sokal score (low risk [Sokal score < 0.8] vs. moderate risk [Sokal score ≥ 0.8 to ≤ 1.2] vs. high risk [Sokal score > 1.2])

From among these characteristics, only the Sokal score for the outcome of MMR was predefined.

Interaction tests are performed whenever at least 10 patients per subgroup were included in the analysis. For binary data, there must also be 10 events in at least 1 subgroup.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Table 16 shows the results of the subgroup analyses.

Table 16: Subgroups (side effects) – RCT, direct comparison: bosutinib vs. imatinib

Study Outcome Characteristic Subgroup	Bosutinib N	Bosutinib Median time to event in weeks [95% CI] Patients with event n (%)	Imatinib N	Imatinib Median time to event in weeks [95% CI] Patients with event n (%)	Bosutinib vs. imatinib HR [95% CI][a]	Bosutinib vs. imatinib p-value[a]
BFORE						
Severe AEs[b]						
Age						
< 65 years	198	24.9 [19.4; 61.1] 139 (70.2)	198	83.3 [41.0; 168.1] 116 (58.6)	1.34 [1.04; 1.71]	0.020
≥ 65 years	48	7.6 [3.7; 12.1] 43 (89.6)	41	163.1 [23.6; NC] 23 (56.1)	2.80 [1.67; 4.69]	< 0.001
Total					Interaction:	0.011[c]

a. Cox proportional hazards model and log rank test.
b. Operationalized as CTCAE grade ≥ 3.
c. The p-value from Cox proportional hazards model with treatment arm, subgroup characteristic, and interaction term between treatment arm and subgroup characteristic.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial

For the outcome of severe AEs (CTCAE grade ≥ 3), there was an interaction by the characteristic of age. For both age groups, there is a statistically significant difference to the disadvantage of bosutinib in comparison with imatinib. This results in a hint of greater harm of bosutinib in comparison with imatinib for both age groups, with the extent differing between them.

This departs from the company's assessment in so far as the company has likewise derived lesser benefit for the outcome of severe AEs, but without differentiating by effect modification using the attribute of age.

2.5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are presented below. The various outcome categories and the effect sizes have been taken into account. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on any added benefit by aggregating the conclusions reached at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

On the basis of the results presented in Section 2.4, the extent of the respective added benefit at outcome level was estimated (see Table 17).

Determination of outcome category for side effects outcomes

For the outcome below, it cannot be inferred from the dossier whether it was serious/severe or non-serious/non-severe. The allocation of this outcome is explained below.

The outcome of discontinuation due to AEs is allocated to the outcome category of non-serious/non-severe side effects due to a lack of information on severity and on the percentage of SAEs or severe AEs.

Table 17: Extent of added benefit at outcome level: bosutinib vs. imatinib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Bosutinib vs. imatinib** **Median time to event (weeks)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: NR vs. NR HR: 0.80 [0.37; 1.73] p = 0.564	Lesser/added benefit not proven
Morbidity		
Transition to blast crisis	Median: –[c] HR: 2.89 [0.30; 28.03] p = 0.336	Lesser/added benefit not proven
Health status (EQ-5D VAS)[d]	Median: NR vs. NR HR: 1.09 [0.78; 1.54] p = 0.608	Lesser/added benefit not proven
Health-related quality of life		
FACT-Leu total score[d]	Median: NR vs. NR HR: 1.16 [0.77; 1.73]; p = 0.477	Lesser/added benefit not proven
Side effects		
SAEs	Median: NR vs. NR HR: 1.37 [1.00; 1.89]; p = 0.051	Greater/lesser harm not proven
Severe AEs		
Age		
< 65 years	Median: 24.9 vs. 83.3 HR: 1.34 [1.04; 1.71] HR: 0.75 [0.58; 0.96][e] p = 0.020 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor
≥ 65 years	Median: 7.6 vs. 163.1 HR: 2.80 [1.67; 4.69] HR: 0.36 [0.21; 0.60][e] p < 0.001 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: major
Discontinuation due to AEs	Median: NR vs. NR HR: 1.82 [1.19; 2.77] HR: 0.55 [0.36; 0.84][e] p = 0.005 Probability: hint	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ Greater harm; extent: minor

Table 17: Extent of added benefit at outcome level: bosutinib vs. imatinib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Bosutinib vs. imatinib** **Median time to event (weeks)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Eye disorders (AEs)	Median: NR vs. 135.4 HR: 0.25 [0.17; 0.36]; p < 0.001 Probability: indication[f]	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: considerable
Gastrointestinal disorders (AEs)	Median: 1.0 vs. 9.4 HR: 1.90 [1.54; 2.35] HR: 0.53 [0.43; 0.65][e] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: considerable
Peripheral oedema (AEs)	Median: NR vs. NR HR: 0.42 [0.24; 0.73] p = 0.002 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: considerable
Musculoskeletal and connective tissue disorders (AEs)	Median: NR vs. 19.1 HR: 0.45 [0.35; 0.59] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm; extent: considerable
Pruritus (AEs)	Median: NR vs. NR HR: 3.02 [1.42; 6.43] HR: 0.33 [0.16; 0.70][e] p = 0.003 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm; extent: considerable
Neutropenia (severe AEs)	Median: NR vs. NR HR: 0.54 [0.29; 1.01] p = 0.049 Probability: hint	Outcome category: serious/severe side effects Lesser harm; extent: minor[g]
Thrombocytopenia (severe AEs)	Median: NR vs. NR HR: 2.31 [1.10; 4.86] HR: 0.43 [0.21; 0.91][e] p = 0.023 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor
Heart disease (severe AEs)	Median: NR vs. NR HR: 3.66 [1.21; 11.04] HR: 0.27 [0.09; 0.83][e] p = 0.014 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable

