Midostaurin
(acute myeloid leukaemia)

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

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Midostaurin (akute myeloische Leukämie) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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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 of persons concerned was received within the framework of the present dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AML	acute myeloid leukaemia
FLT3	FMS-like tyrosine kinase 3
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITD	internal tandem duplication
JALSG	Japan Adult Leukaemia Study Group
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

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 midostaurin. 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 14 November 2023.

Research question

The aim of this report is to assess the added benefit of midostaurin in combination with standard chemotherapy with daunorubicin and cytarabine induction, with high-dose cytarabine consolidation chemotherapy, and thereafter as monotherapy for the maintenance treatment in patients in complete remission compared with the appropriate comparator therapy (ACT) in adult patients with newly diagnosed acute myeloid leukaemia (AML) who have an FMS-like tyrosine kinase (FLT3) mutation.

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

Table 2: Research question for the benefit assessment of midostaurin

Therapeutic indication	**ACT**[a]
Adults with newly diagnosed AML and FLT3 mutation, in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and thereafter as midostaurin monotherapy for the maintenance treatment in patients in complete remission	▪ Induction chemotherapy[b]: ▫ cytarabine in combination with daunorubicin or idarubicin or mitoxantrone or ▫ daunorubicin/cytarabine (liposomal formulation) (only for patients with t-AML or AML-MRC) ▪ followed by a consolidation therapy[c]: individualized treatment choosing from chemotherapy (cytarabine or daunorubicin/cytarabine [liposomal formulation][d]) and allogeneic stem cell transplantation, depending in particular on the AML subtype, the patient's general condition and comorbidities ▪ followed by maintenance treatment[c]: individualized therapy choosing from ▫ azacitidine (only for patients who are ineligible for an allogeneic stem cell transplantation) ▫ sorafenib (only for people with FLT3-ITD mutation after an allogeneic stem cell transplantation) ▫ watchful waiting (only for patients without FLT3-ITD mutation after an allogeneic stem cell transplantation) taking into account the induction and consolidation therapy as well as the FLT3 mutation status

a. Presented is the ACT specified by the G-BA.
b. Induction chemotherapy: The ACT specified here comprises several alternative treatment options. According to the G-BA, individual treatment options only represent a comparator therapy for those patients in the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. For the proof of added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. If the ACT comprises several alternative treatment options without restrictions, the added benefit for the total population can be proven versus one of these alternative treatment options; this can usually be performed in the context of a single-comparator study. b. In contrast, the sole comparison against a treatment option which represents a comparator therapy for only part of the patient population is usually not sufficient to demonstrate added benefit for the overall population.
c. For consolidation and maintenance therapy: For the implementation of individualized treatment in a direct comparative study, according to the G-BA, the investigator is expected to have a selection of several treatment options at disposal 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 treatment 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.
d. According to the SPC, daunorubicin/cytarabine (liposomal formulation) can only be considered as consolidation therapy as part of individualized treatment if patients have already received daunorubicin/cytarabine (liposomal formulation) as part of induction chemotherapy.

AML: acute myeloid leukaemia; AML-MRC: AML with myelodysplastic changes; FLT: FMS-like tyrosine kinase; G-BA: Federal Joint Committee; ITD: internal tandem duplication; t-AML: therapy-related AML; SPC: Summary of Product Characteristics

On 28 November 2023, 2 months after the company had submitted the dossier (14 November 2023), the G-BA modified the ACT as shown in Table 2. Compared to the original ACT of 20 December 2022, the treatment options in maintenance therapy were specified by including the drugs azacitidine and sorafenib as well as watchful waiting.

The company claims to have followed the ACT specified by the G-BA. The information provided by the company in the dossier relates to the original ACT. This has no consequence for the present benefit assessment, as the company did not present suitable data for deriving an added benefit for any of the named ACTs.

The benefit assessment is conducted in comparison with the current ACT.

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) were used for the derivation of any added benefit. This concurs with the company's inclusion criteria.

Results

No relevant RCT on the direct comparison of midostaurin versus the ACT specified by the G-BA was identified by the check.

In contrast, the company identified the two RCTs CPKC412A2301 (hereinafter referred to as RATIFY study) and CPKC415A2220 (hereinafter referred to as study A2220). From the point of view of the company, RATIFY is a relevant study for the derivation of the added benefit.

As a further investigation, the company also presented the results of the single-arm study CPKC412ADE02T (hereinafter referred to as the AMLSG 16-10 study) in comparison with a control cohort. It also presented an adjusted comparison of the single-arm AMLSG 16-10 study with the comparator arm of the RATIFY study.

Overall, the data presented by the company are unsuitable for drawing conclusions on the added benefit of midostaurin in comparison with the ACT. The studies are described below, and the unsuitability is justified.

The RATIFY study presented by the company

The RATIFY study is a completed double-blind RCT on the comparison of midostaurin with placebo. Midostaurin or placebo was used in combination with chemotherapy with daunorubicin and cytarabine for induction, with chemotherapy with high-dose cytarabine for consolidation and then as monotherapy for maintenance treatment.

Adults under the age of 60 with diagnosed AML and a documented FLT3 mutation were included. AML was defined as a proportion of at least 20% blasts in the bone marrow. Patients

with an internal tandem duplication (ITD) or a point mutation in the tyrosine kinase domain (TKD) of the FLT3 gene were eligible to take part.

The RATIFY study included a total of 717 patients who were randomly allocated in a 1:1 ratio to treatment with midostaurin (N = 360) or placebo (N = 357).

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 midostaurin or placebo in combination with cytarabine and daunorubicin. Patients who achieved complete remission after completing induction therapy moved on to the next therapy phase and received consolidation therapy. Consolidation therapy consisted of a total of 4 cycles of treatment with midostaurin or placebo in combination with cytarabine. If the patients were still in complete remission after completing the consolidation therapy, they received maintenance therapy with midostaurin or placebo for 12 cycles.

In the RATIFY study, the investigators were not generally prohibited from treating patients who had achieved complete remission with a stem cell transplantation. However, stem cell transplantation was not explicitly part of the study treatment.

