Quizartinib
(acute myeloid leukaemia)

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

EXTRACT

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

Patient and family involvement

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

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Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

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

I List of figures

Page

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AML	acute myeloid leukaemia
ANC	ANC
BSA	body surface area
CNS	central nervous system
CR	complete remission
CRi	complete remission with incomplete blood count recovery
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
ECG	electrocardiogram
ELN	European LeukemiaNet
FLT	FMS-like tyrosine kinase
FLT3	FMS-like tyrosine kinase 3
FMS	feline McDonough sarcoma
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HSCT	haematopoietic stem cell transplantation
ITD	internal tandem duplication
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IV	Intravenous
QTcF	corrected QT interval (Fridericia)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
WHO	World Health Organisation

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug quizartinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the “company”). The dossier was sent to IQWiG on 01 February 2024.

Research question

The aim of this report is to assess the added benefit of quizartinib in combination with standard cytarabine and anthracycline induction chemotherapy and standard cytarabine consolidation chemotherapy as monotherapy, followed by maintenance therapy with quizartinib as monotherapy compared to the appropriate comparator therapy (ACT) in adults with newly diagnosed FLT3-ITD-positive acute myeloid leukaemia (AML).

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of quizartinib

Therapeutic indication	**ACT**[a]
Adults with newly diagnosed FLT3-ITD-positive AML, in combination with standard cytarabine and anthracycline induction chemotherapy and standard cytarabine consolidation chemotherapy, followed by maintenance therapy with quizartinib as monotherapy	• Induction chemotherapy: o cytarabine in combination with daunorubicin and midostaurin • followed by a consolidation therapy[b]: individualized treatment choosing from chemotherapy (cytarabine in combination with Midostaurin) and allogeneic stem cell transplantation, depending in particular on the AML subtype, the patient's general condition and comorbidities. • followed by maintenance therapy[b]: individualized therapy choosing from o azacitidine (only for patients who are ineligible for an allogeneic stem cell transplantation) o midostaurin (only for patients who are ineligible for an allogeneic stem cell transplantation) o sorafenibc (only for patient after an allogeneic stem cell transplantation) taking into account the induction and consolidation therapy

a. Presented is the ACT specified by the G-BA.
b. For consolidation and maintenance therapy: For the implementation of individualized treatment in a study of direct comparison, according to the G-BA, the investigator is expected to have a choice between several treatment options to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. If only a single-comparator study relating to the therapy phases of consolidation and maintenance is presented, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.
c. For the maintenance therapy of adults with AML and FLT3-ITD mutation who are in first complete remission after a stem cell transplantation, no drug therapies are approved apart from quizartinib under evaluation here. According to the G-BA, the use of sorafenib as an unauthorized treatment option in maintenance therapy is medically necessary for this patient group. In accordance with the generally accepted state of medical knowledge, it can be determined according to the G-BA that the off-label use of sorafenib in the absence of other approved drugs specifically for maintenance therapy after allogeneic stem cell transplantation as part of individualized treatment, taking into account induction and consolidation therapy for relevant patient groups or therapeutic indications, is routinely preferred over drugs previously approved in the therapeutic indication.

ACT: appropriate comparator therapy; AML: acute myeloid leukaemia; FLT: FMS-like tyrosine kinase; G-BA: Joint Federal Committee; ITD: internal tandem duplication

The company deviates from the ACT specified by the G-BA by specifying additional options for each of the 3 therapy phases:

These additional options are the administration of cytarabine in combination with an anthracycline in the induction phase and cytarabine monotherapy as an additional choice for

chemotherapy in the consolidation phase. For the maintenance phase, the company lists midostaurin as an option after allogeneic stem cell transplantation and watchful waiting in addition to the options for individualized treatment specified by the G-BA.

Overall, the company does not present suitable arguments to justify a departure from the ACT specified by the G-BA. The present assessment was conducted in comparison with the comparator therapy specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used to derive the added benefit.

Results

The check for completeness of the study pool revealed no relevant studies comparing quizartinib with the ACT specified by the G-BA.

The company, in contrast, identified the RCT QuANTUM-First and used it in its assessment. The QuANTUM-First study is not suitable for the benefit assessment because it does not allow a comparison with the ACT.

QuANTUM-First study presented by the company

The QuANTUM-First study is a completed, double-blind RCT comparing quizartinib with placebo in the 3 phases of induction, consolidation and maintenance therapy.

