IQWiG Reports – Commission No. A21-82

Venetoclax (acute myeloid leukaemia) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Venetoclax (akute myeloische Leukämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 September 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Venetoclax (acute myeloid leukaemia) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
15 June 2021

Internal Commission No.
A21-82

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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.

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Keywords: Venetoclax, Leukemia – Myeloid – Acute, Benefit Assessment, NCT02993523

Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AML	acute myeloid leukaemia
CR	complete remission
CRi	complete remission with incomplete blood count recovery
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ELN	European LeukemiaNet
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	European Quality of Life Questionnaire-5 Dimensions
ESMO	European Society for Medical Oncology
EU	European Union
FDA	United States Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HMA	hypomethylating agent
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDAC	low-dose cytarabine
MMRM	mixed-effects model with repeated measures
NCCN	National Comprehensive Cancer Network
PROMIS Cancer Fatigue SF 7a	Patient-Reported Outcome Measurement Information System Cancer Fatigue Short Form 7a
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
ULN	upper limit of normal
VAS	visual analogue scale
WHO	World Health Organization

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug venetoclax. 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 15 June 2021.

Research question

The aim of the present report is the assessment of the added benefit of venetoclax in combination with a hypomethylating agent (HMA) in comparison with the appropriate comparator therapy (ACT) in patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.

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

Table 2: Research question of the benefit assessment of venetoclax in combination with an HMA

Therapeutic indication[a]	**ACT**[b]
Adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for intensive chemotherapy	Cytarabine or **azacitidine** or decitabine
a. The G-BA assumes that for all patients in the therapeutic indication at the time of therapy with venetoclax in combination with an HMA, best supportive care treatment alone is not an option. In addition, it is assumed that patients with acute promyelocytic leukaemia are not comprised by the therapeutic indication. b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HMA: hypomethylating agent	

The company followed the G-BA's specification and chose azacitidine as ACT from the options presented.

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 the added benefit.

Study pool and study design

For the assessment of the added benefit of venetoclax in combination with an HMA, the Viale-A study is included, which compared the combination of venetoclax and azacitidine (hereinafter referred to as "venetoclax + azacitidine") with the combination of placebo and azacitidine

(hereinafter referred to as "placebo + azacitidine"). No data are available for the comparison of the combination of venetoclax with another HMA against the ACT.

The Viale-A study is a randomized, double-blind and multicentre study on the comparison of venetoclax + azacitidine with placebo + azacitidine.

The study included treatment-naive adult patients with AML (according to the World Health Organization [WHO] criteria) who were ineligible for treatment with a standard cytarabine and anthracycline induction regimen. In the study, non-eligibility for standard induction therapy was defined on the basis of criteria regarding age and/or comorbidities.

Patients ≥ 75 years of age could have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–2, patients ≥ 18 to 74 years of age an ECOG PS of 0–3. In addition, only patients with intermediate or poor cytogenetic risk (according to the National Comprehensive Cancer Network [NCCN] classification) were enrolled.

The Viale-A study included a total of 433 patients, who were randomly allocated in a 2:1 ratio either to treatment with venetoclax + azacitidine (N = 287) or to placebo + azacitidine (N = 146).

In the Viale-A study, treatment with venetoclax and azacitidine was administered in cycles of 28 days and was largely in compliance with the recommendations of the Summaries of Product Characteristics (SPCs).

Coprimary outcomes of the Viale-A study were overall survival and composite complete remission (complete remission [CR] + complete remission with incomplete blood count recovery [CRi]). Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and adverse events (AEs).

Relevant subpopulation of the Viale-A study

The Viale-A study included patients who were ineligible for intensive standard induction therapy. In Module 4 A, the company referred to 2 consultations with the G-BA, according to which the inclusion criteria used in the Viale-A study are not fully suitable for identifying patients who are ineligible for intensive chemotherapy. Due to this, the company presented analyses of a subpopulation from the Viale-A study in Module 4 A. In comparison with the inclusion criteria of the study, the company applied narrower criteria for defining non-eligibility for treatment with intensive chemotherapy to form the subpopulation. The subpopulation comprises 313 (72.3% of the total population) patients (intervention arm N = 210; comparator arm N = 103).

The approach of the company to forming the subpopulation is considered appropriate. The subpopulation formed by the company is therefore used for the present benefit assessment.

Risk of bias

The risk of bias across outcomes was rated as low for the Viale-A study. Except for overall survival and discontinuation due to AEs, the outcome-specific risk of bias was rated as high for the results of all outcomes for which usable data are available. The certainty of results for the outcome "discontinuation due to AEs" was restricted despite a low risk of bias. A high certainty of results can be assumed for the outcome "severe AEs" despite a high risk of bias.

Results

Mortality

Overall survival

A statistically significant difference in favour of venetoclax + azacitidine compared with placebo + azacitidine was shown for the outcome "overall survival". This resulted in an indication of an added benefit of venetoclax + azacitidine in comparison with azacitidine.

Morbidity

Symptoms (recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30])

There were no usable data for the outcome "symptoms", recorded with the EORTC QLQ-C30. This resulted in no hint of an added benefit of venetoclax + azacitidine in comparison with azacitidine; an added benefit is therefore not proven.

Health status (recorded with the European Quality of Life Questionnaire-5 Dimensions [EQ-5D] visual analogue scale [VAS])

There were no usable data for the outcome "health status", recorded with the EQ-5D VAS. This resulted in no hint of an added benefit of venetoclax + azacitidine in comparison with azacitidine; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

There were no usable data for the outcome "health-related quality of life", recorded with the EORTC QLQ-C30. This resulted in no hint of an added benefit of venetoclax + azacitidine in comparison with azacitidine; an added benefit is therefore not proven.

Side effects

Serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and discontinuation due to AEs

There was no statistically significant difference between the treatment groups for any of the outcomes "SAEs", "severe AEs" and "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm from venetoclax + azacitidine in comparison with azacitidine; greater or lesser harm is therefore not proven.

Specific AEs

Contusion (AE), injury, poisoning and procedural complications (severe AEs)

A statistically significant difference in favour of venetoclax + azacitidine in comparison with placebo + azacitidine was shown for the specific AEs "contusion" (AE) and "injury, poisoning and procedural complications" (severe AEs). In each case, this resulted in a hint of lesser harm from venetoclax + azacitidine in comparison with azacitidine.

Neutropenia (severe AEs)

A statistically significant difference to the disadvantage of venetoclax + azacitidine in comparison with placebo + azacitidine was shown for the outcome "neutropenia" (composed of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, neutropenic sepsis; [severe AEs]). This resulted in a hint of greater harm from venetoclax + azacitidine in comparison with azacitidine.

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

On the basis of the results presented, probability and extent of the added benefit of the drug venetoclax in combination with an HMA in comparison with the ACT are assessed as follows:

The overall consideration shows both positive and negative effects of venetoclax + azacitidine in comparison with azacitidine.

On the side of positive effects, there is an indication of a major added benefit for the outcome "overall survival", and a hint of lesser harm of minor or considerable extent for specific AEs of different severity categories. On the side of negative effects, in contrast, there is a hint of greater harm of major extent for the outcome "severe neutropenia", which in particular does not completely call into question the positive effect in overall survival, however.

There were no usable data for the outcome categories of morbidity and health-related quality of life.