Treatment with midostaurin was largely in compliance with the specifications of the SPC. In contrast, the dosing regimen of daunorubicin deviates from the dose of 20 to 40 mg/m^2 BSA specified in the SPC for a 1-day interval. The dosage of cytarabine during induction and consolidation therapy was in accordance with the specifications of the SPC. Overall, the different dosing of daunorubicin and cytarabine has no impact on the present benefit assessment, as the study is not relevant for other reasons. The study's primary outcome was overall survival. Secondary outcomes were recorded in the categories of morbidity and AEs.

ACT not implemented in the RATIFY study

In the RATIFY study presented by the company, the ACT was not implemented, particularly in the maintenance treatment, as no individualized treatment choosing from azacitidine, sorafenib and watchful waiting took place. The consolidation therapy was also not explicitly designed for individualized treatment and due to a lack of information it remains unclear whether the patients were treated in accordance with the ACT. Overall, the RATIFY study is therefore not suitable for answering the research question of the present benefit assessment.

A2220 study presented by the company

The A2220 study consists of 2 parts. The randomized, double-blind second part included 62 adult patients with newly diagnosed AML and an FLT3 mutation who were randomly assigned in a 1:1 ratio to treatment with midostaurin (N = 30) or placebo (N = 32). Analogous to RATIFY, the second part of the study was divided into the 3 phases of induction, consolidation and maintenance. The treatment regimen used in both treatment arms was the same as that used

in the RATIFY study. For patients who were included in the study in Japan, the Japan Adult Leukaemia Study Group (JALSG) regimen was additionally available as an alternative, which according to the study documents represents the treatment standard in Japan.

The JALSG regimen is similar to the treatment regimen used in the RATIFY study with regard to the drugs used in the individual treatment phases and the number of cycles.

Stem cell transplantation as consolidation therapy was not explicitly planned in study A2220, but could be used at the investigator's discretion. The study medication was discontinued before a stem cell transplantation and was not allowed to be resumed afterwards. The patients remained in the study and were followed up.

The primary outcome of the study was event-free survival.

Assessment of the A2220 study presented by the company

Analogous to the RATIFY study, the ACT was not implemented in the A2220 study. The patients received the same or a similar treatment regimen as in the RATIFY study as comparator therapy. Therefore, the A2220 study is unsuitable for answering the research question of the present benefit assessment.

AMLSG 16-10 study presented by the company

The AMLSG 16-10 study is a single-arm study with midostaurin that included adult patients with an FLT3-ITD mutation and diagnosed AML, AML-related myeloid precursor neoplasia or acute leukaemia of unclear lineage.

The study included 440 patients up to the age of 70 who were eligible for intensive chemotherapy. The patients received 1 to 2 cycles of midostaurin in combination with daunorubicin and cytarabine as induction therapy. Allogeneic stem cell transplantation should be prioritised as consolidation therapy. Patients for whom allogeneic stem cell transplantation was not an option received a total of 4 cycles of cytarabine as consolidation therapy. After consolidation therapy, a 1-year maintenance therapy with midostaurin was planned for all patients.

The primary outcome of the study was event-free survival.

Due to the single-arm design of the AMLSG 16-10 study, the results in the study report for this study were compared with an external control cohort. This consisted of 415 patients aged 18 to 70 years with newly diagnosed AML and FLT3-ITD who had received intensive chemotherapy in 5 studies (conducted between 1993 and 2009) (AMLHD93, AMLHD98A, AMLHD98B, AMLSG 06-04 and AMLSG 07-04). As described in Module 4 A, treatment of patients in the control cohort consisted of induction therapy with idarubicin, cytarabine and etoposide (1 to 3 cycles) followed by high-dose cytarabine-based consolidation therapy.

Allogeneic stem cell transplantation was performed at the discretion of the investigator. For the most part, maintenance treatment for the control cohort was not carried out in the studies.

Assessment of the AMLSG 16-10 study presented by the company

The AMLSG 16-10 study was unsuitable for the derivation of an added benefit of midostaurin in comparison with the ACT. Administration of midostaurin as maintenance therapy after a stem cell transplantation in the AMLSG 16-10 study does not comply with the specifications of the SPC. According to the approval, midostaurin is used exclusively after consolidation with high-dose chemotherapy, but not after allogeneic stem cell transplantation. The use of midostaurin following consolidation therapy with the reduced cytarabine dose (1g/m^2 BSA every 12 hours on Days 1, 3 and 5), which was planned in the study for patients over 65 years of age, is therefore also not covered by the approval of midostaurin (only after consolidation with high-dose chemotherapy).

Moreover, as described in Module 4 A, treatment of patients in the control cohort consisted of induction therapy with idarubicin, cytarabine and etoposide (1 to 3 cycles) followed by high-dose cytarabine-based consolidation therapy, and does thus not correspond to the ACT. There was also no maintenance therapy for the most part. It should also be noted that for a comparison of study results from a single-arm study with the results of a control cohort from various other studies, the necessary structural equality between the treatment groups is not guaranteed despite the use of a propensity score based on selected confounders as an estimate for weighting. There is a lack of detailed information on the specific procedure, e.g. for confounder identification.

Overall, the AMLSG 16-10 study, including the propensity score-adjusted comparison with a control cohort contained therein, is therefore not suitable for the benefit assessment.

The company also presented a comparison of the AMLSG 16-10 study with the comparator arm of the RATIFY study. Since the use of midostaurin in the AMLSG 16-10 study was not in accordance with the SPC and the ACT was not implemented in the comparator arm of the RATIFY study, this comparison is not relevant for the benefit assessment. No further comments are therefore provided.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of midostaurin 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 shows a summary of probability and extent of the added benefit of midostaurin.