Adults up to the age of 75 years with AML diagnosed according to the 2008 World Health Organisation (WHO) classification and a documented FLT3-ITD mutation were included. Patients with acute promyelocytic leukaemia, therapy-related AML, BCR-ABL positive leukaemia, or CNS leukaemia were not allowed to participate in the study. Pronounced comorbidities, especially of the cardiovascular type, were also among the exclusion criteria.

The QuANTUM-First study included a total of 539 patients who were randomly allocated in a 1:1 ratio to the intervention arm (N = 268) or the comparator arm (N = 271). Randomization was stratified according to region, age and leukocyte count at the time of AML diagnosis.

The study treatment was divided into the phases of induction, consolidation and maintenance. As induction therapy, the patients received 1 to 2 cycles of treatment with quizartinib or placebo in combination with cytarabine and daunorubicin or idarubicin. Patients who had not achieved complete remission even after 2 cycles of induction therapy had their study treatment discontinued. Patients with a complete remission after the induction phase could receive quizartinib or placebo in combination with high-dose cytarabine and/or an allogeneic stem cell transplantation during the consolidation phase. The consolidation chemotherapy

consisted of up to 4 cycles. A stem cell transplantation could be performed at any time during the consolidation phase and, under certain conditions, within the first 3 months of the maintenance phase. If the patients were still in complete remission after completing consolidation therapy, they received maintenance therapy with quizartinib or placebo for up to 36 cycles of 28 days each, regardless of the type of consolidation therapy.

Treatment with quizartinib in the intervention arm was in compliance with the specifications of the Summary of Product Characteristics (SPC). The dosing regimens of the chemotherapeutic components were largely in compliance with the specifications of the SPC and guidelines.

The primary outcome of the study was overall survival. Secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and adverse events (AEs).

Appropriate comparator therapy not implemented in the QuANTUM-First study

In the QuANTUM-First study, the ACT specified by the G-BA was not implemented in all 3 therapy phases, in particular there was no comparison with the therapy standard midostaurin.

The G-BA has specified chemotherapy with cytarabine and the anthracycline daunorubicin in combination with midostaurin as the ACT for the induction phase. However, the patients in the comparator arm of the QuANTUM-First study received chemotherapy with cytarabine and the anthracycline daunorubicin or idarubicin without being given midostaurin.

For the consolidation phase, the ACT specified by the G-BA consists of individualized treatment, choosing a chemotherapy with cytarabine in combination with midostaurin and an allogeneic stem cell transplantation. In the study, the patients in the comparator arm, on the other hand, received chemotherapy with high-dose cytarabine without midostaurin and/or a stem cell transplantation.

In the maintenance phase, the ACT consists of individualized treatment with a choice of the drugs azacitidine, midostaurin and sorafenib. The study did not provide for any of these active interventions; during the maintenance phase, placebo was administered.

The ACT was therefore not implemented in the QuANTUM-First study presented by the company. Therefore, the QuANTUM-First study is unsuitable for answering the research question of the present benefit assessment.

Results on added benefit

The company has not submitted any suitable data for assessing the added benefit of quizartinib in comparison with the ACT in adult patients with newly diagnosed FLT3-ITD-

positive AML. There is no hint of an added benefit of quizartinib in comparison with the ACT; an added benefit is therefore not proven.

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

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

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

Table 3: Quizartinib – probability and extent of added benefit (multipage table)

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with newly diagnosed FLT3-ITD-positive AML, in combination with standard cytarabine and anthracycline induction chemotherapy and standard cytarabine consolidation chemotherapy, followed by maintenance therapy with quizartinib as monotherapy	• Induction chemotherapy: ▫ cytarabine in combination with daunorubicin and midostaurin • followed by a consolidation therapy[b]: individualized treatment choosing from chemotherapy (cytarabine in combination with Midostaurin) and allogeneic stem cell transplantation, depending in particular on the AML subtype, the patient's general condition and comorbidities. • followed by maintenance therapy[b]: individualized therapy choosing from ▫ azacitidine (only for patients who are ineligible for an allogeneic stem cell transplantation) ▫ midostaurin (only for patients who are ineligible for an allogeneic stem cell transplantation) ▫ sorafenibc (only for patient after an allogeneic stem cell transplantation) taking into account the induction and consolidation therapy	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. For consolidation and maintenance therapy: For the implementation of individualized treatment in a study of direct comparison, according to the G-BA, the investigator is expected to have a choice between several treatment options to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. If only a single-comparator study relating to the therapy phases of consolidation and maintenance is presented, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.
c. For the maintenance therapy of adults with AML and FLT3-ITD mutation who are in first complete remission after a stem cell transplantation, no drug therapies are approved apart from quizartinib under evaluation here. According to the G-BA, the use of sorafenib as an unauthorized treatment option in maintenance therapy is medically necessary for this patient group. In accordance with the generally accepted state of medical knowledge, it can be determined according to the G-BA that the off-label use of sorafenib in the absence of other approved drugs specifically for maintenance therapy after allogeneic stem cell transplantation as part of individualized treatment, taking into account induction and consolidation therapy for relevant patient groups or therapeutic indications, is routinely preferred over drugs previously approved in the therapeutic indication.

