# Input from manufacturer on the 2nd draft assessment "VENETOCLAX WITH A HYPOMETHYLATING AGENT FOR THE TREATMENT OF ADULT PATIENTS WITH NEWLY-DIAGNOSED ACUTE MYELOID LEUKAEMIA (AML) WHO ARE INELIGIBLE FOR INTENSIVE CHEMOTHERAPY"

Project ID: PTJA16

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

The objective of this reviewer form is to standardise the process of the factual accuracy check of the rapid relative effectiveness assessments.

The 2nd version of the Rapid Assessment of venetoclax with a hypomethylating agent for the treatment of adult patients with newly-diagnosed acute myeloid leukaemia (aml) who are ineligible for intensive chemotherapy was open to review by the manufacturer AbbVie between **07/06/2021 and 11/06/2021**.

Comments received from:

| Market Authorisation Holder |
| --- |
| AbbVie |

All received comments are formally responded in this combined document, to be published on the EUnetHTA website, name of organisation/institution (or individual names of the reviewers/affiliations) disclosed.

Comments from Market Authorisation Holder AbbVie

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| 13 | Line 251-253 | **Consideration:** Misleading language around venetoclax indication and EMA approval date<br>**Text from EUnetHTA draft assessment:**<br>The EMA approved 22 april 2021 the combination of venetoclax with decitabine based on similar mechanism of action and results from the M14-358 study reporting similar efficacy and safety as venetoclax in combination with azacitadine.<br>**Comment from AbbVie:** The 22 April 2021 date was the date of CHMP positive opinion not EC approval. Additionally, since this is the first place in the document that states the CHMP positive opinion of the full indication, it may lead readers to surmise that the CHMP recommended only venetoclax + decitabine.<br><br>Please consider rephrasing to 'The CHMP adopted a positive opinion recommending venetoclax in combination with a HMA (azacitidine or decitabine) on 22 April 2021. While VIALE-A was the primary study for venetoclax in combination with azacitidine, the combination of venetoclax with decitabine was approved based on similar mechanism of action and results from the M14-358 study reporting similar efficacy and safety as venetoclax in combination with azacitidine (VIALE-A).' | 3 | The text was somewhat misleading and has been amended according to suggestion by MAH |
| 13-14<br>36 | Line 271-275<br>Line 873-877 | **Error:** VIALE-A inclusion criteria<br>**Text from EUnetHTA draft assessment:**<br>Included patients were ≥ 75 years of age, had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2–3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, creatinine clearance (CLcr) < 45 mL/min, or other comorbidity (Modified Ferrara criteria).<br>**Comment from AbbVie:** The above inclusion criteria are inaccurate. | 1 | Amended- updated specification in the inclusion criteria |

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| | | Please rephrase to 'Included patients were ≥ 75 years of age, **OR** had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2–3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, creatinine clearance (CLcr) **≥30 to** < 45 mL/min, or other comorbidity **that the physician judges to be incompatible with chemotherapy** (Modified Ferrara criteria). | | |
| 14<br>16<br>69<br>72 | Line 284-285<br>Line 385<br>Line 880<br>Line 982 | **Error:** OS HR confidence intervals<br>**Text from EUnetHTA draft assessment:**<br>HR= 0.662 (95% CI 0.519, 284 0.846, p<0.001).<br>**Comment from AbbVie:**<br>Please update to HR= 0.662 (95% CI 0.518, 284 0.845, p<0.001) (CSR, p126, paragraph 2, line 5) | 1 | Amended and checked that the data are in accordance with data in the preliminary EPAR. |
| 14 | Line 310-313 | **Consideration:** VIALE-A EFS results<br>**Text from EUnetHTA draft assessment:**<br>Venetoclax + azacitidine significantly improved EFS, compared to placebo + azacitidine. The median duration of EFS per investigator assessment was 9.8 months (95% CI: 8.4, 11.8) for the venetoclax + azacitidine arm and 7.0 months (95% CI: 5.6, 9.5) for the control arm.<br>**Comment from AbbVie:**<br>Please consider adding the HR for EFS, 'Venetoclax + azacitidine significantly improved EFS, compared to placebo + azacitidine (HR: 0.63 [95% CI: 0.50, 0.80]; p<0.001). The median duration of EFS per investigator assessment was 9.8 months (95% CI: 8.4, 11.8) for the venetoclax + azacitidine arm and 7.0 months (95% CI: 5.6, 9.5) for the control arm.' | 2 | Not amended.<br>HR of EFS is considered not necessary to include in the summary. The results included in summary are already quite extensive and the<br>HR for EFS is included in the results section 4.6.5 |
| 14 | Line 317-318 | **Consideration:** Misleading language<br>**Text from EUnetHTA draft assessment:**<br>In both treatment arms patients experienced fatigue, but the combination treatment with venetoclax and azacitidine was not associated with any increase in fatigue.<br>**Comment from AbbVie:** | 3 | Partly rephrased |