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

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with newly diagnosed AML and FLT3 mutation, in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and thereafter as midostaurin monotherapy for the maintenance treatment in patients in complete remission	▪ Induction chemotherapy[b]: ▫ cytarabine in combination with daunorubicin or idarubicin or mitoxantrone ▫ or ▫ daunorubicin/cytarabine (liposomal formulation) (only for patients with t-AML or AML-MRC) ▪ followed by a consolidation therapyc: individualized treatment choosing from chemotherapy (cytarabine or daunorubicin/cytarabine [liposomal formulation]d) and allogeneic stem cell transplantation, depending in particular on the AML subtype, the patient's general condition and comorbidities. ▪ followed by maintenance treatmentc: individualized therapy choosing from ▫ azacitidine (only for patients who are ineligible for an allogeneic stem cell transplantation) ▫ sorafenib (only for people with FLT3-ITD mutation after an allogeneic stem cell transplantation) ▫ watchful waiting (only for patients without FLT3-ITD mutation after an allogeneic stem cell transplantation) taking into account the induction and consolidation therapy as well as the FLT3 mutation status.	Added benefit not proven

[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: Midostaurin – 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. Induction chemotherapy: The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. For the proof of added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. If the ACT comprises several alternative treatment options without restrictions, the added benefit for the total population can be proven versus one of these alternative treatment options; this can usually be performed in the context of a single-comparator study. b. In contrast, the sole comparison against a treatment option which represents a comparator therapy for only part of the patient population is usually not sufficient to demonstrate added benefit for the overall population. c. For consolidation and maintenance therapy: For the implementation of individualized treatment in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal 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 treatment 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. d. According to the Summary of Product Characteristics (SPC), daunorubicin/cytarabine (liposomal formulation) can only be considered as consolidation therapy as part of individualized treatment if patients have already received daunorubicin/cytarabine (liposomal formulation) as part of induction chemotherapy. AML: acute myeloid leukaemia; AML-MRC: AML with myelodysplasia-associated changes; FLT: FMS-like tyrosine kinase; G-BA: Federal Joint Committee; ITD: internal tandem duplication; t-AML: therapy-related AML		

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of the market launch in 2017, where the G-BA determined a considerable added benefit of midostaurin. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data due to orphan drug status.

I 2 Research question

The aim of this report is to assess the added benefit of midostaurin in combination with standard chemotherapy with daunorubicin and cytarabine induction, with high-dose cytarabine consolidation chemotherapy, followed by midostaurin monotherapy for the maintenance treatment in case of complete remission compared with the ACT in adult patients with newly diagnosed AML who have an FLT3 mutation.

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

Table 4: Research question for the benefit assessment of midostaurin

Therapeutic indication	**ACT**[a]
Adults with newly diagnosed AML and FLT3 mutation, in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and thereafter as midostaurin monotherapy for the maintenance treatment in patients in complete remission	▪ Induction chemotherapy[b]: ▫ cytarabine in combination with daunorubicin or idarubicin or mitoxantrone or ▫ daunorubicin/cytarabine (liposomal formulation) (only for patients with t-AML or AML-MRC) ▪ followed by a consolidation therapy[c]: individualized treatment choosing from chemotherapy (cytarabine or daunorubicin/cytarabine [liposomal formulation][d]) and allogeneic stem cell transplantation, depending in particular on the AML subtype, the patient's general condition and comorbidities. ▪ followed by maintenance treatment[c]: individualized therapy choosing from ▫ azacitidine (only for patients who are ineligible for an allogeneic stem cell transplantation) ▫ sorafenib (only for people with FLT3-ITD mutation after an allogeneic stem cell transplantation) ▫ watchful waiting (only for patients without FLT3-ITD mutation after an allogeneic stem cell transplantation) taking into account the induction and consolidation therapy as well as the FLT3 mutation status

a. Presented is the ACT specified by the G-BA.
b. Induction chemotherapy: The ACT specified here comprises several alternative treatment options. According to the G-BA, individual treatment options only represent a comparator therapy for those patients in the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. For the proof of added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. If the ACT comprises several alternative treatment options without restrictions, the added benefit for the total population can be proven versus one of these alternative treatment options; this can usually be performed in the context of a single-comparator study. b. In contrast, the sole comparison against a treatment option which represents a comparator therapy for only part of the patient population is usually not sufficient to demonstrate added benefit for the overall population.
c. For consolidation and maintenance therapy: For the implementation of individualized treatment in a direct comparative study, according to the G-BA, the investigator is expected to have a selection of several treatment options at disposal 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 treatment 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.
d. According to the Summary of Product Characteristics (SPC), daunorubicin/cytarabine (liposomal formulation) can only be considered as consolidation therapy as part of individualized treatment if patients have already received daunorubicin/cytarabine (liposomal formulation) as part of induction chemotherapy.

AML: acute myeloid leukaemia; AML-MRC: AML with myelodysplastic changes; FLT: FMS-like tyrosine kinase; G-BA: Federal Joint Committee; ITD: internal tandem duplication; t-AML: therapy-related AML

On 28 November 2023, 2 months after the company had submitted the dossier (14 November 2023), the G-BA modified the ACT as shown in Table 4. Compared to the original ACT of 20 December 2022, the treatment options in maintenance therapy were specified by including the drugs azacitidine and sorafenib as well as watchful waiting.

The company claims to have followed the ACT specified by the G-BA. The information provided by the company in the dossier relates to the original ACT. This has no consequence for the present benefit assessment, as the company did not present suitable data for deriving an added benefit for any of the named ACTs (see Section I 3.1).

The benefit assessment is conducted in comparison with the current ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of any 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 midostaurin (status: 05 September 2023)
- bibliographical literature search on midostaurin (last search on 16 August 2023)
- search in trial registries/trial results databases for studies on midostaurin (last search on 22 August 2023)
- search on the G-BA website for midostaurin (last search on 22 August 2023)

To check the completeness of the study pool:

- search in trial registries for studies on midostaurin (last search on 30 November 2023); for search strategies, see I Appendix A of the full dossier assessment

Direct comparison

No relevant RCT on the direct comparison of midostaurin versus the ACT specified by the G-BA was identified by the check.