In summary, there is an indication of considerable added benefit of venetoclax in combination with an HMA in comparison with azacitidine for patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

[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 shows a summary of probability and extent of the added benefit of venetoclax.

Table 3: Venetoclax in combination with an HMA – probability and extent of added benefit

Therapeutic indication[a]	**ACT**[b]	**Probability and extent of added benefit**
Adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for intensive chemotherapy	Cytarabine or **azacitidine** or decitabine	Indication of considerable added benefit[c]

a. The G-BA assumes that for all patients in the therapeutic indication at the time of therapy with venetoclax in combination with an HMA, best supportive care treatment alone is not an option. In addition, it is assumed that patients with acute promyelocytic leukaemia are not comprised by the therapeutic indication.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. In the Viale-A study, only venetoclax in combination with azacitidine was investigated; Module 4 A contains no data for the combination with decitabine. It remains unclear whether the observed effects from the Viale-A study can be transferred to the combination of venetoclax + decitabine.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HMA: hypomethylating agent

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

Supplementary note on the appropriate comparator therapy

The G-BA changed the ACT after submission of the dossier. The change included glasdegib in combination with low-dose cytarabine as additional option, whereas cytarabine alone is no longer an option of the ACT. The present benefit assessment was based on the originally specified ACT. The use of the modified ACT would have no effects on the result of this benefit assessment.

2.2 Research question

The aim of the present report is the assessment of the added benefit of venetoclax in combination with an HMA in comparison with the ACT in patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

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

Table 4: Research question of the benefit assessment of venetoclax in combination with an HMA

Therapeutic indication[a]	**ACT**[b]
Adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for intensive chemotherapy	Cytarabine or **azacitidine** or decitabine

a. The G-BA assumes that for all patients in the therapeutic indication at the time of therapy with venetoclax in combination with an HMA, best supportive care treatment alone is not an option. In addition, it is assumed that patients with acute promyelocytic leukaemia are not comprised by the therapeutic indication.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HMA: hypomethylating agent

The company followed the G-BA's specification and chose azacitidine as ACT from the options presented.

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 the added benefit. This concurs with the company's inclusion criteria.

2.3 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 venetoclax (status: 6 April 2021)
- bibliographical literature search on venetoclax (last search on 6 April 2021)
- search in trial registries/trial results databases for studies on venetoclax (last search on 6 April 2021)
- search on the G-BA website for venetoclax (last search on 6 April 2021)

To check the completeness of the study pool:

- search in trial registries for studies on venetoclax (last search on 25 June 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Study M15-656 (Viale-A[d])	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6,7]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this abbreviated form.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

For the benefit assessment of venetoclax in combination with an HMA, the Viale-A study is included, which directly compared the combination of venetoclax and azacitidine (hereinafter referred to as "venetoclax + azacitidine") with the combination of placebo and azacitidine (hereinafter referred to as "placebo + azacitidine"). No data are available for the comparison of the combination of venetoclax with another HMA against the ACT. The study pool of the present benefit assessment concurs with that of the company.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Viale-A	RCT, double-blind[b], parallel	▪ Adult patients with previously untreated AML[c] who are ineligible for treatment with a standard cytarabine and anthracycline induction regimen: ▫ age ≥ 75 years or ▫ age 18–74 years and at least one comorbidity[d] ▪ ECOG PS ≤ 2 for patients ≥ 75 years of age ▪ ECOG PS ≤ 3 for patients 18–74 years of age	Venetoclax + azacitidine (N = 287[e]) Placebo + azacitidine (N = 146[e]) Subpopulation analysed by the company: Venetoclax + azacitidine (n = 210) Placebo + azacitidine (n = 103)	Screening: up to 21 days Treatment: ≥ 6 cycles[f] or until disease progression[g], unacceptable toxicity, treatment discontinuation following the physician's or patient's decision Observation[h]: outcome-specific, at most until 2 years after enrolment of the last patient	134 centres in Australia, Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Japan, Norway, Poland, Portugal, Russia, South Africa, South Korea, Spain, Sweden, Taiwan, Turkey, USA 2/2017–ongoing First data cut-off[i]: 1 October 2018 Second data cut-off[j]: 4 January 2020 Third data cut-off[k]: 4 July 2020	Primary[l]: overall survival, CR + CRi Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine (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 only include information on relevant available outcomes for this benefit assessment.
b. Up to 12 Chinese patients were included in the study in an unblinded fashion to assess the safety and pharmacokinetics of venetoclax in combination with azacitidine in the Chinese population. This part of the Chinese population was not included in the analyses on efficacy and safety of the blinded study phase and is therefore no longer shown in the next tables.
c. Diagnosis confirmed by WHO criteria [8].
d. According to the inclusion criteria, ≥ 1 of the following criteria had to be met: ECOG PS of 2–3, cardiac failure requiring treatment, ejection fraction ≤ 50%, chronic stable angina pectoris, diffusing capacity of the lungs for carbon monoxide ≤ 65%, forced expiratory volume in 1 second ≤ 65%, creatinine clearance ≥ 30 to < 45 mL/min,, moderate hepatic impairment (total bilirubin > 1.5 to ≤ 3.0 x ULN) or any other comorbidity that the investigator judges to be incompatible with intensive chemotherapy and was confirmed by the clinical monitor before study enrolment.
e. Each of both study arms includes one patient who was enrolled according to the original protocol. The remaining study population (N = 286 in the intervention arm; N = 145 in the comparator arm) were enrolled after introduction of the first amendment (on 21 December 2016). This amendment comprised, among other things, the inclusion of the cytogenetic risk (intermediate; poor) as a stratification factor. The analysis population for the efficacy outcomes exclusively comprises patients who were included after the first amendment. The analysis population for the tolerability outcomes includes all randomized patients who received at least one dose of the study medication.
f. Patients received at least 6 treatment cycles of azacitidine.
g. According to ELN criteria [9]
h. Outcome-specific information is provided in Table 8.
i. 6 months after randomization of 225 patients.
j. After about 270 deaths.
k. According to the information provided by the company in Module 4 A, the third data cut-off was requested by the FDA.
l. Presentation of the coprimary outcome for the EU, EU reference countries, and Japan. For the US and US reference countries, overall survival is the only primary outcome.