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| | | The CSR (p 153, final paragraph) states 'In both treatment arms patients experienced **a reduction in** fatigue, but the combination treatment with venetoclax and azacitidine was not associated with any increase in fatigue.' Please consider updating. | | |
| 15<br>58 | Line 329<br>Line 427 | **Error:** Time to deterioration (TTD) of quality of life as measured by EQ-5D-5L VAS p value<br>**Text from EUnetHTA draft assessment:**<br>' … with a median TTD of 10.7 months compared to those in the placebo + azacitidine arm, whose median TTD was 3.9 months ($p \leq 0.05$).'<br>**Comment from AbbVie:**<br>Pratz et al. 2020 reports the p value as $p<0.001$. Please update. | 1 | Checked publication and amended |
| 15<br>16<br>70<br>72 | Line 334-336<br>Line 389-391<br>Line 920-922<br>Line 986-988 | **Consideration:** Misleading sentence referring to safety outcomes in VIALE-A<br>**Text from EUnetHTA draft assessment:**<br>The incidence of SAE was approximately 10% higher in venetoclax + azacitidine than in placebo + azacitidine with febrile neutropenia, pneumonia and sepsis being the most common among treatment groups.<br>**Comment from AbbVie:** The somewhat ambiguous wording of this sentence may lead readers to infer that incidence of febrile neutropenia, pneumonia and sepsis are higher in the intervention arm vs the control arm. Please consider rephrasing to 'The incidence of SAE was approximately 10% higher in venetoclax + azacitidine than in placebo + azacitidine. The most common SAEs across both treatment arms were febrile neutropenia (29.7 vs. 10.4), pneumonia (16.6 vs 22.2) and sepsis (5.7 vs 8.3) in the venetoclax + azacitidine arm and placebo + azacitidine arm, respectively.' | 3 | Partially amended |
| 15<br>70 | Line 346-352<br>Line 930 | **Consideration:** The main results from the supportive study M14-358<br>**Text from EUnetHTA draft assessment:**<br>•The reported complete composite remisson rate (CR + CRi ) was 74.2% and. 71.4% in the groups of venetoclax + decitabine and venetoclax + azacitidine respectively, | 2 | Not amended.<br>The OS results in this non-randomised phase 1b study are of high uncertainty both due to study design and limited patient number. No comparisons of OS |

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| | | which is in line with the reported remission rate achieved on venetoclax + azacitidine in VIALE-A .<br>•For venetoclax + azacitidine 61.9% achieved postbaseline transfusion independence for both RBC and platelets and for venetoclax + decitabine (61.3%) achieved postbaseline transfusion independence for both RBC and platelets<br>**Comment from AbbVie:**<br>The primary objectives of the expansion stage of M14-358 were to confirm the safety and to assess efficacy including determining overall survival (OS), complete remission (CR) and complete remission with incomplete blood count recovery (CRi) of venetoclax combined with decitabine or azacitidine in newly diagnosed AML. Therefore, in addition to the included results, please also consider including a bullet point on the OS results from M14-358 'The median duration of follow up was 29 months (range: 0.4-42) in the venetoclax (400 mg) plus azacitidine group, and the median OS was 16.4 months (95% CI 11.3-24.5). Median duration of follow up was 40 months (range: 0.7-43) in the venetoclax (400 mg) plus decitabine group, with a median OS of 16.2 months (95% CI 9.1-27.8) (Pollyea et al. 2020).' | | between treatment arms or across studies should be made since OS is strongly dependent on the underlying prognosis of the patients included. Due to this inherent uncertainties a short description of the OS results for the supportive study are included in the results section 4.10.2 but not highlighted in the summary or the discussion sections. |
| 15<br>16 | Line 360-361<br>Line 375<br>Line 377 | **Consideration:** Misleading language around feasibility of NMA by referring to ITC rather than NMA<br>**Text from EUnetHTA draft assessment:**<br>The feasibility assessment of possible network metaanalysis by the MAH concluded that an ITC's was not feasible for any other comparators specified in the PICO.<br>**Comment from AbbVie:**<br>As an ITC was deemed feasible and conducted via propensity score weighting analysis, please consider rewording the statement to 'The feasibility assessment of a possible network meta-analysis by the MAH concluded that a network meta-analysis which included the comparators specified in the PICO was not feasible.' | 3 | Amended |
| 15 | Line 370 | **Consideration:** GRADE assessment | 1 | |

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| 16<br>61<br><br>70<br>72 | Line 392<br>Section 4.10.9<br>Line 905<br>Line 989 | **Text from the EUnetHTA draft assessment:**<br>e.g., the certainty of the evidence reported for OS and safety according to GRADE is considered moderate.<br>**Comment from AbbVie:**<br>VIALE-A is the first and only randomised controlled trial in AML. AML is an orphan disease thereby limiting the ability to perform a large RCT or multiple RCTs across Europe, especially when only recruiting patients who are ineligible for standard induction therapy (30-50% of AML patients). The previous pivotal trial in this patient population, BRIGHT-AML 1003, was a phase 2, randomized, open-label, multicenter study with a sample size of 132 patients of which only 116 were in the population relevant to this assessment. Compared to previous studies in this patient population, VIALE-A provides high precision with a large sample size (n=400) and provided a sufficient number of events to adequately power the trial. Additionally, the subgroup analysis for CR+CRi rate indicated that the risk differences and 95% CIs were all above 0 indicating a clear benefit (Dinardo 2020, supplementary appendix, figure S1). Given these points, please consider changing the certainty of evidence for OS, CR+CRi, TI and safety according to GRADE as high. | | We do not question quality of the study, but assess certainty of the overall evidence for venetoclax in the specified patient population. According to GRADE considering imprecision; as long as the results are not confirmed by another study, the total evidence is graded as moderate.<br><br>The certainty of OS reported in the BRIGHT- AML study was graded as low in the EUnetHTA report of glasdegib+ LDAC. |
| 15 | Line 371-372 | **Consideration:** Language in reference to ITC analyses<br>**Text from the EUnetHTA draft assessment:** Relative efficacy of venetoclax vs. identified comparators such as BSC, decitabine, and glasdegib in combination with LDAC was not assessed.<br>**Comment from AbbVie:** Please consider updating to 'Relative efficacy of venetoclax vs. LDAC was assessed, although relative efficacy vs. other identified comparators from the PICO such as BSC, decitabine, and glasdegib in combination with LDAC was not assessed.' | 3 | Amended |
| 16 | Line 375<br>Line 377 | **Consideration:** Misleading language - NMA vs ITC.<br>**Comment from AbbVie:**<br>Please consider referring to NMA rather than ITCs on lines 375 and 377 as an ITC using propensity score weighting analysis was feasible and submitted. | 3 | Amended |