In contrast, the company identified the two RCTs CPKC412A2301 (hereinafter referred to as RATIFY study) [3] and CPKC415A2220 (hereinafter referred to as study A2220 [4]). The company used the RATIFY study for the derivation of an added benefit. Although the company lists RCT A2220 in its study pool, it did not consider it for the derivation of an added benefit. The reason for this is that the relevant patient population of the A2220 study only accounts for a small proportion (approx. 6%) of the patients in the studies RATIFY and A2220 (779 patients in total). According to the company's assessment, no relevant influence of the results of study A2220 on the overall assessment of the added benefit of midostaurin versus the ACT is therefore to be expected. The company also refers to the shorter median observation period in the A2220 study (3 years) compared to the RATIFY study (10 years).

The company's approach has no consequences, as neither the RATIFY study nor the A2220 study allows a comparison with the ACT (see below).

Further investigations

As a further investigation, the company additionally presented the results of the single-arm study CPKC412ADE02T (hereinafter referred to as the AMLSG 16-10 study) in comparison with an external control cohort with adjustment for confounders using propensity score weighting [5]. Moreover, it presents an adjusted comparison of the single-arm AMLSG 16 study-10 with the comparator arm of the RATIFY study to enable a comparison with a more recent external

control cohort (studies of the external control cohort were conducted in the period from 1993 to 2009). The company stated that it used the AMLSG 16-10 study exclusively to support the transferability of the results of the RATIFY study to older patients. In Module 4 A, the company provided no data on the information retrieval on further studies with the drug to be assessed or on the ACT; the completeness of the study pool is therefore unclear. Irrespective of this, the data presented by the company are not relevant for the benefit assessment due to a missing or inappropriate comparison with the ACT. The completeness for further investigations was not checked.

Overall, the data presented by the company are unsuitable for drawing conclusions on the added benefit of midostaurin in comparison with the ACT. The studies are described below, and the unsuitability is justified.

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

I 3.1.1 RATIFY study

Study characteristics

Table 5 and Table 6 describe the RATIFY study.

Table 5: Characteristics of the study included by the company – RCT, direct comparison: midostaurin 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]
RATIFY	RCT, double-blind, parallel	Adults (< 60 years) with diagnosed AML[b] ▪ documented FLT3 mutation (ITD or TKD)c ▪ ≥ 20% blasts in the bone marrow ▪ no previous chemotherapy against leukaemia or myelodysplasia[d]	Midostaurin (N = 360)[e] ▪ induction: daunorubicin + cytarabine + midostaurin ▪ consolidation: cytarabine + midostaurin ▪ maintenance: midostaurin placebo (N = 357)[e] ▪ induction: daunorubicin + cytarabine + placebo ▪ consolidation: cytarabine + placebo ▪ maintenance: placebo	Screening: ND treatment: ▪ induction: 1-2 cyclesf ▪ consolidationg, h: 4 cycles ▪ maintenanceh, [i]: 12 cycles observation: outcome-specific, at most up to 10 years after study inclusion	177 study centres in Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Slovakia, Spain, USA 05/2008–03/2022 data cut-offs: 1. 06/2012[j] 2. 1 April 2015[k] 3. 7 March 2016[l] 4. 5 September 2016[m] 5. 26 March 2022[n]	Primary: overall survival secondary: morbidity, AEs

Table 5: Characteristics of the study included by the company – RCT, direct comparison: midostaurin 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. Patients with acute promyelocytic leukaemia, therapy-related AML following prior radiotherapy or chemotherapy for another cancer disease as well as with evidence of AML blasts in the spinal fluid were excluded.
c. Proven by an analysis in an FTL3 screening laboratory specified in the protocol; defined as a ratio of mutant to non-mutant FLT3 alleles of ≥ 0.05.
d. Exceptions: emergency leukapheresis, emergency treatment for hyperleukocytosis with hydroxycarbamide (≤ 5 days), cranial radiotherapy for CNS leukostasis (only one dose) and growth factor/cytokine support.
e. No treatment was received by 5 versus 3 patients (midostaurin arm versus placebo arm).
f. One cycle comprised 21 days. Patients with a blast percentage of ≥ 5% in the bone marrow aspirate (with a cellularity of > 20%) on Day 21 after the start of study treatment received the second cycle as part of the induction therapy. 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 for selected outcomes. Complete remission was defined as absolute neutrophil count (ANC) ≥ 1000/µL, platelets ≥ 100.000/µL, the absence of blasts and an adequate red blood cell count (no red blood cell transfusion required) in the peripheral blood. At the same time, the bone marrow aspirate had to contain < 5% blasts and no Auer rods at adequate cellularity, and there had to be no extramedullary manifestations. Complete remission was also present if the platelet count in the peripheral blood was < 100.000/µL, but all other criteria were met.
g. Patients who achieved complete remission after induction therapy received consolidation therapy. One cycle lasted 28 days.
h. Discontinuation of study treatment in patients with recurrence; inclusion in the follow-up phase.
i. If complete remission persists (detected in bone marrow aspirate and peripheral blood) after 4 cycles of consolidation. Each cycle of the maintenance therapy lasted 28 days.
j. Pre-specified interim analysis of overall survival after 50% of the 509 expected events have occurred.
k. Pre-specified primary analysis, which was planned after 509 deaths and was carried out with amendment 10 of the study protocol (15 June 2015) regardless of the event rate.
l. Non-prespecified data cut-off for a publication of the study results in the New England Journal of Medicine.
m. Non-pre-specified data cut-off within the scope of the approval.
n. Pre-specified supportive (final) analysis on overall survival that had been planned to take place 10 years after randomization of the last patient or after 509 deaths.