AE: adverse event; AML: acute myeloid leukaemia; CR + CRi: composite complete remission (complete remission with incomplete blood count recovery); ECOG PS: Eastern Cooperative Oncology Group Performance Status; ELN: European LeukemiaNet; EU: European Union; FDA: Food and Drug Administration; n: relevant subpopulation; N: number of randomized (included) patients; RCT: randomized controlled trial; ULN: upper limit of normal; WHO: World Health Organization

Table 7: Characteristics of the intervention – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine

Study	Intervention	Comparison
Viale-A	Up-titration regimen of venetoclax[a] in cycle 1: ▪ day 1: 100 mg ▪ day 2: 200 mg ▪ from day 3: 400 mg	
	Venetoclax[b]: 400 mg, orally, once/day + azacitidine 75 mg/m^2 BSA, IV or SC, on day 1-7 of each cycle Duration of cycle: 28 days	Placebo[a, b]: orally, once/day + azacitidine 75 mg/m^2 BSA, IV or SC, on day 1-7 of each cycle Duration of cycle: 28 days
	Dose adjustments and treatment interruptions of venetoclax/placebo ▪ Dose adjustments and treatment interruptions[c] due to toxicities and depending on response largely in compliance with the SPC **Dose adjustments of azacitidine** ▪ Dose reduction[d, e] due to lack of recovery of ANC or platelet count ≥ 25% above the nadir (after 14 days) allowed after cycle 4.	
	Pretreatment <u>Allowed</u> ▪ hydroxyurea[f] or white blood cell apheresis for patients with white blood cell count > 25 x 10^9/L <u>Not allowed</u> ▪ hypomethylating agents, venetoclax and/or chemotherapeutic agents for MDS ▪ chimeric antigen receptor T-cell therapy ▪ investigational products for the treatment of MDS or AML ▪ strong and/or moderate CYP3A inducers ≤ 7 days prior to the initiation of study medication **Concomitant treatment** <u>Required</u> ▪ anti-infective prophylaxis (for viral, bacterial, and fungal infections) for all patients with ANC < 500/µL <u>Allowed</u> ▪ strong and moderate CYP3A inhibitors[g], moderate CYP3A inducers[h], P-gp inhibitors[g] <u>Not allowed</u> ▪ strong CYP3A inducers ▪ intrathecal chemotherapy or radiotherapy for CNS prophylaxis	

a. All patients were hospitalized during the up-titration phase from day 1 to day 4.
b. On the days of application of azacitidine, venetoclax or placebo had to be administered beforehand.
c. Treatment with azacitidine was also interrupted.
d. If the duration of venetoclax/placebo medication was reduced.
e. 50% of the azacitidine dose for bone marrow cellularity of 15–50%, and 33% of the azacitidine dose for bone marrow cellularity of < 15% if recovery is not achieved within 21 days.
f. Also allowed during the study treatment in cycle 1.
g. At least 2-fold reduction of the venetoclax dose if co-administered with moderate CYP3A or P-gp inhibitors and at least 8-fold reduction if co-administered with strong CYP3A inhibitors.
h. Not allowed during the up-titration phase.

AML: acute myeloid leukaemia; ANC: absolute neutrophil count; BSA: body surface area; CNS: central nervous system; CYP3A: cytochrome P450; IV: intravenous; MDS: myelodysplastic syndrome; P-gp: P-glycoprotein; RCT: randomized controlled trial; SC: subcutaneous

The Viale-A study is a randomized, double-blind and multicentre study on the comparison of venetoclax + azacitidine with placebo + azacitidine.

The study included treatment-naive adult patients with AML (according to the WHO criteria [8]) who were ineligible for treatment with a standard cytarabine and anthracycline induction regimen. In the study, non-eligibility for standard induction therapy was defined as follows:

- patients ≥ 75 years, or
- patients ≥ 18 to 74 years who met ≥ 1 of the following criteria:
  - ECOG PS of 2–3,
  - cardiac history of cardiac failure requiring treatment or ejection fraction ≤ 50% or chronic stable angina pectoris,
  - diffusing capacity of the lungs for carbon monoxide ≤ 65% or forced expiratory volume in 1 second ≤ 65%,
  - creatinine clearance ≥ 30 to < 45 mL/min,
  - moderate hepatic impairment (total bilirubin > 1.5 to ≤ 3 x upper limit of normal [ULN]), or
  - any other comorbidity that the investigator judged to be incompatible with intensive chemotherapy.

Patients ≥ 75 years of age could have an ECOG PS of 0–2, patients ≥ 18 to 74 years of age an ECOG PS of 0–3. In addition, only patients with intermediate or poor cytogenetic risk (according to the NCCN classification) were enrolled.

The Viale-A study included a total of 433 patients, who were randomly allocated in a 2:1 ratio either to treatment with venetoclax + azacitidine (N = 287) or to placebo + azacitidine (N = 146). According to the original protocol, stratification was by the characteristics of age (≥ 18 to < 75 years; ≥ 75 years) and region (European Union [EU]; Japan, USA; rest of the world). After Amendment 1 of the study protocol (21 December 2016), randomization was additionally stratified by the characteristic of cytogenetic risk (intermediate; poor), and China was added as a new category to the characteristic of region. Before Amendment 1, only one patient had been randomized into each of the treatment arms.

According to the SPC, azacitidine is approved as monotherapy for the treatment of AML [10]. The combination therapy of venetoclax + azacitidine is described in the SPC of venetoclax [11]. In the Viale-A study, treatment with venetoclax and azacitidine was administered in accordance with the regimen of 28-day cycles described in Table 7 and was in compliance with the recommendations of the SPCs [10,11]. In the Viale-A study, interruptions of the venetoclax therapy were without relevant deviations from the SPC [11]. Azacitidine dose reductions due to haematological side effects were allowed based on bone marrow cellularity and the duration of recovery, but the definition of haematological recovery differs from the SPC of azacitidine

[10]. Overall, only few patients in the Viale-A study (8.4% of the total population, information at the second data cut-off) had their azacitidine dosing reduced.

Study treatment was given until disease progression according to the European LeukemiaNet (ELN) criteria [9], until the occurrence of unacceptable toxicity, or until the decision of the investigator or the patient. In addition, treatment with the study medication could be continued after disease progression or relapse if the investigator considered it to be in the best interest of the patient. The SPC does not recommend continuation of treatment with venetoclax after disease progression. Information on how many patients were affected by this is not available.

Coprimary outcomes of the Viale-A study were overall survival and composite complete remission (CR + CRi). Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and AEs.

Relevant subpopulation of the Viale-A study

The Viale-A study included patients who were ineligible for intensive standard induction therapy (see Section on the Viale-A study). In Module 4 A, the company referred to 2 consultations with the G-BA, according to which the inclusion criteria used in the Viale-A study are not fully suitable for identifying patients who are ineligible for intensive chemotherapy. For this reason, the company presented analyses of a subpopulation from the Viale-A study in Module 4 A, which it used for the assessment of the added benefit of venetoclax in combination with an HMA.

Approach of the company to forming the relevant subpopulation

In comparison with the inclusion criteria of the study, the company applied the narrower criteria mentioned below for defining non-eligibility for treatment with intensive chemotherapy to form the relevant subpopulation from the total population of the Viale-A study.

The subpopulation comprises 313 (72.3% of the total population) patients (intervention arm N = 210; comparator arm N = 103) with the following composition:

- 261 (83,4% of the subpopulation) patients ≥ 75 years and with at least one other pre-existing condition (e.g. vascular [77%], cardiac [49%], renal [32%] or hepatobiliary disorders[15%])
- 19 (6.1% of the subpopulation) patients ≥ 18 to < 75 years and with an ECOG PS = 3
- 33 (10.5% of the subpopulation) patients ≥ 18 to < 75 years, with an ECOG PS = 2 and ≥ 1 of the following comorbidities:
  - cardiac history of cardiac failure requiring treatment, ejection fraction ≤ 50% or angina pectoris
  - diffusing capacity of the lungs for carbon monoxide ≤ 65% or forced expiratory volume in 1 second ≤ 65%

- creatinine clearance ≥ 30 to < 45 mL/min
- moderate hepatic impairment (total bilirubin > 1.5 to ≤ 3 x ULN)

Assessment of the approach of the company to forming the relevant subpopulation

The criteria applied by the company for the selection of patients who are ineligible for intensive chemotherapy correspond to the recommendations of the German Society for Haematology and Medical Oncology (DGHO) [12] and the European Society for Medical Oncology (ESMO) [13]. Both guidelines define age ≥ 75 years, ECOG PS ≥ 3, and other comorbidities, such as liver, kidney or heart disease as criteria for non-eligibility for intensive chemotherapy [12,13]. The other comorbidities are mostly not defined more precisely on the basis of clinical parameters. In comparison with the total population, mainly patients ≥ 18 to < 75 years with an ECOG PS = 2 and without any comorbidities were excluded due to the narrower inclusion criteria applied by the company for selecting the subpopulation. This approach is appropriate, as, in accordance with recommendations by the DGHO and the ESMO [12,13], these patients are eligible for treatment with intensive chemotherapy.