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| 16<br>72 | Line 397-398<br>Line 998-1000 | **Consideration:** Language in reference to ITC analyses<br>**Text from the EUnetHTA draft assessment:** The only indirect comparisons submitted by the MAH included a comparison vs. LDAC but no firm conclusion of the comparative effectiveness or safety vs LDAC can be drawn.<br>**Comment from AbbVie:** As effectiveness outcomes were assessed via the ITC (safety outcomes were not) the comparative effectiveness is more certain than comparative safety and the two should be separated when referring to the ITC conclusions. Please consider updating this sentence to 'The only indirect comparisons submitted by the MAH included comparisons vs. LDAC, which indicated that venetoclax + azacitidine was associated with responses and time-to-event outcomes that are generally well above those reported on LDAC. No conclusion of the comparative safety vs LDAC can be drawn.' | 1 | Partly rephrased |
| 16<br>71 | Line 400<br>Line 965 | **Consideration:** Misleading language around ITCs submitted<br>**Text from EUnetHTA draft assessment:** Since relevant comparisons (direct or indirect) are not submitted for venetoclax in combination with azacitidine versus certain comparators.<br>**Comment from AbbVie:** As comparisons vs azacitidine (direct) and LDAC (indirect) were submitted please consider rephrasing to 'Since **other** relevant comparisons (direct or indirect) were not submitted …' | 3 | Amended |
| 19 | Line 535-537 | **Consideration:** Age as a criterion for ineligibility.<br>**Text from EUnetHTA draft assessment:** However, the decision on the treatment strategy should be based on the evaluation of fitness of elderly patients and not on the calendric age itself (27).<br>**Comment from AbbVie:** The ESMO guidelines and the Ferrara criteria specifically highlight the age cutoff of ≥75 years as an indication of ineligibility, thereby age being the sole criterion for ineligibility according to those sources. Please consider updating this sentence to read 'Age is one of the important patient-specific prognostic factors and patients ≥75 years are not considered suitable for intensive treatment (Ferrara et al. 2013; Heuser et al. 2020; Vey et al. 2013). However, the decision on the treatment | 3 | Not amended<br><br>The MAH was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check |

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| | | strategy should include the evaluation of fitness of patients and calendric age is not the only factor to consider.' | | |
| 19 | Line 564-567 | **Error:** When referring to the ESMO guidelines, HMA's are not referred to as first choice over LDAC and BSC.<br><br>**Text from EUnetHTA draft assessment:**<br>As a first line treatment of AML patients ineligible for standard intensive therapy, participation in a clinical trial is strongly encouraged. If there is none available, treatment with hypomethylating agents (HMAs) azacytidine and decitabine, low-dose cytarabine (LDAC) or best supportive care (BSC) with, for example, hydroxycarbamide are currently the first choice for newly diagnosed unfit AML patients (5).<br><br>**Comment from AbbVie:**<br>ESMO guidelines state that 'The HMAs azacitidine and decitabine are currently the first choice in newly diagnosed unfit AML patients' (Heuser et al. 2020, p704, column 2, paragraph 5, line 1-2). Please update the sentence to '… If there is none available, treatment with hypomethylating agents (HMAs) azacytidine and decitabine are currently the first choice for newly diagnosed unfit AML patients. Alternatively, low-dose cytarabine (LDAC) or best supportive care (BSC) with, for example, hydroxycarbamide, may also be used.' | 1 | A more precise representation of the text in the guidelines has been included |
| 20 | Line 629-631 | **Consideration:** Venetoclax indication in NCCN AML guidelines.<br>**Text from EUnetHTA draft assessment:**<br>In 2021 NCCN guidelines, venetoclax in combination with HMA or LDAC is recommended for treatment of patients aged ≥60 years and who are not candidates for intensive chemotherapy or decline it, without actionable mutations or with IDH1, IDH2, or FLT3 mutation (2).<br>**Comment from AbbVie:**<br>The current wording is somewhat ambiguous, and may lead readers to understand that venetoclax is not recommended for patients with an actionable mutation. | 3 | A more precise description of the NCCN recommendations for the use of venetoclax + HMA or LDAC is included . |