AE: adverse event; AML: acute myeloid leukaemia; CNS: central nervous system; FLT3: FMS-like tyrosine kinase; ITD: internal tandem duplication; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; TKD: tyrosine kinase domain

Table 6: Characteristics of the intervention – RCT, direct comparison: midostaurin versus placebo (multipage table)

Study	Intervention	Comparison
RATIFY	**Induction: 1 to 2 cycles[a]** ▪ midostaurin 100 mg/day orally (twice daily 50 mg) (Days 8 to 21 per cycle) ▪ + ▪ cytarabine IV 200 mg/m² BSA/day ▪ (Days 1 to 7 per cycle) ▪ + ▪ daunorubicin IV 60 mg/m² BSA/day (Days 1 to 3 per cycle) ▪ consolidation[b]: 4 cycles ▪ midostaurin 100 mg/day orally (twice daily 50 mg) (Days 8 to 21 per cycle) ▪ + ▪ cytarabine IV 6 g/m² BSA/day (3 g/m² BSA every 12 hours) (Day 1, 3 and 5 per cycle) **maintenance[c]: 12 cycles** ▪ midostaurin 100 mg/day orally (twice daily 50 mg) (Days 1 to 28 per cycle)	**Induction: 1 to 2 cycles[a]** ▪ placebo orally twice daily (Days 8 to 21 per cycle) ▪ + ▪ cytarabine IV 200 mg/m² BSA/day (Days 1 to 7 per cycle) ▪ + ▪ daunorubicin IV 60 mg/m² BSA/day (Days 1 to 3 per cycle) ▪ consolidation[b]: 4 cycles ▪ placebo orally twice daily (Days 8 to 21 per cycle) ▪ + ▪ cytarabine IV 6 g/m² BSA/day (3 g/m² BSA every 12 hours) (Day 1, 3 and 5 per cycle) **maintenance[c]: 12 cycles** ▪ placebo orally twice daily (Days 1 to 28 per cycle)
	Dose adjustment: ▪ midostaurin/placebo: dose interruption, reduction and/or discontinuation in the event of pulmonary and cardiac toxicity and other non-haematological toxicity (grade 3 and 4) during induction, consolidation and maintenance, and, during maintenance, additionally in the event of grade 4 neutropenia (ANC < 0.5 × 10^9/l) and persistent toxicity (grade 1 and 2) according to the SPC ▪ daunorubicin: dose reduction permitted in case of hepatotoxicity[d] ▪ high-dose cytarabine (consolidation): interruption of treatment with high-dose cytarabine for the duration of the current cycle in the presence of neurotoxicity ≥ grade 2. If the neurotoxicity is reduced to ≤ grade 1, a dose adjustment to 2 g/m² BSA can be considered for the next cycle. If neurotoxicity ≥ grade 2 occurs again, treatment with high-dose cytarabine should be permanently discontinued.	

Table 6: Characteristics of the intervention – RCT, direct comparison: midostaurin versus placebo (multipage table)

Study	Intervention	Comparison
	Pretreatment ▪ no previous chemotherapy against leukaemia or myelodysplasia[e] **stem cell transplantation** ▪ it was not generally forbidden to perform a stem cell transplantation if a complete remission was achieved (patients received no study medication after a stem cell transplantation) **allowed concomitant treatment** ▪ supportive treatment with blood, blood products, antibiotics, antiemeticsf and allopurinol, among other things ▪ myeloid growth factors, provided they have been used according to American Society of Clinical Oncology (ASCO) guidelines in patients with neutropenia with prognostic factors for clinical deterioration; these include, for example pneumonia, hypotension, multiple organ dysfunction or a fungal infection ▪ granulocyte-stimulating factors such as filgrastim, PEG-filgrastim or sargramostim ▪ epoetin or darbepoetin (administration not recommended) **disallowed concomitant treatment** ▪ aprepitant ▪ hormones or other chemotherapeutic agents with the exception of the use of steroids for adrenal insufficiency or for the treatment or prevention of hypersensitivity or transfusion reactions as well as hormones for non-AML-related conditions	

a. If a second cycle was required, treatment was to be initiated on Day 24 after the first administration of the study medication or shortly thereafter.
b. One cycle lasted 4 weeks and started within 2 weeks of achieving haematological recovery (ANC ≥ 1000/µL and platelets ≥ 100.000/µL), but no earlier than 4 weeks after the start of the previous cycle.
c. Start of treatment as soon as haematological regeneration, defined as ANC ≥ 1000/µl and platelet count ≥ 100.000/µL, was achieved after completion of consolidation. However, no earlier than 14 days after administration of the last dose of consolidation therapy. Before initiating the maintenance therapy, all essential acute toxicities had to be subsided to < grade 2 due to the consolidation.
d. Reduction of the dosage by 25% for a total bilirubin > 2 and ≤ 3 mg/dL, by 50% for a value > 3.
e. Exceptions were emergency leukapheresis, emergency treatment for hyperleukocytosis with hydroxycarbamide for ≤ 5 days, cranial radiotherapy for CNS leukostasis and growth factor/cytokine support.
f. Including the short-term use of glucocorticoids, provided the patient was not immunosuppressed.

AML: acute myeloid leukaemia; ANC: absolute neutrophil count; ASCO: American Society of Clinical Oncology; BSA: body surface area; IV: intravenous; PEG: polyethylene glycol; RCT: randomized controlled trial

The RATIFY study is a completed double-blind RCT on the comparison of midostaurin with placebo. Midostaurin or placebo was used in combination with chemotherapy with daunorubicin and cytarabine for induction, with chemotherapy with high-dose cytarabine for consolidation and then as monotherapy for maintenance treatment.