ACT: appropriate comparator therapy; AML: acute myeloid leukaemia; FLT: FMS-like tyrosine kinase; G-BA: Joint Federal Committee; ITD: internal tandem duplication

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of quizartinib in combination with standard cytarabine and anthracycline induction chemotherapy and standard cytarabine consolidation chemotherapy as monotherapy, followed by maintenance therapy with quizartinib as monotherapy compared to the appropriate comparator therapy (ACT) in adults with newly diagnosed FLT3-ITD-positive acute myeloid leukaemia (AML).

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of quizartinib

Therapeutic indication	**ACT[a]**
Adults with newly diagnosed FLT3-ITD-positive AML, in combination with standard cytarabine and anthracycline induction chemotherapy and standard cytarabine consolidation chemotherapy, followed by maintenance therapy with quizartinib as monotherapy	• Induction chemotherapy: ▫ cytarabine in combination with daunorubicin and midostaurin • followed by a consolidation therapy[b]: individualized treatment choosing from chemotherapy (cytarabine in combination with Midostaurin) and allogeneic stem cell transplantation, depending in particular on the AML subtype, the patient's general condition and comorbidities. followed by maintenance therapy[b]: individualized therapy choosing from ▫ azacitidine (only for patients who are ineligible for an allogeneic stem cell transplantation) ▫ midostaurin (only for patients who are ineligible for an allogeneic stem cell transplantation) ▫ sorafenibc (only for patient after an allogeneic stem cell transplantation) taking into account the induction and consolidation therapy

a. Presented is the ACT specified by the G-BA.
b. For consolidation and maintenance therapy: For the implementation of individualized treatment in a study of direct comparison, according to the G-BA, the investigator is expected to have a choice between several treatment options to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. If only a single-comparator study relating to the therapy phases of consolidation and maintenance is presented, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment.
c. For the maintenance therapy of adults with AML and FLT3-ITD mutation who are in first complete remission after a stem cell transplantation, no drug therapies are approved apart from quizartinib under evaluation here. According to the G-BA, the use of sorafenib as an unauthorized treatment option in maintenance therapy is medically necessary for this patient group. In accordance with the generally accepted state of medical knowledge, it can be determined according to the G-BA that the off-label use of sorafenib in the absence of other approved drugs specifically for maintenance therapy after allogeneic stem cell transplantation as part of individualized treatment, taking into account induction and consolidation therapy for relevant patient groups or therapeutic indications, is routinely preferred over drugs previously approved in the therapeutic indication.

ACT: appropriate comparator therapy; AML: acute myeloid leukaemia; FLT: FMS-like tyrosine kinase; G-BA: Joint Federal Committee; ITD: internal tandem duplication

The company deviates from the ACT specified by the G-BA by specifying additional options for each of the 3 therapy phases:

These additional options are the administration of cytarabine in combination with an anthracycline in the induction phase and cytarabine monotherapy as an additional choice for chemotherapy in the consolidation phase. For the maintenance phase, the company lists midostaurin as an option after allogeneic stem cell transplantation and watchful waiting in addition to the options for individualized treatment specified by the G-BA.

To explain the deviations in the induction and consolidation phase, the company refers to a quantitative online survey among European physicians commissioned by the company itself. For the inclusion of midostaurin after allogeneic stem cell transplantation as an option for the maintenance phase, the company refers to the approval status of midostaurin[3], the recommendations of the European LeukemiaNet (ELN) guideline[4], the lack of approval of sorafenib and the above-mentioned online survey. The company did not provide a rationale for the addition of watchful waiting as a treatment option in the maintenance phase.