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| | | Please consider updating to 'In the NCCN guidelines, venetoclax in combination with HMAs is recommended as the preferred treatment for patients with newly diagnosed AML ≥60 years of age with and without actionable mutations who are not candidates for intensive remission induction therapy or decliners (Tallman et al 2021).' | | |
| 21 | Figure 1 | **Consideration:** Regional difference in venetoclax positioning.<br>**Comment from AbbVie:** The figure suggests that all the therapeutic options for patients who are ineligible for induction chemotherapy are equivalent, however, there are regional differences. Please consider adding the footnote 'Regional differences exist for the preferred / first-choice therapies across Europe.' | 3 | Not amended<br>Not considered necessary to include this information.eg |
| 21 | Line 655-656 | **Consideration:** Clarification on mechanism of action. No reference to synergistic effect.<br>**Text from EUnetHTA draft assessment:** HMAs indirectly increase sensitivity to BCL-2 inhibition in AML cells by modifying the relative levels of BCL-2 family members (22).<br>**Comment from AbbVie:** The current language does not explicitly state the benefit of the combination of venetoclax and HMA's. Please consider adding 'venetoclax provides a synergistic effect in combination with HMAs, thereby improving efficacy versus HMA monotherapy.' | 3 | Not amended<br>This details of the MoA will not be included. This information is also not included in the SmPC for venetoclax. |
| 30 | Line 736 | **Error:** VIALE-A comparator<br>**Text from EUnetHTA draft assessment:** Only one study, VIALE A, with direct comparison of efficacy and safety of venetoclax in combination with HMA versus a relevant comparator (azacitidine and LDAC) was identified.<br>**Comment from AbbVie:** Please remove 'and LDAC' since the comparator for VIALE-A is azacitidine. | 1 | Amended- LDAC removed |
| 37 | Line 926 | **Error:** M14-358 inclusion criteria<br>**Text from EUnetHTA draft assessment:**<br>' … in treatment naïve patients with AML ≥ 60 years old and/or who are not eligible for standard induction therapy due to | 1 | Amended |

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| | | comorbidity or other factors.'<br>**Comment from AbbVie:**<br>Please remove **and/or** so the sentence reads<br>'… in treatment naïve patients with AML ≥ 60 years old who are not eligible for standard induction therapy due to comorbidity or other factors.' | | |
| 38 | Line 948 | **Consideration:** Description of VIALE-C<br>**Text from EUnetHTA draft assessment:**<br>VIALE C was a randomised (2:1), double blind, placebo controlled phase 3 study.<br>**Comment from AbbVie:**<br>Please consider adding that VIALE-C was also a **multicentre study.** | 3 | Amended |
| 38 | Line 956-960 | **Consideration:** Description of VIALE-C OS results<br>**Text from the EUnetHTA draft assessment:** At the time of the primary analysis for OS, patients had a median follow-up of 12 months. The median OS in the venetoclax + LDAC arm was 7.2 months (95% CI: 5.6, 10.1) compared to 4.1 months (95% CI: 3.1, 8.8) in the placebo + LDAC arm. The hazard ratio was 0.75 (95% CI: 0.52, 1.07; p = 0.114) and the study failed to establish a statistically significant benefit of OS of venetoclax + LDAC compared to LDAC alone.<br>**Comment from AbbVie:** Please consider adding 'A 6-month follow-up OS analysis was also performed, in which survival was improved among patients treated with venetoclax plus LDAC by 30% compared with LDAC only (HR: 0.70 [95% CI: 0.50, 0.99]; p=0.04). Median OS was 8.4 months (95% CI: 5.9, 10.1) after a median duration of 17.5 months follow-up in patients treated with venetoclax plus LDAC compared with 4.1 months (95% CI: 3.1, 8.1) after a median of 17.5 months follow-up' (Wei et al. 2020) as this data was also requested by the EMA during their assessment. | 2 | Partly amended.<br>The 6 months follow-up OS analyses was included in the Appendix 4 including Key efficacy outcomes of VIALE-C. That this OS data was based on the 6 months follow-up post-hoc analyses is now clarified. |
| 43 | Line 39<br>Line 44 | **Error:** M14-358<br>**Text from EUnetHTA draft assessment:** M14-359<br>**Comment from AbbVie:** Please correct to M14-358 | 1 | Amended |