In contrast to DGHO and ESMO, the ELN recommends that age should not be the sole determinant of treatment decisions concerning AML [9]. The company described in Module 4 A that in clinical practice, there is no uniform definition of the patient population who are ineligible for intensive chemotherapy and discussed the criteria on age, comorbidities and ECOG PS. With regard to age, the company described that in the Viale-A study, all patients aged ≥ 75 years had additional pre-existing conditions, so that the presence of a comorbidity also applied to these patients, in addition to the criterion of age.

Overall, the approach of the company to forming the subpopulation is considered appropriate. The subpopulation formed by the company is therefore used for the present benefit assessment.

Data cut-offs

The Viale-A study is still ongoing. At the time of the benefit assessment, 3 data cut-offs are available:

- First data cut-off (1 October 2018): a priori planned interim analysis 6 months after randomization of 225 patients
- Second data cut-off (4 January 2020): planned interim analysis after about 270 deaths
- Third data cut-off (4 July 2020): 6 months follow-up, according to information provided by the company in Module 4 A, on request of the Food and Drug Administration (FDA)

In the dossier, the company used the third data cut-off from 4 July 2020 to derive the added benefit and presented results for all patient-relevant outcomes for this data cut-off. It additionally presented the study results for the second data cut-off as supplementary information in Module 4 A, Appendix 4-G2. According to the company, due to the longer observation period, the third data cut-off provided the most mature and robust data for all

patient-relevant outcomes compared with previous, a priori planned data cut-offs. Although the company did not provide any source from which the FDA's requirement can be derived, the company's justification for using the third data cut-off is comprehensible and is accepted for the benefit assessment. The present benefit assessment uses the presented data of the third data cut-off.

The final data cut-off of the Viale-A study is still pending and planned for the time point after 360 deaths.

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine

Study **Outcome category** **Outcome**	**Planned follow-up observation**
Viale-A	
Mortality	
Overall survival	At most 2 years after enrolment of the last patient
Morbidity	
Symptoms (EORTC QLQ-C30)	Until treatment discontinuation[a]
Health status (EQ-5D VAS)	Until treatment discontinuation[a]
Health-related quality of life (EORTC QLQ-C30)	Until treatment discontinuation[a]
Side effects	
All outcomes in the category of side effects	Until 30 days after treatment discontinuation[b]

a. Discrepant information in the study protocol and Module 4 A. According to the study protocol, the outcome was recorded until treatment discontinuation (final study visit). According to information provided in Module 4 A, the outcome was recorded for as long as the patient was under observationin the study.
b. If the final study visit was conducted > 30 days after treatment discontinuation, the follow-up observation after 30 days was omitted.

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; VAS: visual analogue scale

The observation periods for the outcomes of the category of side effects are systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days). The outcomes of the categories "morbidity" and "health-related quality of life" may also be systematically shortened. To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Characteristics of the relevant subpopulation

Table 9 shows the characteristics of the patients of the relevant subpopulation in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine (relevant subpopulation) (multipage table)

Study Characteristic Category	**Venetoclax + azacitidine N[a] = 210**	**Placebo + azacitidine N[a] = 103**
Viale-A		
Age [years], mean (SD)	78 (5)	78 (4)
Sex [F/M], %	41/60	38/62
Family origin, n (%)		
Indo-American or native Alaskan	0 (0)	1 (1)
Asian	47 (22)	22 (21)
Black or African American	3 (1)	1 (1)
White	160 (76)	79 (77)
Region, n (%)		
China	14 (7)	5 (5)
EU	84 (40)	43 (42)
Japan	20 (10)	12 (12)
United States	32 (15)	16 (16)
Rest of the world	60 (29)	27 (26)
ECOG PS; n (%)		
0	33 (16)	19 (18)
1	96 (46)	46 (45)
2	65 (31)	33 (32)
3	16 (8)	5 (5)
Cytogenetic risk according to EDC; n (%)		
Intermediate	138 (66)	66 (64)
Poor	72 (34)	37 (36)
CTC grade of neutropenia, n (%)		
0	42 (20)	18 (18)
1	4 (2)	9 (9)
2	14 (7)	12 (12)
3	33 (16)	21 (20)
4	117 (56)	43 (42)
CTC grade of anaemia, n (%)		
0	1 (1)	0 (0)
1	29 (14)	13 (13)
2	122 (58)	55 (53)
3	58 (28)	35 (34)
CTC grade of thrombocytopenia, n (%)		
0	24 (11)	15 (15)
1	49 (23)	20 (19)
2	33 (16)	19 (18)
3	59 (28)	24 (23)

Table 9: Characteristics of the study population – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine (relevant subpopulation) (multipage table)

Study Characteristic Category	**Venetoclax + azacitidine N[a] = 210**	**Placebo + azacitidine N[a] = 103**
4	45 (21)	25 (24)
AML type; n (%)		
De novo	156 (74)	77 (75)
Secondary	54 (26)	26 (25)
Platelet or red blood cell transfusion[b]; n (%)		
Yes	114 (54)	58 (56)
No	96 (46)	45 (44)
Hepatic impairment at baseline, n (%)		
Yes	43 (21)	31 (30)
No	167 (80)	71 (70)
Missing	0 (0)	1 (1)
Renal impairment at baseline, n (%)		
Yes	180 (86)	86 (84)
No	30 (14)	17 (17)
Non-eligibility for intensive chemotherapy; n (%)		
Age category of the patients		
≥ 75 years (including pre-existing conditions)	174 (83)	87 (85)
≥ 18–74 years	36 (17)	16 (16)
Patients aged ≥ 18–74 years; n (%)[c]		
ECOG PS 3	14 (39)	5 (31)
ECOG PS 2 and additional other comorbidities[d]	22 (61)	11 (69)
Cardiac history of cardiac failure requiring treatment	17 (77[e])	6 (55[e])
Ejection fraction ≤ 50%	1 (5[e])	3 (27[e])
Angina pectoris	11 (50[e])	2 (18[e])
Diffusing capacity of the lungs for carbon monoxide ≤ 65%	4 (18[e])	3 (27[e])
Forced expiratory volume in 1 second ≤ 65%	5 (23[e])	1 (9[e])
Creatinine clearance ≥ 30 and < 45 mL/min	17 (77[e])	5 (45[e])
Moderate hepatic impairment with total bilirubin > 1.5 and ≤ 3.0 x ULN	1 (5[e])	2 (18[e])
Treatment discontinuation, n (%)	ND[f]	ND[f]
Study discontinuation, n (%)	ND[g]	ND[g]