Adults under the age of 60 with diagnosed AML and a documented FLT3 mutation were included. AML was defined as a proportion of at least 20% blasts in the bone marrow. Patients with ITD or a point mutation in the TKD of the FLT3 gene were eligible to take part. A further

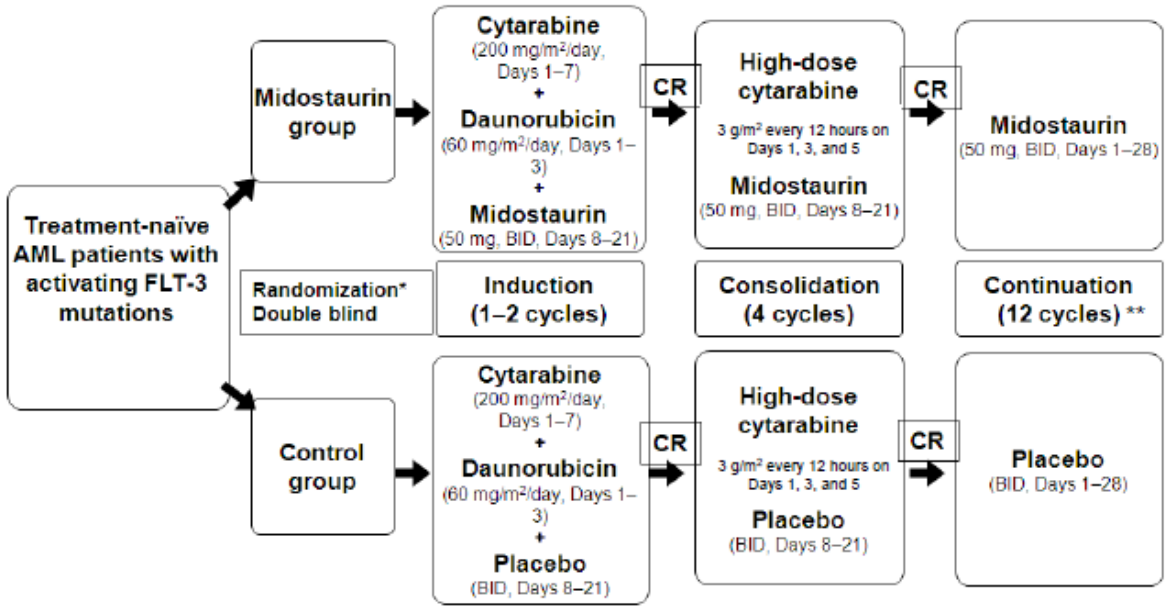
requirement was that the patients had not received previous chemotherapy for leukaemia or myelodysplasia. However, a history of myelodysplasia was not per se a reason for exclusion (see Table 5). Patients with acute promyelocytic leukaemia, therapy-related AML following previous radiotherapy or chemotherapy and CNS leukaemia were not allowed to participate in the study. In addition, the protocol contains further criteria, particularly regarding the presence of comorbidities, which are no explicit inclusion criteria but should be taken into account by the investigators when deciding whether to include a patient in the study.

The RATIFY study included a total of 717 patients who were randomly allocated in a 1:1 ratio to treatment with midostaurin (N = 360) or placebo (N = 357). Randomization was stratified by FLT3 mutation status (ITD with an allele ratio of < 0.7 vs. ITD with an allele ratio of ≥ 0.7 vs. TKD).

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 midostaurin or placebo in combination with cytarabine and daunorubicin. On Day 21, a bone marrow aspiration was performed to decide whether a second cycle was necessary. This was indicated in the presence of at least 5% blasts in the bone marrow (with appropriate cellularity [> 20%]). Patients who had not achieved complete remission even after 2 cycles of induction therapy had their study treatment discontinued. Patients who achieved complete remission after completing induction therapy moved on to the next therapy phase and received consolidation therapy. Consolidation therapy consisted of a total of 4 cycles of treatment with midostaurin or placebo in combination with cytarabine. If the patients were still in complete remission after completing the consolidation therapy, they received maintenance therapy with midostaurin or placebo for 12 cycles.

In the RATIFY study, the investigators were not generally prohibited from treating patients who had achieved complete remission with a stem cell transplantation. However, stem cell transplantation was not explicitly part of the study treatment (see below). In the intervention arm, treatment with midostaurin was largely in compliance with the specifications of the SPC [6]. In contrast, the dosing regimen of daunorubicin deviates from the dose of 20 to 40 mg/m^2 BSA specified in the SPC for a 1-day interval [7]. However, it should be noted that the SPC contains examples of combination regimens with other cytostatic drugs, some of which specify higher dosages. However, the dosing regimen used in the study reflects the consensus across guidelines [8-10]. The dosage of cytarabine during induction and consolidation therapy complied with the specifications of the SPC [11]. For consolidation therapy, however, the majority of guidelines recommend the use of intermediate-dose cytarabine [8-10]. Overall, the deviating dosing of daunorubicin and cytarabine has no consequence for the present benefit assessment, as the study is not relevant for other reasons.

Switching to the treatment of the other study arm was not planned. The study's primary outcome was overall survival. Secondary outcomes were recorded in the categories of morbidity and AEs.



AML = acute myeloid leukemia; bid = twice a day; CR = complete remission

* Central randomization within 3 strata: FLT3-TKD, FLT3-ITD with allelic ratio ≥ 0.7; FLT3-ITD with allelic ratio <0.7

** Up to 12 cycles

Figure 1: RATIFY study design

Assessment of the RATIFY study presented by the company

ACT not implemented in the RATIFY study

The G-BA specified an individualized treatment as ACT for the consolidation and maintenance therapy. In order to implement an individualized treatment, the investigator should have a choice of several treatment options in a study that enables an individualized treatment decision, taking into account the criteria specified in the ACT (see Table 4). The ACT specified by the G-BA was not implemented in the RATIFY study. The main reason for this is that in the study no individualized therapy was carried out during maintenance therapy. In addition, it is also questionable to what extent consolidation therapy represents an individualized therapy in the sense of the ACT.

The deviations from the ACT in the treatment phases of consolidation and maintenance therapy are explained below.

Consolidation therapy

According to the ACT, individualized treatment choosing from chemotherapy and allogeneic stem cell transplantation should be used as consolidation therapy. The treatment decision should depend on the AML subtype, the patient's general condition and comorbidities.

The design of the RATIFY study did not intend individualized treatment as consolidation therapy in accordance with the ACT, but instead mandated chemotherapy with high-dose cytarabine for all patients (see Figure 1). Although the option of allogeneic stem cell transplantation listed in the ACT was not prohibited in principle, allogeneic stem cell transplantation was not explicitly part of the study treatment. If an allogeneic stem cell transplantation was performed, the patients received no further treatment with the study medication and were only followed up for individual outcomes. The study documents provide no information on the decision criteria for or against allogeneic stem cell transplantation. Against the background of the study design, it is unclear whether all patients in the study for whom allogeneic stem cell transplantation was indicated as consolidation therapy depending on the AML subtype, general condition and comorbidities - as specified in the ACT - also received this.