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| 43 | Line 39 | **Error:** M14-358 n number<br>**Text from EUnetHTA draft assessment:** Patient population in ventoclax (400 mg) + azacitidine (n=83) arm.<br>**Comment from AbbVie:** Please correct to n=84. | 1 | Amended |
| 43 | Line 48-49 | **Consideration:** Ambiguous / incomplete sentence<br>**Text from EUnetHTA draft assessment:** A lower percentage of patients in both dose arms had 48 ECOG ≥ 2.<br>**Comment from AbbVie:** Please consider adding 'compared to the venetoclax + azacitidine arm in VIALE-A' at the end of this sentence. | 3 | Amended |
| 43-44 | Table 4.6 | **Error:** Baseline characteristics for VIALE-A **Text from EUnetHTA draft assessment:**<br>Azacitidine (n=145)<br>Age categories 18 to <75 4 (44.1)<br>Age (years) median range 76.9 (60.0, 90.0)<br>**Comment from AbbVie:** Please update to -<br>Azacitidine (n=145)<br>Age categories 18 to <75 **64** (44.1)<br>Age (years) median range **76.0** (60.0, 90.0) | 1 | Amended |
| 45 | Line 85 | **Error:** VIALE-A statistics<br>**Text from EUnetHTA draft assessment:** A total of **227** patients would give 88% power to detect statistically significant differences.<br>**Comment from AbbVie:** Please revise the number of patients to **225.** | 1 | Amended |
| 45 | Line 96-98 | **Error:** VIALE-A stratification<br>**Text from EUnetHTA draft assessment:** strata assigned at the time of randomization bases on IVRS/IWRS namely age (18 to < 75, ≥ 75) and cytogenetic risk (intermediate and poor).<br>**Comment from AbbVie:** Please also include stratification by region (US, EU, China, Japan and the rest of the world). | 1 | Partly amended. |
| 47 | Line 153-154 | **Consideration:** Rationale for OS as the primary endpoint.<br>**Text from EUnetHTA draft assessment:** It is acknowledged that OS is the preferred endpoint in newly diagnosed AML as this is considered the gold standard endpoint in clinical trials both by | 2 | Amended |

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| | | physicians and health regulatory agencies (60).<br>**Comment from AbbVie:** In addition to physician and regulator perspectives, there could also be an opportunity to acknowledge the patient perspective. Please consider adding 'Additionally, OS is considered a key benefit based on patient feedback.' | | |
| 47 | Line 166-168 | **Error:** Omission<br>**Text from EUnetHTA draft assessment:** … following categories based on the investigator assessment: complete remission; complete remission with incomplete blood count recovery; morphologic leukemia free state; resistant disease; progressive disease; indeterminate (not assessable, insufficient data); morphologic relapse.<br>**Comment from AbbVie:** Please also include 'partial remission.' | 1 | Amended |
| 48 | Line 181-183 | **Error:** HRQoL outcomes<br>**Text from EUnetHTA draft assessment:** Additional PRO assessment were included as exploratory endpoint; The impact of venetoclax on the remaining subscales/items from the EORTC QLQ-C30 and EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L).<br>**Comment from AbbVie:** Please update to 'Additional PRO assessment were included as exploratory endpoints; the impact of venetoclax on EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L) and the remaining subscales/items from the EORTC QLQ-C30 and PROMIS Cancer Fatigue SF 7a.' | 1 | Amended |
| 48 | Line 184-185 | **Consideration:** Clarification on the data submitted.<br>**Text from EUnetHTA draft assessment:** The submitted/provided data for health related quality of life is rather limited but will be included in this assessment.<br>**Comment from AbbVie:** Please consider clarifying this statement by saying 'The submitted/provided data for health-related quality of life included in the MAH submission dossier is rather limited but further analyses will be included in this assessment from the CSR and trial publications.' | 3 | Partly rephrased.<br>"The submitted/provided data for health-related quality of life included in the MAH submission dossier is rather limited but some additional analyses was included in this assessment on the basis of results reported in the CSR and trial publications" |
| 49 | Line 218-219 | **Consideration:** % of patients discontinuing the study due to death | 3 | Amended |

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| | | **Text from EUnetHTA draft assessment:** More patients discontinued the study because of death in the azacitidine alone arm (74.7 %) than in the venetoclax + azacitidine arm (56 %)<br>**Comment from AbbVie:** Please consider clarifying how the percentages were calculated as the calculation is different to that presented in the CSR, 'Of patients assigned to study treatment, more patients discontinued the study because of death in the azacitidine alone arm (74.7 %) than in the venetoclax + azacitidine arm (56 %).' | | |
| 49 | Table 4.9 | **Consideration:** Patient disposition, use of percentages<br>**Comment from AbbVie:** While the N numbers stated in the table are correct, the percentages stated have been calculated differently to those presented in the CSR, and therefore may be misleading. Please consider adding a footnote to clarify how the percentages have been calculated. | 3 | Percentage calculations are removed and only the number of patients in the different categories are shown. |
| 49 | Line 227 | **Error:** Number of patients who withdrew consent in the azacitidine arm should be 1 not 0.<br>**Comment from AbbVie:** DiNardo et al. 2020, figure 1 states 1 patient withdrew in the placebo + azacitidine arm. | 1 | Amended<br>Checked vs publication |
| 50 | Line 245-250 | **Consideration:** External validity<br>**Text from EUnetHTA draft assessment:** The criteria used to define ineligibility of high intensive chemo in the clinical studies may not be completely aligned with the selection criteria in clinical practice, also contributing to uncertainty in the generalizability of the study results.<br>**Comment from AbbVie:** ESMO Clinical Practice Guidelines for AML use the Ferrara criteria to define ineligibility (Ferrara et al. 2013; Ferrara 2014; Heuser et al. 2020). Please consider prefacing this statement with 'AbbVie collaborated with the EMA and FDA to operationalize objective criteria for VIALE-A, using the Ferrara criteria as a starting point, the criteria used in the ESMO guidelines to define ineligibility (Ferrara et al. 2013; Ferrara 2014; Heuser et al. 2020). These objective criteria are similar to those used in the trials for other recently approved agents to | 3 | Not amended.<br>The details on the process establishing the modified criteria used in the VIALE a study is considered not necessary to include in this context i.e. a short discussion of the main issues for external validity. |