Table 9: Characteristics of the study population – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine (relevant subpopulation) (multipage table)

Study Characteristic Category	Venetoclax + azacitidine N[a] = 210	Placebo + azacitidine N[a] = 103
a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. Within 8 weeks before initiation of dosing or randomization if there was no treatment. c. Percentages are in relation to patients ≥ 18–74 years of age. d. Data on the listed comorbidities refer to patients ≥ 18–74 years of age and with ECOG PS = 2. One patient could have several comorbidities. e. Institute's calculation. f. Data on treatment discontinuations are only available for the total population of the Viale-A study (intervention arm N = 287; comparator arm N = 146), for the second data cut-off (4 January 2020): intervention arm n = 210; comparator arm n = 128. Reasons for discontinuation included, among other things, disease progression or morphologic relapse, death, withdrawal of consent, decision of the investigator, or AEs. g. Data on study discontinuations are only available for the total population of the Viale-A study (intervention arm N = 287; comparator arm N = 146), for the second data cut-off (4 January 2020): intervention arm N = 12; comparator arm N = 3; in each case without deaths. Reasons for discontinuations were decision of the patient and lost to follow-up. AE: adverse event; AML: acute myeloid leukaemia; CTC: Common Terminology Criteria; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EDC: electronic data capture; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; ULN: upper limit of normal		

The characteristics of the patients in the included subpopulation were largely comparable between the 2 treatment arms. The mean age of the patients was 78 years, about 60% were male, and about 76% were of white family origin. Slightly fewer than half of the patients had an ECOG PS = 1. On average, 74% of the patients had de novo AML and 65% had an intermediate cytogenetic risk. In addition, 55% of the patients had received platelet or red blood cell transfusion within 8 weeks prior to randomization.

Information on the course of the study

Table 10 shows the mean and median treatment duration of the patients and the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine (relevant subpopulation) (multipage table)

Study **Duration of the study phase** **Outcome category**	**Venetoclax + azacitidine** **N = 210**	**Placebo + azacitidine** **N = 103**
Viale-A		
Treatment duration[a] [months]		
Venetoclax/placebo + azacitidine[b]		
Median [Q1; Q3]	7.8 [1.9; 19.0]	3.9 [1.4; 10.0]
Mean (SD)	11.0 (10.2)	6.8 (7.5)
Venetoclax/placebo		
Median [Q1; Q3]	7.8 [1.9; 19.0]	3.9 [1.4; 10.0]
Mean (SD)	11.0 (10.2)	6.8 (7.5)
Azacitidine		
Median [Q1; Q3]	7.3 [1.4; 18.9]	3.5 [1.2; 9.5]
Mean (SD)	10.6 (10.2)	6.3 (7.5)
Observation period [months]		
Overall survival		
Median [Q1; Q3]	12.0 [2.6; 24.6]	9.1 [2.3; 15.2]
Mean (SD)	13.6 (10.8)	10.4 (8.4)
Morbidity		
Symptoms (EORTC QLQ-C30)	ND[c]	ND[c]
Health status (EQ-5D VAS)	ND[c]	ND[c]
Health-related quality of life (EORCT QLQ-C30)	ND[c]	ND[c]
Side effects[d]		
Median [Q1; Q3]	8.6 [2.4; 19.4]	4.8 [1.8; 10.6]
Mean (SD)	11.6 (10.1)	7.4 (7.6)

a. Data refer to patients with treatment: 206 vs. 101 patients.
b. At least one drug of the combination therapy had to be taken.
c. Discrepant data on follow-up observation of the outcomes "symptoms", "health status" and "health-related quality of life" (see Table 8). According to the study protocol, the outcomes were recorded until treatment discontinuation, but the observation period of these outcomes (median [Q1; Q3]: approx. 12.8 [6.4; 21.0] vs. 6.8 [3.4; 11.9] months; mean [SD]: 14.1 [8.9] vs. 9.1 [7.5] months) is substantially longer than the treatment duration with the study medication. These data refer exclusively to patients with a value at baseline and a value after baseline. Overall, it remains unclear how the provided observation periods occurred.
d. Data refer to patients who received at least one dose of the study medication (safety analysis set): 207 vs. 102 patients.

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; N: number of randomized patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

In the Viale-A study, the median treatment duration of the relevant subpopulation with ≥ 1 drug of the combination therapy was twice as long in the intervention arm (7.8 months) as in the

comparator arm (3.9 months). This difference was also shown in the treatment duration with only one drug (venetoclax/placebo or azacitidine), with treatment with azacitidine being slightly shorter than with venetoclax/placebo in both study arms.

The median observation period for the time point "overall survival" was 12 months in the intervention arm and 9.1 months in the comparator arm. No completely comprehensible data are available for the outcomes from the categories of morbidity and health-related quality of life. For side effects, the observation period in the intervention arm was about twice as long as in the comparator arm.

Information on subsequent therapies

The Viale-A study had no restrictions regarding the type of subsequent therapies. The information on subsequent therapies in the relevant subpopulation are presented in Appendix D of the full dossier assessment.

At the present data cut-off, a small proportion of the relevant subpopulation had received subsequent systemic therapy (13.8% in the intervention arm and 24.3% in the comparator arm). Patients with subsequent therapy after discontinuation of the study medication most frequently received subsequent therapy with cytarabine (41.4% in the intervention arm and 44% in the comparator arm). Furthermore, subsequent therapies included the HMAs azacitidine (13.8% vs. 32%) or decitabine (10.3% vs. 28%), among others. According to guideline recommendations [12-14], these are relevant options for subsequent therapies.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
Viale-A	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the Viale-A study. This concurs with the company's assessment.

Transferability of the study results to the German health care context

The company described that the inclusion criteria of the relevant subpopulation corresponded to those in the German DGHO guideline for the assessment of ineligibility for treatment with intensive chemotherapy [12] and that, in Germany, HMAs (azacitidine and decitabine) as well as low-dose cytarabine (LDAC) were standard treatment options for leukaemia for these patients. In addition, the company stated that azacitidine was recommended and preferred in everyday health care in Germany.

The company pointed out that conclusions could be drawn about the German health care context due to the design of the Viale-A study. In this regard, the company stated that the Viale-A study was also conducted in German study centres, that 76.4% of the study participants were of white family origin and that 40.6% came from Western Europe. Furthermore, the company described that the median age of the relevant subpopulation was even higher than that in German everyday health care, that the proportion of male patients (approx. 60%) in the Viale-A study was comparable to the patient population of German AML patients and that the proportion of patients with secondary AML corresponded to the everyday health care setting.

Finally, the company stated that the methods used in the Viale-A study to record and evaluate a response to anti-leukaemia treatment corresponded to the check of key findings at the start and during the course of anti-leukaemia treatment in Germany recommended by the DGHO guideline [12].