The approach of the company is not appropriate. Thus, the sources provided by the company are insufficient for deriving an ACT. For induction and consolidation therapy, the current national and international guidelines, including the ELN guideline[4-7] cited by the company, indicate the value of midostaurin as the therapy standard for patients with FLT3-ITD-positive AML. For the maintenance therapy of adults with AML and FLT3-ITD mutation who are in first complete remission after a stem cell transplantation, no drug therapies are approved as a whole. However, current guidelines[6,7] recommend maintenance therapy with sorafenib in this therapeutic situation.

Overall, the company’s arguments are unsuitable for justifying a departure from the ACT specified by the G-BA. The present assessment was conducted in comparison with the comparator therapy specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive the added benefit. This concurs with the company’s inclusion criteria.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on quizartinib (status: 13 December 2023)
- bibliographical literature search on quizartinib (last search on 13 December 2023)
- search in trial registries/trial results databases for studies on quizartinib (last search on 13 December 2023)
- search on the G-BA website for quizartinib (last search on 13 December 2023)

To check the completeness of the study pool:

- search in trial registries for studies on quizartinib (last search on 14 February 2024); for search strategies, see I Appendix A of the full dossier assessment

The check for completeness of the study pool revealed no relevant studies comparing quizartinib with the ACT specified by the G-BA.

The company, in contrast, identified the RCT QuANTUM-First [8] and used it in its assessment.

The QuANTUM-First study is not suitable for the benefit assessment because it does not allow a comparison with the ACT. The study is described below, and the unsuitability is justified.

I 3.1 Presentation and assessment of the evidence presented by the company

I 3.1.1 QuANTUM-First study

Study characteristics

Table 5 and Table 6 present the QuANTUM-First study.

Table 5: Characteristics of the study included by the company – RCT, direct comparison: quizartinib vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
QuANTUM-First	RCT, double-blind, parallel-group	Adults (< 75 years) with diagnosed AML[b, c] ▪ evidence of an FLT3-ITD mutation[c] ▪ no therapy-related AML[d] ▪ no prior therapy against AML[e] ▪ without pronounced cardiovascular risk factors, especially QTcF ≤ 450 ms	Quizartinib (N = 268) ▪ induction: daunorubicin/idarubicin + cytarabine + quizartinib ▪ consolidation: cytarabine + quizartinib and/or allogeneic HSCT ▪ maintenance: quizartinib Placebo (N = 271) ▪ induction: daunorubicin/idarubicin + cytarabine + placebo ▪ consolidation: cytarabine + placebo and/or allogeneic HSCT maintenance: placebo	Screening: day 7 before to day 6 after the start of induction chemotherapy Treatment: ▪ induction: 1-2 cycles[f] ▪ consolidation[g, h]: chemotherapy: up to 4 cycles ▪ maintenance[h]: 3 years ▪ or until treatment failure, unacceptable toxicity or treatment discontinuation at the patient's discretion Observation: outcome-specific, at most until death or end of study	193 study centres in Australia, Belgium, Brazil, Bulgaria, Canada, China, Croatia, Czech Republic, France, Germany, Hungary, Hong Kong, Israel, Italy, Japan, Poland, Portugal, Romania, Russia, Serbia, Singapore, South Korea, Spain, Taiwan, Ukraine, United Kingdom, United States 09/2016–06/2023 Data cut-off: 13 August 2021[i]	Primary: overall survival Secondary: morbidity, health-related quality of life, AEs

Table 5: Characteristics of the study included by the company – RCT, direct comparison: quizartinib vs. placebo (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes comprise exclusively data based on the information provided by the company's Module 4 A.
b. Diagnosis according to the WHO Classification of 2008.
c. Proven by an analysis in an FTL3 screening laboratory specified in the protocol; defined as an allele ratio of FLT3-ITD to total FLT3 of ≥ 0.03.
d. Patients with AML due to myelodysplastic syndrome or myeloproliferative neoplasia were also included. Patients with acute promyelocytic leukaemia, BCR/ABL-positive leukaemia and patients with CNS leukaemia including detection of AML blasts in the cerebrospinal fluid were also excluded.
e. Exceptions: leukapheresis, treatment for hyperleukocytosis with hydroxyurea, cranial radiotherapy for CNS leukostasis prophylactic intrathecal therapy and growth factor/cytokine support.
f. One cycle comprised 21 days. Patients with a blast percentage of ≥ 5% in the bone marrow aspirate on day 21 or, in the absence of assessability in a repeat sample, no later than day 56 after the start of study treatment could receive a second cycle of induction therapy. In addition to the standard regimen ("7+3"), a reduced-dose regimen ("5+2") was also allowed. If there was no proof of complete remission even after the second cycle, the study treatment was terminated and the patients were included in the follow-up phase.
g. Patients who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) after induction therapy were able to enter the consolidation phase of the study.
h. Discontinuation of study treatment in patients with recurrence; inclusion in the follow-up phase.
i. Prespecified data cut-off for OS analysis, scheduled no later than 30 months, no earlier than 24 months (if 287 events are reported) after completion of enrolment.