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| | | define this patient population, glasdegib and ivosidenib (Cortes et al. 2020 and Roboz et al. 2020). However, the criteria may not be completely aligned with the selection criteria in clinical practice, also contributing to uncertainty in the generalizability of the study results.' | | |
| 50 | Line 258-260 | **Consideration:** External validity of venetoclax + decitabine.<br>**Text from EUnetHTA draft assessment:**<br>Clinical study data for this combination is based on a limited number of patients in a phase 1b study, leading to a higher level uncertainty of the actual efficacy and safety of this combination in clinical practice.<br>**Comment from AbbVie:** We suggest to add additional context to this statement, since the CHMP found the data on venetoclax + decitabine certain enough to approve the combination. Further, venetoclax + decitabine is also supported by VIALE-A because azacitidine and decitabine have comparable effectiveness (Zeidan et al. 2020; Wen et al. 2020) and similar mechanisms of action. Please consider rewording the above sentence to 'Venetoclax + decitabine is considered by the CHMP to be supported by VIALE-A because azacitidine and decitabine have comparable effectiveness (Zeidan et al. 2020; Wen et al. 2020) and similar mechanisms of action, however, the clinical study data for this combination is based on a limited number of patients in a phase 1b study, leading to a higher level uncertainty of the actual efficacy and safety of this combination in clinical practice.' | 3 | Not amended<br>The basis for the CHMP positive opinion of venetoclax and decitabine is described in section 4.4.2 and in executive summary |
| 50 | Line 261 | **Consideration:** Duration of treatment<br>**Text from EUnetHTA draft assessment:** In VIALE A the median duration of exposure in the venetoclax + azacitidine arm was 7.6 months, but whether this will reflect the actual treatment length in clinical practice is not yet known.<br>**Comment from AbbVie:** Please consider replacing with 'In VIALE A the median duration of exposure in the venetoclax + azacitidine arm was 7.6 months. Actual treatment length in clinical practice warrants continued research as availability of Venetoclax expands across geographies." | 3 | Not amended<br><br>The MAH was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check |

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| 51 | Table 4.11 | **Error:** OS unstratified analyses<br>**Text from EUnetHTA draft assessment:**<br>Unstratified analyses 0.641 [0.502, 0.8419]<br>**Comment from AbbVie:** Please update to unstratified analyses 0.641 [0.502, **0.819**] | 1 | Amended |
| 53<br>54<br>55 | Line 333-334<br>Figure 4<br>Figure 5 | **Error:** Age subgroup analysis<br>**Text from EUnetHTA draft assessment:**<br>A potential difference of treatment effect by age on OS and complete composite remisson rates i.e. CR+CRi (smaller treatment difference in patients < 75 years) was also observed.<br>**Comment from AbbVie:** The age subgroup analysis was not prespecified for efficacy endpoints based on this cut (<75 vs ≥75 years) (please see VIALE-A SAP p41). The prespecified subgroup analysis was 18 – < 65 years, 65 – < 75 years, ≥ 75 years. Please replace the current data for OS and CR+CRi with that presented in the CSR p171-172. | 1 | The Forest plots referred to in the CRS page 171 -172 and the main publication DiNardo (the source of the included Forest Plots) also includes this cut off for age (<75 vs ≥75 years). For clarification the text now states that patients < 75 years are compared with patients > 75 years |
| 61 | Table 4.16 | **Consideration:** Footnotes<br>**Comment from AbbVie:** Please could you consider adding footnotes to the table stating that transfusion independence rate refers to RBC and platelets and that the HR for HRQoL refers to time to deterioration on the EORTC-QLQ-C30. | 2 | Amended |
| 63 | Line 598 | **Error:** DACO-16 reporting<br>**Text from EUnetHTA draft assessment:** Dotted lines for DACO-016 indicates that while patients were not randomized to LDAC, OS is reported separately for LDAC.<br>**Comment from AbbVie:** This is inaccurate, please update to 'Dotted lines for DACO-016 indicate that the OS hazard ratio was reported for decitabine vs. treatment choice (LDAC or BSC).' | 1 | Amended |
| 63 | Line 620 | **Error:** BRIGHT-AML 1003 dosing<br>**Text from EUnetHTA draft assessment:** Patients were randomised 2:1 to receive glasdegib (100 mg orally once daily) with LDAC (**20 mg/m2** s.c. cytarabine twice daily.<br>**Comment from AbbVie:** This is inaccurate, please update to 20 mg twice daily. | 1 | Amended |
| 64 | Line 653 | **Error:** AZA-AML-001 treatment arms | 1 | Amended |