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms, recorded with the EORTC QLQ-C30
  - health status measured with the EQ-5D VAS
- Health-related quality of life
  - recorded with the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)

- discontinuation due to AEs
- further specific AEs, if any

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

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine

Study	Outcomes									
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Contusion[b] (PT, AEs)	Injury, poisoning and procedural complications (SOC, severe AEs[a])	Neutropenia[c] (PTs, severe AEs[a])
Viale-A	Yes	No[d]	No[d]	No[d]	Yes	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Events may be included that can be both side effects and symptoms of the disease.
c. Predefined outcome, which is presented as AE of special interest in Module 4 A. Composed of the following CTCAE grade ≥ 3 events (MedDRA coding): neutropenia (PT), neutrophil count decreased (PT), febrile neutropenia (PT), agranulocytosis (PT), neutropenic infection (PT), neutropenic sepsis (PT).
d. No usable data available; for reasons, see running text below.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on outcomes of the categories "morbidity" and "health-related quality of life"

- Symptoms and health-related quality of life recorded with the EORTC QLQ-C30 scales, and health status recorded with the EQ-5D VAS:
  - For the EORTC QLQ-C30 and the EQ-5D VAS, the company presented responder analyses for the time to first deterioration by ≥ 10 points (EORTC QLQ-C30) and ≥ 7 points (EQ-5D VAS) in Module 4 A. The company presented the results of these

outcomes in Module 4 A, but did not use them to assess the added benefit of venetoclax, as a possible bias of the results could not be ruled out due to low response rates in both study arms (< 70%). In addition, it claimed that there were incomplete observations for potentially informative reasons, as no further questionnaires were recorded in case of progression.
In the present data situation, this assessment is appropriate: Already at cycle 3, the first documentation time during treatment with the study medication, the response rates for the questionnaires EORTC QLQ-C30 and EQ-5D VAS were approx. 69% in the intervention arm and 64% in the comparator arm. Therefore, no usable data are available for the outcomes "symptoms", "health status" and "health-related quality of life" for the present benefit assessment, as > 30% of the patients were not considered in the analysis.

- In Module 4 A (Appendix 4-G1) , the company presented supplementary analyses of the mean change from baseline, calculated on the basis of a linear mixed model (mixed-effects model with repeated measures [MMRM]). Due to the reasons mentioned above, these analyses also do not provide adequate results for the assessment of the outcomes on symptoms, health status and health-related quality of life.
- The following should be noted regarding the response criterion chosen by the company for the EQ-5D VAS: As explained in the *General Methods* of the Institute [1,15], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range).

- Fatigue recorded with the Patient-Reported Outcome Measurement Information System (PROMIS) Cancer Fatigue Short Form (SF) 7a:
  - The company presented responder analyses for the time to first deterioration by ≥ 5 points for the PROMIS Cancer Fatigue SF 7a in Module 4 A. The company also presented supplementary analyses of the mean change from baseline, calculated on the basis of an MMRM. Analogous to the outcomes "symptoms", "health status" and "health-related quality of life", the company presented the results of the outcome "fatigue" in Module 4 A, but did not use this outcome for the assessment of the added benefit of venetoclax (for reasons, see Section on symptoms, health status and health-related quality of life).
    In the present data situation, this approach is appropriate: Already at cycle 3, the first documentation time during treatment with the study medication, the response rates were approx. 70% in the intervention arm and 66% in the comparator arm. Hence, no usable data are available for the outcome "fatigue", as > 30% of the patients were not considered in the analysis. Therefore, no further investigation of the validity of the used survey instrument and the relevance of the response criterion was conducted for the present benefit assessment.

- Freedom from transfusion
  - In Module 4 A, the company presented data on the outcomes “platelet transfusion independence” and “red blood cell transfusion independence”. Transfusion independence was defined as proportion of patients with no platelet or red blood cell transfusion for ≥ 8 weeks (binary data). Patients must have achieved uninterrupted transfusion independence for ≥ 8 weeks between the first dose of study drug and either the last dose of study drug (+ 30 days), or before death or before the initiation of subsequent therapy (whichever was earliest). In Module 4 A, the company presented additional sensitivity analyses on the proportion of patients who achieved platelet or red blood cell transfusion independence over a period of ≥ 16 and ≥ 24 weeks.

    Complete freedom from transfusion is generally considered to be patient-relevant, since transfusions in the present therapeutic indication are also administered as a symptom-oriented component of supportive therapy to patients with AML [12,14,16,17] and freedom from transfusion can mean avoidance of symptoms as well as late complications. However, in contrast to the company, freedom from transfusion would be considered overall and not separately for platelets and red blood cells.

    Furthermore, the results presented by the company were not used for the following additional reasons:

    - It is not clear from the study documents on the basis of which criteria transfusions were administered in the Viale-A study. According to information provided by the company in Module 4 A, transfusions were given on the basis of objective and quantitative methods based on local guidelines as well as on the basis of a patient-specific assessment by the investigator using objective laboratory and clinical parameters. However, there is no uniform guideline with criteria (e.g. on laboratory parameters or symptoms) for the administration of transfusions in the Viale-A study.
    - In addition, the observation period of the outcome was substantially longer in the intervention arm than in the comparator arm (median: 8.7 versus 4.9 months), so that a higher proportion of patients in the intervention arm had the opportunity to achieve uninterrupted freedom from transfusion over a longer period than in the control arm.

Notes on outcomes of the category “side effects”

- In deviation from the specification in the dossier template [18], besides treatment-related AEs, the analyses of the overall rates of AEs, SAEs, severe AEs and discontinuations due to AEs also include AEs that can be attributed to progression of the underlying disease. In Module 4 A, the company described that, due to the difficult specific delineation between AEs and progression events in this therapeutic indication, no analysis of the outcomes on tolerability was conducted without the possible, but not clearly assignable disease-related Preferred Terms (PTs). Since the overall rates of the outcomes in the category of side

effects in the Viale-A study in each case included only few events that can represent a progression of the underlying disease, e.g. in the System Organ Class (SOC) "neoplasms benign, malignant and unspecified (incl cysts and polyps)", these were used for the benefit assessment without restrictions.
On the level of specific AEs, however, a statistically significant difference in favour of the intervention was shown for the SOC "neoplasms benign, malignant and unspecified (incl cysts and polyps)" (SAEs). This cannot be interpreted in the present data situation, as it is unclear to what extent this is due to included events that are attributable to progression of the underlying disease. This outcome was therefore not used for the benefit assessment.

- Discontinuation due to AEs: In Module 4 A, this outcome was defined as AEs that led to discontinuation of any medication. It is unclear for this operationalization whether it reflects the discontinuation of all drug components (venetoclax/placebo and azacitidine) or the discontinuation of ≥ 1 drug component. It is not clear from the information in the study protocol whether both drug components were to be discontinued in principle when the study medication was discontinued or whether treatment could be continued with one drug component (venetoclax/placebo or azacitidine). In the context of the benefit assessment, the operationalization "discontinuation of ≥ 1 drug component" is preferred, as each AE that leads to a discontinuation of therapy is relevant. In total, 69 (24.4%) patients in the intervention arm and 29 (20.1%) patients in the comparator arm discontinued venetoclax/placebo due to AEs in the Viale-A study (data are only available for the second data cut-off for the total population). There are identical or very similar event rates for discontinuation of azacitidine due to AEs (68 [24.0%] versus 29 [20.1%] patients). These results suggest that, generally, both drug components were discontinued together, and thus all treatment discontinuations due to AEs were included in the present analysis.