AE: adverse event; AML: acute myeloid leukaemia; CNS: central nervous system; FLT3: FMS-like tyrosine kinase 3; HSCT: haematopoietic stem cell transplantation; ITD: internal tandem duplication; N: number of randomized patients; QTcF: corrected QT interval (Fridericia); RCT: randomized controlled trial; WHO: World Health Organisation

Table 6: Characteristics of the intervention – RCT, direct comparison: quizartinib vs. placebo (multipage table)

Study	Intervention	Comparison
QuANTUM-First	**Induction (up to 2 cycles):** First cycle: quizartinib orally 40 mg/day orally (days 8–21) + ▪ cytarabine 100 mg/m² BSA/day[a] IV (days 1–7) + ▪ daunorubicin 60 mg/m² BSA IV or idarubicin 12 mg/m² BSA/day IV (days 1–3) Second cycle: either like first cycle or: ▪ quizartinib 40 mg/day orally (days 6–19) + ▪ cytarabine 100 mg/m² BSA/day[a] IV (days 1–5) + ▪ daunorubicin 60 mg/m² BSA/day IV or idarubicin 12 mg/m² BSA/day IV (days 1–2) **Consolidation (up to 4 cycles):** <u>Option 1:</u> ▪ quizartinib 40 mg/day orally (days 6–19) + ▪ cytarabine IV (days 1,3,and 5) ▫ patients < 60 years: 3 g/m² BSA, twice daily ▫ patients ≥ 60 years: 1.5 g/m² BSA, twice daily <u>Option 2:</u> ▪ allogeneic HSZT[b] <u>Option 3:</u> Option 1 + followed by Option 2[b]	**Induction (up to 2 cycles):** First cycle: placebo orally (days 8–21) + ▪ cytarabine 100 mg/m² BSA/day[a] IV (days 1–7) + ▪ daunorubicin 60 mg/m² BSA/day IV or idarubicin 12 mg/m² BSA/day IV (days 1–3) Second cycle: either like first cycle or: ▪ placebo orally (days 6–19) + ▪ cytarabine 100 mg/m² BSA/day[a] IV (days 1–5) + ▪ daunorubicin 60 mg/m² BSA/day IV or idarubicin 12 mg/m² BSA/day IV (days 1–2) **Consolidation (up to 4 cycles):** <u>Option 1:</u> ▪ placebo orally (days 6–19) + ▪ cytarabine IV (days 1,3,and 5) ▫ patients < 60 years: 3 g/m² BSA, twice daily ▫ patients ≥ 60 years: 1.5 g/m² BSA, twice daily <u>Option 2:</u> ▪ allogeneic HSZT[b] <u>Option 3:</u> Option 1 + followed by Option 2[b]

Table 6: Characteristics of the intervention – RCT, direct comparison: quizartinib vs. placebo (multipage table)

Study	Intervention	Comparison
	Consolidation (up to 36 cycles)[c] First cycle: ▪ quizartinib 30 mg/day orally (days 1–15) ▪ quizartinib 60 mg/day orally (from day 16) From second cycle: ▪ quizartinib 60 mg/day orally (days 1–28) length of cycle: 28 days each	**Consolidation (up to 36 cycles)[c]** First cycle: ▪ placebo orally (days 1–15) ▪ placebo orally (from day 16) From second cycle: ▪ placebo orally (days 1–28) length of cycle: 28 days each
	Dose adjustment: ▪ quizartinib/placebo: ▫ with concurrent administration of strong CYP3A4-inhibitors, dose reduction to 20 mg/day in the induction and consolidation phase as well as in the maintenance phase (days 115) or from 60 mg/day to 30 mg/day in the maintenance phase (from day 16) ▫ in addition, dose reductions and interruptions allowed in all 3 therapy phases in the event of QTcF prolongation, other non-haematological toxicities, or myelosuppression ▪ cytarabine, daunorubicin, idarubicin: dose adjustments to renal and liver function permitted in accordance with local SPCs for institutional guidelines; during consolidation, discontinuation of chemotherapy due to intolerance possible in each cycle	
	Disallowed pretreatment ▪ AML therapy[e] ▪ quizartinib or other FLT3-ITD inhibitors ▪ any study medication or study medicinal products ≤ 30 days before randomization ▪ experimental or approved immunotherapy ≤ 20 days before randomization **Allowed concomitant treatment** ▪ anti-emetics, before and after the administration of quizartinib/placebo ▪ to prevent conjunctival/corneal pain: dexamethasone or ophthalmic steroid equivalent 12 hours before and 2448 hours after cytarabine administration ▪ granulocyte-stimulating factors during consolidation[f] ▪ supportive care with antibiotics, antimycotics, virostatic drugs ▪ after allogeneic HSCT: donor lymphocyte infusion **Disallowed concomitant treatment** ▪ other chemotherapies, immunotherapy, radiotherapy, or additional therapies for AML ▪ strong and moderate CYP3A4 inducers	