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| | | **Text from EUnetHTA draft assessment:** Azacitidine plus conventional care (CCR) (n = 241) was compared to CCR (n= 653 247).<br>**Comment from AbbVie:** This is inaccurate, please update to 'Azacitidine plus BSC (n = 241) was compared to CCR (n= 653 247). | | |
| 65 | Line 697-698 | **Consideration:** Misleading language around feasibility<br>**Text from EUnetHTA draft assessment:** Hence, the MAH concludes that central similarity assumption for valid ITCs is ultimately violated.<br>**Comment from AbbVie:**<br>Please consider updating to 'is ultimately **likely to be** violated.' | 3 | Not amended since the text is in accordance with text in the MAH's core submission dossier |
| 65 | Line 702-704 | **Consideration:** Missing context considering Glasdegib assessment.<br>**Text from EUnetHTA draft assessment:** It is the authors opinion, that it would be of value to actually perform the potential comparisons and based on the outputs in the analysis assess the robustness.<br>**Comments from AbbVie:** In a previous assessment, EUnetHTA judged ITCs involving the same studies as 'non-informative for decision making' (EUnetHTA 2020). Specifically, BRIGHT-AML 1003, AZA-AML-001 and DACO-016 were deemed too heterogeneous to produce meaningful ITC results, even via a simulated treatment comparison, and therefore the central similarity assumption for ITCs would likely be violated. Please consider adding this context as follows: ' It is the authors opinion, that it would be of value to actually perform the potential comparisons and based on the outputs in the analysis assess the robustness, although it is worth nothing that a previous EUnetHTA assessment in the same indication (EUnetHTA 2020) has also deemed trials too heterogeneous to perform meaningful ITC results.' | 3 | Not amended.<br>VIALE-A could potentially be compared using population adjusted methods vs the glasdegib study and VIALE-A was not a part of the glasdegib assessment. |
| 65 | Line 721 | **Error:** Patient ECOG status<br>**Text from the EUnetHTA draft assessment:** The patients ECOG status were more favourable in azacitidine studies | 1 | Amended |

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| | | compared to VIALE-A; i.e. 22.8% and **4%** with ECOG status 2 in the azacitidine arms in AZA-AML-001 and AZA-001 respectively.<br>**Comment from AbbVie:** Please update to ' The patients ECOG status were more favourable in azacitidine studies compared to VIALE-A; i.e. 22.8% and **7.3%** with ECOG status 2 in the azacitidine arms in AZA-AML-001 and AZA-001 respectively.' | | |
| 66 | Line 730 | **Error:** Venetoclax combination<br>**Text from EUnetHTA draft assessment:** A potential comparison of venetoclax + venetoclax vs glasdegib + LDAC<br>**Comment from AbbVie:** Please update to 'A potential comparison of venetoclax + azacitidine vs glasdegib + LDAC' | 1 | Amended |
| 66 | Line 777 | **Error:** Patients included in the propensity score analysis.<br>**Text from the EUnetHTA draft assessment:** All patients treated with LDAC in VIALE-C without prior HMA use **or** without favourable cytogenetic risk (n=50) were included.<br>**Comment from AbbVie:** Please update to 'All patients treated with LDAC in VIALE-C without prior HMA use **and** without favourable cytogenetic risk (n=50) were included.' | 1 | Amended |
| 66<br>75 | Line 761-763<br>Line 965-967 | **Consideration:** Language misleading regarding ITC's submitted.<br>**Text from the EUnetHTA draft assessment:** Since relevant comparisons (direct or indirect) are not submitted for venetoclax in combination with azacitidine versus certain comparators of interest (e.g., BSC and glasdegib in combination with LDAC) this is considered an evidence gap.<br>**Comment from AbbVie:**<br>This sentence may be misinterpreted as no relevant comparisons were submitted if the reader is not familiar with the comparators included in the PICO.<br><br>Please consider updating the sentence to say 'Relevant comparisons were submitted for venetoclax in combination with azacitidine versus azacitidine (direct) and LDAC (indirect); however, relevant comparisons (direct or indirect) were not submitted for venetoclax in combination with azacitidine versus other comparators of interest (e.g., BSC and glasdegib in | 3 | Partly rephrased |

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| | | combination with LDAC) and so this is considered an evidence gap.' | | |
| 67 | 780-781 | **Consideration:** Language in reference to ITC analyses.<br>**Text from the EUnetHTA draft assessment:** Regarding the PSA 'Due to high uncertainty in the methods used the results should be regarded as descriptive only.'<br>**Comment from AbbVie:** Propensity score analysis was chosen for this ITC as AbbVie had the unique opportunity of having IPD available for two high-quality, similarly-designed clinical trials thereby reducing bias and improving the robustness of the comparative efficacy measure. The propensity score weighting methodology is a well-established approach to adjust for cross-trial differences. During implementation, a broad set of prognostic factors and effect modifiers were adjusted for to ensure a balanced 'apples-to-apples' comparison. Although statistical uncertainty exists, it was characterized by valid 95% confidence intervals, which indicated that the benefit associated with venetoclax + azacitidine was statistically significant. Please consider rewording to 'Due to the indirect nature of the analysis, interpretation of the results should be considered with acknowledgement of limitations.' | 3 | Not amended<br><br>The MAH was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check |
| 67 | Table 4.17 | **Error:** Wrong table used<br>**Comment from AbbVie:** This table is for EFS, not OS. Please use the OS table instead, in which the after weighting HR was 0.50 (0.35, 0.73). | 1 | Amended |
| 69 | Line 883-885 | **Error:** Reference to immature OS data.<br>**Text from the EUnetHTA draft assessment:** The median duration of follow-up was 20.5 month and the analyses based on the data cut off 04 Jan 2020 are still considered immature.<br>**Comment from AbbVie:** The submitted analysis was 75% mature (270/360 events). EMA guidance states that if a clear majority of the total number of expected events in the long term has been observed and a difference has been documented, this is normally accepted as an indicator that the study is reasonably mature and that the study results will remain stable over | 1 | Not amended. Even if 75% of the expected events are reported, the data at this stage are still considered immature but we have added that the uncertainty is related to the long-term OS that can be achieved with venetoclax combined with a HMA in clinical practice. |