Specific information on the proportion of patients in the study who received an allogeneic stem cell transplantation as consolidation therapy is not available. An approximation is possible on the basis of analyses on the number of patients who achieved complete remission within 60 days of randomization and who received an allogeneic stem cell transplantation if the first complete remission persisted in the further course of the study (not limited to consolidation therapy). Of these, 60 patients in the placebo arm (28.6% of patients who received consolidation therapy) received allogeneic stem cell transplantation. Patients who achieved a complete remission as late as after Day 60 from randomization could also receive a stem cell transplantation. Information on how many patients were affected by this is not available.

Maintenance therapy

Individualized treatment with a choice of azacitidine (only for patients for whom allogeneic stem cell transplantation was not suitable), sorafenib (only for patients with FLT3-ITD mutation following allogeneic stem cell transplantation) and watchful waiting (only for patients without FLT3-ITD mutation after allogeneic stem cell transplantation) as maintenance therapy was specified as ACT. The choice of the therapy was to take into account the induction and consolidation therapy as well as the FLT3 mutation status. In the RATIFY study presented by the company, patients in the control arm received placebo as maintenance therapy. The individualized treatment options of azacitidine and sorafenib listed in the ACT were not available in the study.

The maintenance treatment with placebo and regular study visits in the comparator arm carried out in the RATIFY study represents a sufficient approximation to watchful waiting in accordance with the ACT. This option of the ACT is only an option for patients without FLT3-ITD mutation following an allogeneic stem cell transplantation. However, in accordance with the specifications in the study protocol, none of the 85 patients in the comparator arm who received maintenance therapy had allogeneic stem cell transplantation . According to the ACT, treatment with azacitidine would thus potentially have been an option for the 85 patients who received maintenance therapy, but this was not used in the RATIFY study. As described above, patients did not receive any further study medication after an allogeneic stem cell transplantation. Information on the subsequent therapy after allogeneic stem cell transplantation is not available for patients in the RATIFY study. Itis therefore not possible to assess whether these patients were subsequently treated with sorafenib (in the presence of FLT3-ITD mutation) and watchful waiting (in the absence of FLT3-ITD mutation)in accordance with the ACT. The number of patients in the RATIFY study with and without FLT3-ITD mutation who received an allogeneic stem cell transplantation (at least 60 patients) and for whom maintenance therapy would have been an option cannot be inferred from the study documents.

Summary

In the RATIFY study presented by the company, the ACT was not implemented, particularly in the maintenance treatment, as no individualized treatment choosing from azacitidine, sorafenib and watchful waiting took place. The consolidation therapy was also not designed for individualized treatment and due to a lack of information it remains unclear whether the patients were treated in accordance with the ACT. Overall, the RATIFY study is therefore not suitable for answering the research question of the present benefit assessment.

I 3.1.2 A2220 study

Design of the A2220 study

The A2220 study consists of 2 parts: The risk profile and tolerability of midostaurin in combination with daunorubicin/cytarabine in the induction phase and high-dose cytarabine in the consolidation phase in Japanese patients with newly diagnosed AML were investigated in the open-label, single-arm part 1 of the study. Part 1 of the study does not allow a comparison with the ACT and is therefore not considered further below.

After completion of part 1 of the study or in parallel, the study was continued in Japan with a randomized, double-blind part 2, with patient recruitment also taking place in countries outside of Japan. The second part included 62 adult patients with newly diagnosed AML and an FLT3 mutation who were randomly assigned in a 1:1 ratio to treatment with midostaurin (N = 30) or placebo (N = 32). Randomisation was stratified by the chemotherapy regimen used and the FLT3 mutation status (ITD with an allele ratio of < 0.7 vs. ITD with an allele ratio of ≥

0.7 vs. TKD). Analogous to RATIFY, the second part of the study was divided into the 3 phases of induction, consolidation and maintenance. The treatment regimen used in both treatment arms was the same as that used in the RATIFY study (see Table 6). For patients who were included in the study in Japan, the JALSG regimen was additionally available as an alternative, which according to the study documents represents the treatment standard in Japan. The JALSG regimen is similar to the treatment regimen used in the RATIFY study with regard to the drugs used in the individual treatment phases and the number of cycles. However, with the exception of midostaurin or placebo, the dosage and/or the interval of the other drugs differ. Stem cell transplantation as consolidation therapy was not explicitly planned in study A2220, but could be used at the investigator's discretion. The study medication was discontinued before a stem cell transplantation and was not allowed to be resumed afterwards. The patients remained in the study and were followed up for selected outcomes.

The primary outcome of the study was event-free survival.

Assessment of the A2220 study presented by the company

Analogous to the RATIFY study, the ACT was not implemented in the A2220 study. The patients received the same or a similar treatment regimen as in the RATIFY study as comparator therapy. Accordingly, in study A2220, no individualized treatment with a choice of azacitidine, sorafenib and watchful waiting was carried out in maintenance therapy. Even in the consolidation phase, the study design was not designed for individualized treatment, although stem cell transplantation was generally permitted in addition to the planned cytarabine chemotherapy. In the midostaurin arm, of 21 patients who achieved complete remission after induction therapy, 2 patients (10%) received an allogeneic stem cell transplantation if the first complete remission persisted in the further course of the study (not limited to consolidation therapy). In the placebo arm, this was the case in 3 out of 25 patients (12%). Both treatment regimens used in study A2220 do not adequately reflect the ACT of an individualized therapy defined by the G-BA (see Section I 3.1.1). Therefore, the A2220 study is unsuitable for answering the research question of the present benefit assessment.

I 3.1.3 AMLSG 16-10 study

Study design of the AMLSG 16-10 study

The AMLSG 16-10 study is a single-arm study with midostaurin that included adult patients with an FLT3-ITD mutation and diagnosed AML, AML-related myeloid precursor neoplasia or acute leukaemia of unclear lineage. Prerequisite for the participation was that the disease had not been treated with chemotherapy before.