Table 6: Characteristics of the intervention – RCT, direct comparison: quizartinib vs. placebo (multipage table)

Study	Intervention	Comparison
a. Or 200 mg/m^2 BSA/day, if this was in line with the institutional or local standard. b Allogeneic HSCT for consolidation was possible after achieving CR or CRi, and after consulting with the medical study monitor, even within the first 3 months of the maintenance phase. The study medication had to be discontinued at least 7 days before the start of conditioning. c. The treatment was carried out as soon as haematological regeneration, defined as ANC > 500/mm^3 and platelet count > 50 000/mm^3 without platelet transfusion within 24 hours of blood draw, was present after completion of consolidation. In patients who had received allogeneic HSCT, maintenance therapy began at any time between 30 and 180 days after HSCT. d. The prerequisite for increasing the dose to 60 mg was an average QTcF interval of ≤ 450 ms with an ECG triple measurement on day 15 of cycle 1. If the dose could not be increased, it could be increased on day 2 of cycle 2 with an average QTcF interval of ≤ 450 ms with an ECG triple measurement on day 1 of cycle 2. e. Exceptions: leukocyte apheresis, treatment for hyperleukocytosis with hydroxyurea, cranial radiotherapy for CNS leukostasis prophylactic intrathecal chemotherapy, growth factors, and cytokines. f. During induction also in patients with sepsis and life-threatening infection; 7 days (14 days for pegylated granulocyte-stimulating factors) before a bone marrow aspirate, they had to be discontinued if there was no urgent medical need. AML: acute myeloid leukaemia; ANC: absolute neutrophil count; BSA: body surface area; CNS: central nervous system; CR: complete remission; CRi: complete remission with incomplete blood count recovery; CYP3A4: cytochrome P450 3A4; ECG: electrocardiogram; FLT3: FMS-like tyrosine kinase 3; FMS: feline McDonough sarcoma; HSCT: haematopoietic stem cell transplantation; ITD: internal tandem duplication; IV: intravenous; QTcF: corrected QT interval (Fridericia); RCT: randomized controlled trial		

The QuANTUM-First study is a completed, double-blind RCT comparing quizartinib with placebo in the 3 phases of induction, consolidation and maintenance therapy.

Adults up to the age of 75 years with AML diagnosed according to the 2008 WHO classification and a documented FLT3-ITD mutation were included. Patients with acute promyelocytic leukaemia, therapy-related AML, BCR-ABL positive leukaemia, or CNS leukaemia were not allowed to participate in the study. Pronounced comorbidities, especially of the cardiovascular type, were also among the exclusion criteria.