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| | | prolonged follow-up (EMA 2017). Please consider rephrasing to 'The median duration of follow-up was 20.5 month and the analyses were based on 75% OS interim data.' | | The KM curve for the venetoclax+ aza arm is heavily censored after 15 months (the majority of censorings may be due patients ongoing in study follow-up at data cut-off date)<br>With additional follow-up and reporting of the final OS analyses at approximately 360 events, data up to 2 years is expected to be less heavily censored and more mature. |
| 70 | Line 912-914 | **Consideration:** Patients reporting HRQoL<br>**Text from the EUnetHTA draft assessment:** The interpretation of the reported PRO data are hampered by the small number of patients still reporting beyond early treatment cycles.<br>**Comment from AbbVie:** Please consider adding ', although it's worth acknowledging that patients who have progressed or died would not be able to contribute to the data.' | 3 | Not amended<br>For PRO data the proportions patients still reporting is substantially lower than for other outcomes i.e. OS and EFS. (Comparing number at risk in the KM curves for the different outcomes) |
| 70 | Line 940-942 | **Consideration:** Language misleading regarding ITC's submitted.<br>**Text from the EUnetHTA draft assessment:** The relevant ITC's were not submitted by the MAH although it was requested as missing item during formal check of completeness of the submission dossier.<br>**Comment from AbbVie:** This sentence may be easily misinterpreted as no relevant comparisons were submitted if the reader is not familiar with the comparators included in the PICO.<br><br>Please consider updating the sentence to say 'Relevant comparisons were submitted for venetoclax in combination with azacitidine versus azacitidine (direct) and LDAC (indirect); however, other relevant comparisons (direct or indirect) of venetoclax in combination with azacitidine versus other | 3 | Amended |

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| | | comparators of interest (e.g., BSC and glasdegib in combination with LDAC) were not submitted by the MAH although it was requested as missing item during formal check of completeness of the submission dossier.' | | |
| 78 | 1200 | **Error:** VIALE-A cytogenetic and molecular risk stratification was based on NCCN 2016 not NCCN 2014.<br>**Text from the EUnetHTA draft assessment:** NCCN 2014 (M14-358, VIALE-A)<br>**Comment from AbbVie:** "VIALE-A" should be moved to header of next column to the right (NCCN 2016). | 1 | Amended |
| 78 | 1200 | **Error:** Mutation in NCCN 2014 column, adverse/poor/unfavourable row<br>**Text from the EUnetHTA draft assessment:** Normal cytogenetics: with<br>FLT3-IDT mutation<br>**Comment from AbbVie:** Should be FLT3-ITD | 1 | Amended |
| 86 | 1222 | **Error:** Last bullet of exclusion criteria for M14-358 missing.<br>**Text from the EUnetHTA draft assessment:** Received a strong and/or moderate CYP3A inducer within 7 days prior to the initiation of study treatment.<br>**Comment from AbbVie:** Correct formatting error to ensure this point is clearly taken as an exclusion criterion. | 3 | Amended |
| 86 | 1222 | **Error:** Secondary outcomes missing from M14-358 trial row<br>**Comment from AbbVie:** Secondary outcomes column is blank and should be populated from appropriate section of the submitted dossier. | 1 | Amended with secondary outcomes including adjustments for primary outcomes |
| 102 | 1289 | **Error:** Incorrect values for grade ≥3 AEs for VIALE-C<br>**Text from the EUnetHTA draft assessment:** VEN + LDAC 87 (61.3%) vs 39 (57.4%) Placebo + LDAC<br>**Comment from AbbVie:** Please update to VEN + LDAC 138 (97.2%) vs 65 (95.6 %) Placebo + LDAC (please see p233 VIALE-C CSR). | 1 | Amended according to CSR (table 0.6 . 102) |
| 102 | 1289 | **Error:** Incorrect values for discontinuation due to AEs for VIALE-C for VEN + LDAC. | 1 | Not amended. Correct value according to EPAR. Not able to |

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| | | **Text from the EUnetHTA draft assessment:** VEN + LDAC 36 (25.4%)<br>**Comment from AbbVie:** Please update to be VEN + LDAC 37 (26.1%) (please see p233 VIALE-C CSR). | | identify the value in CSR (Tab.06.p.102) |
| 107 | 1357 | **Error:** Platelet count decreased and white blood cell count decreased under investigations are missing relative risk and relative difference values.<br>**Comment from AbbVie:** These values can be taken from p170 of the submitted dossier. | 1 | Amended/included |
| 108 | 1357 | **Error:** Malignant neoplasm progression row is missing relative risk and relative difference values.<br>**Comment from AbbVie:** These values can be taken from p170 of the submitted dossier. | 1 | Amended/included |
| 108 | 1357 | **Error:** All PT row under reproductive system and breast disorders has n (%) values duplicated where the relative risk and relative difference values should be.<br>**Comment from AbbVie:** These values can be taken from p171 of the submitted dossier. | 1 | Amended/included |

[i] Character of comment
- 'major'=1
- minor'= 2

'linguistic'=3

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