The study included 440 patients up to the age of 70 who were eligible for intensive chemotherapy. The patients received 1 to 2 cycles of midostaurin in combination with daunorubicin and cytarabine as induction therapy. Allogeneic stem cell transplantation should

be prioritised as consolidation therapy. Patients for whom allogeneic stem cell transplantation was not an option received a total of 4 cycles of cytarabine as consolidation therapy. After consolidation therapy, a 1-year maintenance therapy with midostaurin was planned for all patients.

The primary outcome of the study was event-free survival.

Due to the single-arm design of the AMLSG 16-10 study, the results in the study report for this study were compared with an external control cohort. This consisted of 415 patients aged 18 to 70 years with newly diagnosed AML and FLT3-ITD who had received intensive chemotherapy in 5 studies (conducted between 1993 and 2009) (AMLHD93, AMLHD98A, AMLHD98B, AMLSG 06-04 and AMLSG 07-04 [12-16]). As described in Module 4 A, treatment of patients in the control cohort consisted of induction therapy with idarubicin, cytarabine and etoposide (1 to 3 cycles) followed by high-dose cytarabine-based consolidation therapy. Allogeneic stem cell transplantation was performed at the discretion of the investigator. For the most part, maintenance treatment for the control cohort was not carried out in the studies.

Assessment of the AMLSG 16-10 study presented by the company

For the reasons described below, the AMLSG 16-10 study was unsuitable for the derivation of an added benefit of midostaurin in comparison with the ACT.

Administration of midostaurin as maintenance therapy after a stem cell transplantation in the AMLSG 16-10 study does not comply with the specifications of the SPC [6]. According to the approval, midostaurin is used exclusively after consolidation with high-dose chemotherapy, but not after allogeneic stem cell transplantation. The use of midostaurin following consolidation therapy with the reduced cytarabine dose (1g/m^2 BSA every 12 hours on Days 1, 3 and 5), which was planned in the study for patients over 65 years of age, is therefore also not covered by the approval of midostaurin (only after consolidation with high-dose chemotherapy).

Moreover, as described in Module 4 A, treatment of patients in the control cohort consisted of induction therapy with idarubicin, cytarabine and etoposide (1 to 3 cycles) followed by high-dose cytarabine-based consolidation therapy, and does thus not correspond to the ACT. For the most part, maintenance treatment for the control cohort was not carried out in the studies.

It should also be noted that for a comparison of study results from a single-arm study with the results of a control cohort from various other studies, the necessary structural equality between the treatment groups is not guaranteed. The study documents describe that propensity scores based on selected confounders were used as an estimate for weighting to correct for potential bias due to structural differences between the patient populations.

However, in Module 4 A, the company does not provide detailed information on the specific approach, e.g. for confounder identification.

Overall, the AMLSG 16-10 study, including the propensity score-adjusted comparison with a control cohort contained therein, is therefore not suitable for the benefit assessment.

Comparison of the AMLSG 16-10 study with the comparator arm of the RATIFY study

The company also presented a comparison of the AMLSG 16-10 study with the comparator arm of the RATIFY study. Since the use of midostaurin in the AMLSG 16-10 study was not in accordance with the SPC and the ACT was not implemented in the comparator arm of the RATIFY study, this comparison is not relevant for the benefit assessment. No further comments are therefore provided.

I 4 Results on added benefit

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

I 5 Overall conclusion on added benefit

The result of the assessment of the added benefit of risdiplam in comparison with the ACT is summarized in Table 7.

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

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with newly diagnosed AML and FLT3 mutation, in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and thereafter as midostaurin monotherapy for the maintenance treatment in patients in complete remission	▪ Induction chemotherapy[b]: ▫ cytarabine in combination with daunorubicin or idarubicin or mitoxantrone or ▫ daunorubicin/cytarabine (liposomal formulation) (only for patients with t-AML or AML-MRC) ▪ followed by a consolidation therapy[c]: individualized treatment choosing from chemotherapy (cytarabine or daunorubicin/cytarabine [liposomal formulation][d]) and allogeneic stem cell transplantation, depending in particular on the AML subtype, the patient's general condition and comorbidities. ▪ followed by maintenance treatment[c]: individualized therapy choosing from ▫ azacitidine (only for patients who are ineligible for an allogeneic stem cell transplantation) ▫ sorafenib (only for people with FLT3-ITD mutation after an allogeneic stem cell transplantation) ▫ watchful waiting (only for patients without FLT3-ITD mutation after an allogeneic stem cell transplantation) taking into account the induction and consolidation therapy as well as the FLT3 mutation status.	Added benefit not proven

Table 7: Midostaurin – 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. Induction chemotherapy: The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. For the proof of added benefit for the total population, any treatment option can be used that is not restricted by patient and disease characteristics given in brackets. If the ACT comprises several alternative treatment options without restrictions, the added benefit for the total population can be proven versus one of these alternative treatment options; this can usually be performed in the context of a single-comparator study. b. In contrast, the sole comparison against a treatment option which represents a comparator therapy for only part of the patient population is usually not sufficient to demonstrate added benefit for the overall population. c. For consolidation and maintenance therapy: For the implementation of individualized treatment in a direct comparative study, the investigator is expected to have a selection of several treatment options at disposal 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 treatment 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. d. According to the Summary of Product Characteristics (SPC), daunorubicin/cytarabine (liposomal formulation) can only be considered as consolidation therapy as part of individualized treatment if patients have already received daunorubicin/cytarabine (liposomal formulation) as part of induction chemotherapy. AML: acute myeloid leukaemia; AML-MRC: AML with myelodysplasia-associated changes; FLT: FMS-like tyrosine kinase; G-BA: Federal Joint Committee; ITD: internal tandem duplication; t-AML: therapy-related AML		

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

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of the market launch in 2017, where the G-BA determined a considerable added benefit of midostaurin. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data due to orphan drug status.

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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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-110.html.