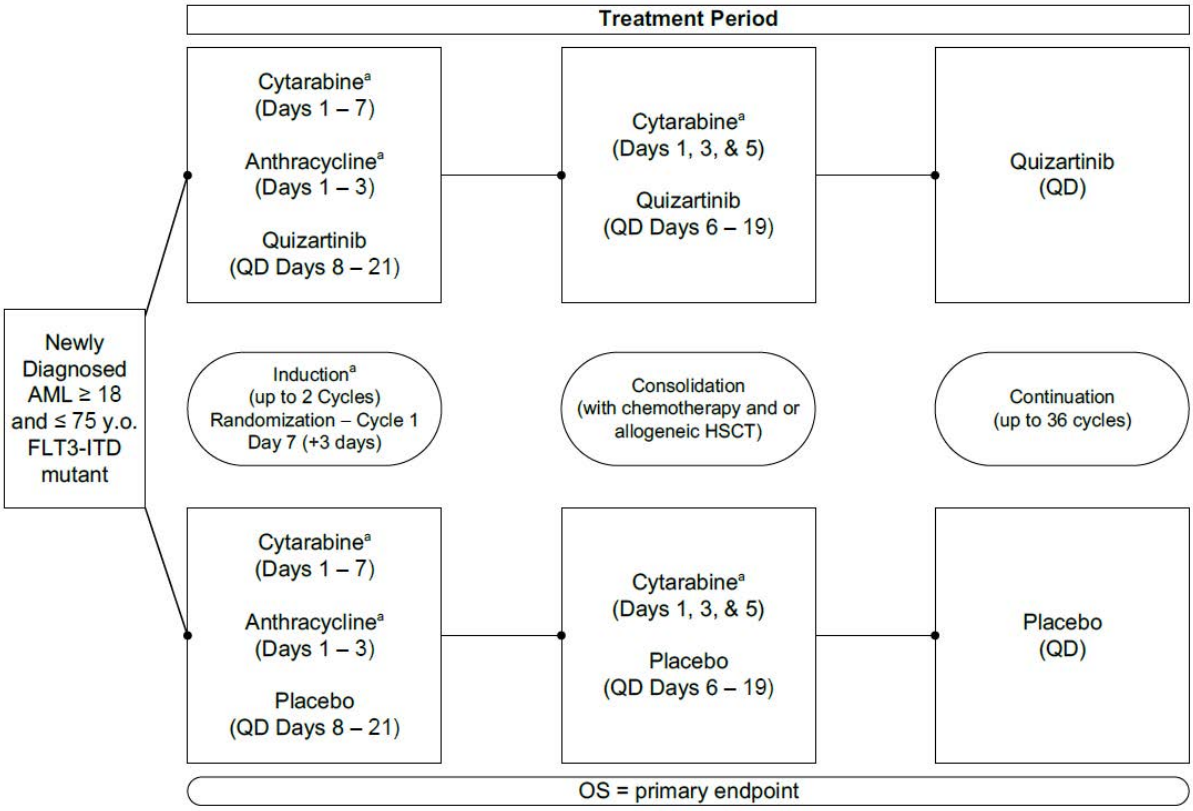
The QuANTUM-First study included a total of 539 patients who were randomly allocated in a 1:1 ratio to the intervention arm (N = 268) or the comparator arm (N = 271). Randomization was stratified according to region, age and leukocyte count at the time of AML diagnosis.

The study treatment was divided into the phases of induction, consolidation and maintenance (see Figure 1). As induction therapy, the patients received 1 to 2 cycles of treatment with quizartinib or placebo in combination with cytarabine and daunorubicin or idarubicin. On day 21, a bone marrow aspiration was performed to decide whether a second cycle was necessary. This was indicated in the absence of a complete remission, i.e. the presence of at least 5% blasts in the bone marrow. Patients who had not achieved complete remission even after 2 cycles of induction therapy had their study treatment discontinued. Patients with a

complete remission after the induction phase could receive quizartinib or placebo in combination with high-dose cytarabine and/or an allogeneic stem cell transplantation during the consolidation phase. The consolidation chemotherapy consisted of up to 4 cycles. A stem cell transplantation could be performed at any time during the consolidation phase and, under certain conditions, within the first 3 months of the maintenance phase. Patients who underwent stem cell transplantation ended the study treatment 7 days before the start of a conditioning regimen. If the patients were still in complete remission after completing consolidation therapy, they received maintenance therapy with quizartinib or placebo for up to 36 cycles of 28 days each, regardless of the type of consolidation therapy.

Treatment with quizartinib in the intervention arm was in compliance with the specifications of the SPC [9]. The dosing regimens of the chemotherapeutic components were in compliance with the specifications of the SPC [10-12] and guidelines [4-7], except for minor deviations. The majority of current guidelines recommend an intermediate dosage for the use of cytarabine in consolidation therapy [4-7], but this is of no consequence for the present benefit assessment.

The primary outcome of the study was overall survival. Secondary outcomes were recorded in the categories of morbidity, health-related quality of life, and AEs.



AML=acute myeloid leukemia; FLT3=FMS-like tyrosine kinase 3; ITD=internal tandem duplication; OS = overall survival; QD=once a day; y.o. =years old
[a] During Induction Cycle 2 investigators may choose to administer the "7+3" chemotherapy regimen, or the "5+2" chemotherapy regimen, and quizartinib/placebo will therefore start on Day 8 or Day 6, respectively.