2.4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine

Study	Outcomes											
	Study level	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Contusion[b] (PT, AEs)	Injury, poisoning and procedural complications (SOC, severe AEs[a])	Neutropenia[c] (PTs, severe AEs[a])
Viale-A	L	L	-[d]	-[d]	-[d]	H[e]	H[e]	L[f]	H[e]	H[e]	H[e]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Events may be included that can be both side effects and symptoms of the disease.
c. Predefined outcome, which is presented as AE of special interest in Module 4 A. Composed of the following CTCAE grade ≥ 3 events (MedDRA coding): neutropenia (PT), neutrophil count decreased (PT), febrile neutropenia (PT), agranulocytosis (PT), neutropenic infection (PT), neutropenic sepsis (PT).
d. No usable data are available for the outcomes of the categories of morbidity and health-related quality of life; for reasons, see Section 2.4.1.
e. Incomplete observations for potentially informative reasons with large difference in the median observation period between the intervention arm (8.6 months) and the control arm (4.8 months).
f. Despite low risk of bias, the certainty of results for the outcome "discontinuation due to AEs" was assumed to be limited (see running text below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Concurring with the company, the risk of bias of the results on overall survival was rated as low.

No usable data are available for the outcomes of the categories of morbidity and health-related quality of life; for reasons (for reasons, see Section 2.4.1), so that the risk of bias was not assessed. This deviates from the company's approach in that the company rated the risk of bias as high, but also did not use the results for the derivation of the added benefit.

The risk of bias of the results of the outcomes "SAEs", "severe AEs" and "specific AEs" (contusion [AEs], injury, poisoning and procedural complications [severe AEs] and neutropenia [severe AEs]) was rated as high, as observation of these outcomes was incomplete for

potentially informative reasons (largely determined by discontinuation of observation after disease progression). This concurs with the company's assessment.

However, for the outcome "severe AEs", due to the very early occurrence of the events (median time to occurrence 0.2 months in the intervention arm and 0.5 months in the comparator arm) in comparison with the median observation period of the outcome and in view of the few censorings (see Figure 3 in the full dossier assessment), it is not assumed that the observation periods shortened for possibly informative reasons call the observed effect into question. Hence, a high certainty of results in this outcome is assumed despite the high risk of bias. Due to the high certainty of results, at most an indication, e.g. of an added benefit, can therefore be determined for the outcome "severe AEs".

Deviating from the company, the risk of bias for the results of the outcome "discontinuation due to AEs" was rated as low. Despite a low risk of bias, the certainty of results is restricted for the outcome "discontinuation due to AEs". Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome "discontinuation due to AEs" to be recorded. This means that, after discontinuation for other reasons, AEs that would have led to discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It cannot be estimated how many AEs are concerned.

2.4.3 Results

Table 14 summarizes the results for the comparison of venetoclax + azacitidine with placebo + azacitidine in patients with newly diagnosed AML who are ineligible for intensive chemotherapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Results on common AEs, SAEs and severe AEs, as well as on all AEs that led to treatment discontinuation are presented in Appendix B of the full dossier assessment. Kaplan-Meier curves on the event time analyses are presented in Appendix C of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine (relevant subpopulation) (multipage table)

Study Outcome category Outcome	Venetoclax + azacitidine		Placebo + azacitidine		Venetoclax + azacitidine vs. placebo + azacitidine
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value[b]
Viale-A					
Mortality					
Overall survival	210	12.6 [9.9; 17.6] 138 (65.7)	103	9.1 [6.6; 11.9] 90 (87.4)	0.61 [0.46; 0.80]; < 0.001
Morbidity					
Symptoms (EORTC QLQ-C30) Health status (EQ-5D VAS)	No usable data[c]				
Health-related quality of life					
EORTC QLQ-C30	No usable data[c]				
Side effects					
AEs (supplementary information)	207	0.1 [0.0; 0.1] 207 (100.0)	102	0.1 [0.1; 0.1] 102 (100.0)	-
SAEs	207	1.3 [0.9; 1.7] 175 (84.5)	102	1.6 [1.0; 2.6] 77 (75.5)	1.12 [0.85; 1.47]; 0.429
Severe AEs[d]	207	0.2 [0.1; 0.4] 204 (98.6)	102	0.5 [0.2; 0.6] 97 (95.1)	1.28 [1.00; 1.64]; 0.061
Discontinuation due to AEs	207	NA 58 (28.0)	102	NA [22.2; NC] 23 (22.5)	1.08 [0.66; 1.76]; 0.767
Contusion[e] (PT, AEs)	207	NA 9 (4.3)	102	NA 11 (10.8)	0.31 [0.13; 0.77]; 0.008
Injury, poisoning and procedural complications (SOC, severe AEs[d])	207	NA 11 (5.3)	102	NA [20.7; NC] 10 (9.8)	0.40 [0.16; 1.00]; 0.043
Neutropenia[f] (PTs, severe AEs[d])	207	1.8 [1.0; 2.5] 141 (68.1)	102	7.5 [3.1; NC] 40 (39.2)	2,04 [1.43; 2.91]; < 0.001

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: venetoclax + azacitidine vs. placebo + azacitidine (relevant subpopulation) (multipage table)

Study Outcome category Outcome	Venetoclax + azacitidine		Placebo + azacitidine		Venetoclax + azacitidine vs. placebo + azacitidine
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value[b]

a. Effect and CI: Cox proportional hazards model stratified by age (18-74 years, ≥ 75 years) and cytogenetic risk (intermediate, poor).
b. p-value from log-rank test, stratified by age (18-74 years, ≥ 75 years) and cytogenetic risk (intermediate, poor).
c. No usable data are available for the outcomes of the categories of morbidity and health-related quality of life; for reasons, see Section 2.4.1.
d. Operationalized as CTCAE grade ≥ 3.
e: Events may be included that can be both side effects and symptoms of the disease.
f. Predefined outcome, which is presented as AE of special interest in Module 4 A. Composed of the following CTCAE grade ≥ 3 events (MedDRA coding): neutropenia (PT), neutrophil count decreased (PT), febrile neutropenia (PT), agranulocytosis (PT), neutropenic infection (PT), neutropenic sepsis (PT).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

On the basis of the available information, at most indications, e.g. of an added benefit, can be determined for the outcomes “overall survival” and “severe AEs” (see Section 2.4.2); due to the high risk of bias or, for the outcome “discontinuation due to AEs”, due to a limited certainty of results, at most hints can be determined for the remaining outcomes of the category of side effects.

Mortality

Overall survival

A statistically significant difference in favour of venetoclax + azacitidine compared with placebo + azacitidine was shown for the outcome “overall survival”. This resulted in an indication of an added benefit of venetoclax + azacitidine in comparison with azacitidine.

This concurs with the company’s assessment.

Morbidity

Symptoms (EORTC QLQ-C30)

There were no usable data for the outcome "symptoms", recorded with the EORTC QLQ-C30 (for reasons, see Section 2.4.1). This resulted in no hint of an added benefit of venetoclax + azacitidine in comparison with azacitidine; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health status (EQ-5D VAS)

There were no usable data for the outcome "health status", recorded with the EQ-5D VAS (for reasons, see Section 2.4.1). This resulted in no hint of an added benefit of venetoclax + azacitidine in comparison with azacitidine; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

EORTC QLQ-C30

There were no usable data for the outcome "health-related quality of life", recorded with the EORTC QLQ-C30 (for reasons, see Section 2.4.1). This resulted in no hint of an added benefit of venetoclax + azacitidine in comparison with azacitidine; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

The company did not conduct an outcome-specific derivation of the added benefit for the outcomes of the category of side effects, but concluded on the basis of the results on tolerability that no additional harm was proven for venetoclax. Therefore, the extent to which the conclusion of the added benefit deviates from that of the company is not described below.