Table 17: Extent of added benefit at outcome level: bosutinib vs. imatinib (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Bosutinib vs. imatinib** **Median time to event (weeks)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Diarrhoea (severe AEs)	Median: NR vs. NR HR: 7.35 [2.20; 24.56] HR: 0.14 [0.04; 0.45][e] p < 0.001 Probability: indication[f]	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: major
Hepatic function abnormal (severe AEs)	Median: NR vs. NR HR: 7.08 [3.64; 13.77] HR: 0.14 [0.07; 0.27][e] p < 0.001 Probability: indication[f]	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: major
Elevated lipase (severe AEs)	Median: NR vs. NR HR: 2.44 [1.28; 4.65] HR: 0.41 [0.22; 0.78][e] p = 0.005 Probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm; extent: considerable

a. Probability is stated whenever a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper limit of the confidence interval (CI_u).
c. Given the small number of events, the medians indicated by the company do not permit a meaningful interpretation.
d. Patients with a deterioration by ≥ 15% of the scale range. This corresponds to a deterioration by the following values: EQ-5D VAS: ≥ 15 points; FACT-Leu total score: ≥ 26.4 points.
e. IQWiG calculations, reversed direction of effect to enable use of limits to derive the extent of added benefit.
f. The certainty of results is deemed high despite the high risk of bias because the biasing aspects do not call into question the observed effect due to the early occurrence of effects in the Kaplan Meier curves as well as the size of the effects.
g. Discrepancy between p-value (log rank test) and CI (Cox proportional hazards model) due to different calculation methods; derived using p-value.

AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; CMQ: Customized MedDRA Queries; CTCAE: Common Terminology Criteria for Adverse Events; PT: preferred term; SAE: serious adverse event; SOC: system organ class

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

Table 18: Favourable and unfavourable effects from the assessment of bosutinib in comparison with imatinib

Favourable effects	**Unfavourable effects**
Serious/severe side effects ▪ Neutropenia (severe AEs) Hint of lesser harm – extent: minor	Serious/severe side effects ▪ Severe AEs: ▫ < 65 years: hint of greater harm – extent: minor ▫ ≥ 65 years: hint of greater harm – extent: major ▪ Thrombocytopenia (severe AEs): hint of greater harm – extent: minor ▪ Cardiac disease (severe AEs): hint of greater harm – extent: considerable ▪ Diarrhoea (severe AEs): indication of greater harm – extent: major ▪ Abnormal hepatic function (severe AEs): indication of greater harm – extent: major ▪ Elevated lipase (severe AEs): hint of greater harm – extent: considerable
Non-serious/non-severe side effects ▪ Eye disorders (AEs): indication of lesser harm – extent: considerable ▪ Peripheral oedema (AEs): hint of lesser harm – extent: considerable ▪ Musculoskeletal and connective tissue disorders (AEs): hint of lesser harm – extent: considerable	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent: minor ▪ Gastrointestinal disorders (AEs): hint of greater harm – extent: considerable ▪ Pruritus (AEs): hint of greater harm – extent: considerable
AEs: adverse events	

Overall, the comparison of bosutinib with imatinib showed favourable and unfavourable effects exclusively for the outcome category of side effects.

For the dimension of serious/severe side effects, the total rate of severe AEs shows a hint of greater harm from bosutinib in comparison with imatinib, with an extent of minor or major, dependent on patient age. For the dimension of non-serious/non-severe side effects, the total rate of discontinuation due to AEs shows a hint of greater harm from bosutinib in comparison with imatinib. Further disadvantages of different extents were found for several specific AEs.

The disadvantages are offset by advantages in individual specific AEs for the dimension of serious/severe as well as non-serious/non-severe side effects.

In summary, for patients with newly diagnosed Ph^+ CML in chronic phase, there is a hint of lesser benefit of bosutinib in comparison with imatinib. This is in line with the results of the initial assessment [10].

Table 19 presents a summary of the results of the benefit assessment of bosutinib in comparison with the ACT.

Table 19: Bosutinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Treatment of adults with newly diagnosed Ph^+ CML in chronic phase	**Imatinib** or nilotinib or dasatinib	Hint of lesser benefit[b]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is marked in **bold**.
b. Only patients with an ECOG-PS of 0 or 1 were included in the BFORE study. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2.

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; Ph^+-CML: Philadelphia chromosome-positive chronic myeloid leukaemia

The above assessment deviates from that of the company, which derived an indication of minor added benefit.

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

References for English extract

Please see full dossier assessment for full reference list.

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

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