Figure 1: Design of the QuANTUM-First study

I 3.1.2 Assessment of the QuANTUM-First study presented by the company

Appropriate comparator therapy not implemented in the QuANTUM-First study

In the QuANTUM-First study, the ACT specified by the G-BA was not implemented in all 3 therapy phases, in particular there was no comparison with the therapy standard midostaurin.

The G-BA has specified chemotherapy with cytarabine and the anthracycline daunorubicin in combination with midostaurin as the ACT for the induction phase. However, the patients in the comparator arm of the QuANTUM-First study received chemotherapy with cytarabine and the anthracycline daunorubicin or idarubicin without being given midostaurin.

For the consolidation phase, the ACT specified by the G-BA consists of individualized treatment, choosing a chemotherapy with cytarabine in combination with midostaurin and an allogeneic stem cell transplantation. In the study, the patients in the comparator arm, on the other hand, received chemotherapy with high-dose cytarabine without midostaurin and/or a stem cell transplantation.

In the maintenance phase, the ACT consists of individualized treatment with a choice of the drugs azacitidine, midostaurin and sorafenib. The study did not provide for any of these active interventions; during the maintenance phase, placebo was administered.

The ACT was therefore not implemented in the QuANTUM-First study presented by the company. Therefore, the QuANTUM-First study is unsuitable for answering the research question of the present benefit assessment.

I 4 Results on added benefit

The company has not submitted any suitable data for assessing the added benefit of quizartinib in comparison with the ACT in adult patients with newly diagnosed FLT3-ITD-positive AML. There is no hint of an added benefit of quizartinib in comparison with the ACT; an added benefit is therefore not proven.

I 5 Overall conclusion on added benefit

Table 7 summarizes the result of the assessment of added benefit of quizartinib in comparison with the ACT.

Table 7: Quizartinib – probability and extent of added benefit (multipage table)

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with newly diagnosed FLT3-ITD-positive AML, in combination with standard cytarabine and anthracycline induction chemotherapy and standard cytarabine consolidation chemotherapy, followed by maintenance therapy with quizartinib as monotherapy	▪ Induction chemotherapy: ▫ cytarabine in combination with daunorubicin and midostaurin ▪ followed by a consolidation therapy[b]: individualized treatment choosing from chemotherapy (cytarabine in combination with Midostaurin) and allogeneic stem cell transplantation, depending in particular on the AML subtype, the patient's general condition and comorbidities. ▪ followed by maintenance therapy[b]: individualized therapy choosing from o azacitidine (only for patients who are ineligible for an allogeneic stem cell transplantation) o midostaurin (only for patients who are ineligible for an allogeneic stem cell transplantation) o sorafenib[c] (only for patient after an allogeneic stem cell transplantation) taking into account the induction and consolidation therapy	Added benefit not proven

Table 7: Quizartinib – probability and extent of added benefit (multipage table)

Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the ACT specified by the G-BA. b. For consolidation and maintenance therapy: For the implementation of individualized treatment in a study of direct comparison, according to the G-BA, the investigator is expected to have a choice between several treatment options to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. If only a single-comparator study relating to the therapy phases of consolidation and maintenance is presented, the extent to which conclusions on a subpopulation can be derived will be examined as part of the benefit assessment. c. For the maintenance therapy of adults with AML and FLT3-ITD mutation who are in first complete remission after a stem cell transplantation, no drug therapies are approved apart from quizartinib under evaluation here. According to the GBA, the use of sorafenib as an unauthorized treatment option in maintenance therapy is medically necessary for this patient group. In accordance with the generally accepted state of medical knowledge, it can be determined according to the G-BA that the off-label use of sorafenib in the absence of other approved drugs specifically for maintenance therapy after allogeneic stem cell transplantation as part of individualized treatment, taking into account induction and consolidation therapy for relevant patient groups or therapeutic indications, is routinely preferred over drugs previously approved in the therapeutic indication. ACT: appropriate comparator therapy; AML: acute myeloid leukaemia; FLT: FMS-like tyrosine kinase; G-BA: Joint Federal Committee; ITD: internal tandem duplication		

The assessment described above departs from that of the company, which, based on the results of the QuANTUM-First study, derived an indication of considerable added benefit compared to the ACT designated by the company.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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