SAEs, severe AEs and discontinuation due to AEs

There was no statistically significant difference between the treatment groups for any of the outcomes "SAEs", "severe AEs" and "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm from venetoclax + azacitidine in comparison with azacitidine; greater or lesser harm is therefore not proven.

Specific AEs

Contusion (AE), injury, poisoning and procedural complications (severe AEs)

A statistically significant difference in favour of venetoclax + azacitidine in comparison with placebo + azacitidine was shown for the specific AEs "contusion" (AE) and "injury, poisoning and procedural complications" (severe AEs). In each case, this resulted in a hint of lesser harm from venetoclax + azacitidine in comparison with azacitidine.

Neutropenia (severe AEs)

A statistically significant difference to the disadvantage of venetoclax + azacitidine in comparison with placebo + azacitidine was shown for the outcome "neutropenia" (composed of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, neutropenic sepsis; [severe AEs]). This resulted in a hint of greater harm from venetoclax + azacitidine in comparison with azacitidine.

2.4.4 Subgroups and other effect modifiers

The following potential effect modifiers are relevant for the present benefit assessment:

- sex (female versus male)
- age (≥ 18 to < 65 years versus ≥ 65 to < 75 years versus ≥ 75 years)
- cytogenetic risk (intermediate versus poor)

All subgroup characteristics used in the present benefit assessment were defined a priori, although partly only for the co-primary outcome of the Viale-A study. Subgroup analyses are available for all included patient-relevant outcomes for which usable data are available.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least one subgroup.

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

Using the methods described above, the available subgroup results did not show any effect modifications.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 15).

Determination of the outcome category for the outcomes on side effects

It cannot be inferred from the dossier for the following outcome whether it is serious/severe or non-serious/non-severe. The classification for this outcome is justified.

Specific AEs

The specific AE "contusion" (AEs) was allocated to the outcome category "non-serious/non-severe side effects" because only CTCAE grade ≤ 2 events occurred.

Table 15: Extent of added benefit at outcome level: venetoclax + azacitidine vs. placebo + azacitidine (relevant subpopulation) (multipage table)

Outcome category **Outcome**	**Venetoclax + azacitidine vs. placebo + azacitidine** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	12.6 vs. 9.1 months HR: 0.61 [0.46; 0.80]; p < 0.001 probability: "indication"	Outcome category "mortality" $CI_u < 0.85$ added benefit, extent: "major"
Morbidity		
Symptoms (EORTC QLQ-C30)	No usable data[c]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data[c]	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No usable data[c]	Lesser benefit/added benefit not proven
Side effects		
SAEs	1.3 vs. 1.6 months HR: 1.12 [0.85; 1.47]; p = 0.429	Greater/lesser harm not proven
Severe AEs	0.2 vs. 0.5 months HR: 1.28 [1.00; 1.64]; p = 0.061	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA HR: 1.08 [0.66; 1.76]; p = 0.767	Greater/lesser harm not proven
Contusion (AEs)	NA vs. NA HR: 0.31 [0.13; 0.77] p = 0.008 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Injury, poisoning and procedural complications (severe AEs)	NA vs. NA HR: 0.40 [0.16; 1.00]; p = 0.043 probability: "hint"	Outcome category: serious/severe side effects $CI_u \geq 0.90$ lesser harm, extent: "minor"
Neutropenia[d] (severe AEs)	1.8 vs. 7.5 months HR: 2.04 [1.43; 2.91] HR: 0.49 [0.34; 0.70][e] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"

Table 15: Extent of added benefit at outcome level: venetoclax + azacitidine vs. placebo + azacitidine (relevant subpopulation) (multipage table)

Outcome category **Outcome**	**Venetoclax + azacitidine vs. placebo + azacitidine** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). c. See Section 2.4.1 for reasons. d. Composed of the following CTCAE grade ≥ 3 events (MedDRA coding): neutropenia (PT), neutrophil count decreased (PT), febrile neutropenia (PT), agranulocytosis (PT), neutropenic infection (PT), neutropenic sepsis (PT). e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; NA: not achieved; PT: Preferred Term; SAE: serious adverse event; VAS: visual analogue scale		

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of venetoclax + azacitidine in comparison with azacitidine (relevant subpopulation)

Positive effects	**Negative effects**
Mortality ▪ Overall survival indication of added benefit – extent: "major"	–
Serious/severe side effects ▪ Injury, poisoning and procedural complications (severe AEs) hint of lesser harm - extent: "minor"	Serious/severe side effects ▪ Neutropenia[a] (severe AEs) hint of greater harm – extent: "major"
Non-serious/non-severe side effects ▪ Contusion (AEs) hint of lesser harm – extent: "considerable"	–
There were no usable data on outcomes of the categories "morbidity" and "health-related quality of life".	
a. Composed of the following CTCAE grade ≥ 3 events (MedDRA coding): neutropenia (PT), neutrophil count decreased (PT), febrile neutropenia (PT), agranulocytosis (PT), neutropenic infection (PT), neutropenic sepsis (PT). CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term	

The overall consideration shows both positive and negative effects of venetoclax + azacitidine in comparison with azacitidine.

On the side of positive effects, there is an indication of a major added benefit for the outcome "overall survival", and a hint of lesser harm of minor or considerable extent for specific AEs of different severity categories. On the side of negative effects, in contrast, there is a hint of greater harm of major extent for the outcome "severe neutropenia", which in particular does not completely call into question the positive effect in overall survival, however.

There were no usable data for the outcome categories of morbidity and health-related quality of life.

In summary, there is an indication of considerable added benefit of venetoclax in combination with an HMA in comparison with azacitidine for patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

The result of the assessment of the added benefit of venetoclax in combination with an HMA in comparison with the ACT is summarized in Table 17.

Table 17: Venetoclax in combination with an HMA – probability and extent of added benefit

Therapeutic indication[a]	**ACT**[b]	**Probability and extent of added benefit**
Adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for intensive chemotherapy	Cytarabine or **azacitidine** or decitabine	Indication of considerable added benefit[c]

a. The G-BA assumes that for all patients in the therapeutic indication at the time of therapy with venetoclax in combination with an HMA, best supportive care treatment alone is not an option. In addition, it is assumed that patients with acute promyelocytic leukaemia are not comprised by the therapeutic indication.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. In the Viale-A study, only venetoclax in combination with azacitidine was investigated; Module 4 A contains no data for the combination with decitabine. It remains unclear whether the observed effects from the Viale-A study can be transferred to the combination of venetoclax + decitabine.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HMA: hypomethylating agent

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

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

Supplementary note on the appropriate comparator therapy

The G-BA changed the ACT after submission of the dossier. The change included glasdegib in combination with low-dose cytarabine as additional option, whereas cytarabine alone is no

longer an option of the ACT. The present benefit assessment was based on the originally specified ACT. The use of the modified ACT would have no effects on the result of this benefit assessment.

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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