Input from external expert and manufacturer on the **2nd draft assessment**
"Midostaurin with standard chemotherapy in
FLT3-positive acute myeloid leukaemia"

Project ID: PTJA01

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA JA3 WP4 - Pharmaceuticals, PTJA01
Comments on the 2nd draft rapid assessment on Midostaurin with standard chemotherapy in FLT3-positive acute myeloid leukaemia

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

The 2nd version of the Rapid Assessment on Midostaurin with standard chemotherapy in FLT3-positive acute myeloid leukaemia was open to review by external reviewer(s) between **between 17/10 and 24/10/2017**.

Comments received from

External expert
Dr. Baron, chairman of the leukaemia group of EORTC/Belgium
Dr. G.A. Huls, UMCG/Netherlands
Manufacturer
Novartis Oncology Novartis Farma S.p.A.

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 clinical expert

Page	Line	Organisation	Comment	Reply from author
14	324	University of Liège, Chairman of the EORTC Leukemia group	I would suggest to provide the HR for the CIR after censuring for SCT.	HR for the CIR censored at SCT has been added.
35		University of Liège, Chairman of the EORTC Leukemia group	Line 768 i would mention that FLT3-TKD mutations have not been associated with a poor prognosis in recent large studies (Bacher U et al., Blood 2008 PMID: 17965322)	Noted in text and reference added.
38		University of Liège, Chairman of the EORTC Leukemia group	Line 920. Allo-SCT can be recommended also with an HLA-matched unrelated donor or alternative donors (cord blood, haploidentical donor) for poor risk groups	Suggested information added to the text.
38		University of Liège, Chairman of the EORTC Leukemia group	Figure 3. I'm not sure i agree with this figure; allo SCT is generally given in patients fit for chemotherapy.	Figure 3 has been slightly modified to adopt this suggestion. Additional clarifying text is added.

Comments from Manufacturer

Page	Line	Organisation	Comment	Reply from author
5	148	Novartis	change "r" to" R"	Changed accordingly.
6	169	Novartis	change " EUnenHTA" to" EUnetHTA"	Changed accordingly.
11	196	Novartis	Please add the word „adult" in "for "adult" patients with newly diagnosed acute myeloid leukaemia" and also do so throughout the document.	Added as suggested. In case this is not separately mentioned somewhere in the document we always refer to adult patients. Patients under 18 years old are out of the scope of this assessment.
11	202	Novartis	Please add „..for adult patients"	Added as suggested.
11	219	Novartis	Please add the study number for the investigator-initiated trial: "AMLSG 16-10 / CPKC412DE02T" **New text** In total, three studies (RATIFY, IIT (AMLSG 16-10 / CPKC412DE02T) and UK NCRI AML17 trials) were included in the assessment.	Added as suggested.

Page	Line	Organisation	Comment	Reply from author
11	225	Novartis	We do not consider that, in the European-wide context, the "10 + 3" regimen used in the AML17 trial can be referred to as *standard* induction for patients, because although daunorubicin 90 mg/m2/day for induction is recommended in the Norwegian guideline, it is far from the standard "7 + 3" regimen used across Europe and it is not recommended in the ELN2017 guideline. Further, the AML17 trial included a second cycle of daunorubicin 50mg/m2 for all favourable and intermediate risk patients, whereas the typical regimen used in centres across Europe only includes a second cycle in patients failing to achieve a CR with the first cycle. Lastly, as the indirect comparison uses the OS data for the FLT3-ITD sub-group in the AML17 trial, please add the second course details relevant to this sub-group, i.e. that they could also be randomised to receive lestaurtinib alongside the daunorubicin 50 mg/m2. **Previous text** "Indirect comparison of midostaurin with standard induction and consolidation therapy versus standard induction and consolidation chemotherapy with high-dose daunorubicin (90 mg/m2/day) during induction was performed by the authors using the Bucher method according to the EUnetHTA guideline" **New text** Indirect comparison of midostaurin with standard induction ("7 + 3" regimen) and consolidation therapy (high dose cytarabine) versus induction ("10 + 3" regimen) and consolidation chemotherapy with high-dose daunorubicin (90 mg/m2/day) during induction was performed by the authors using the Bucher method according to the EUnetHTA guideline. In the AML17 randomisation scheme, FLT3 patients had a second course with daunorubicin 50 mg/m2/day plus cytarabine +/- lestaurtinib and one or two further courses of high dose cytarabine.	Suggested details added.
12	234	Novartis	Please add here the EU approval date: „...and granting of the Marketing Authorisation (EC decision) for “Rydapt – midostaurin”, an orphan medicinal product, on 18th September 2017 for the following indication...”	Adapted.
12	238	Novartis	Please update regulatory information as follows: **Previous text** Midostaurin gained regulatory approval from the FDA in April 2017, from Swissmedic in May 2017 and from Health Canada in July 2017 **Updated new text** "Midostaurin gained the first regulatory approval worldwide from the US Food and Drug Administration (FDA) on 28th April 2017 and from Swissmedic on 4th May 2017 followed by Health Canada approval on 21st July 2017 and EU approval (EC decision) on 18th September 2017. While the FDA and Health Canada approvals were restricted to the induction and consolidation phase, the EMA and Swissmedic approvals included induction, consolidation and the maintenance phases."	Adapted partly as suggested.

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12	250	Novartis	Novartis recommends to remove the word *"standard"* from "standard induction and consolidation chemotherapy", here and throughout the document when referring to daunorubicin 90 mg/m2/day, because although daunorubicin 90 mg/m2/day for induction is recommended in the Norwegian guideline it is not recommended in the ELN2017 European guideline. The ELN2017 guideline, referring to the AML17 trial data states, "A recent exploratory analysis from this study suggests the potential for improved outcomes among patients with FLT3-ITD with anthracycline intensification, although this finding requires further validation." The guideline then goes on to state, "Current evidence suggests that the dose of daunorubicin should not be <60 mg/m2."	'standard' has been removed from the text.
12	253	Novartis	Since the MAA (including the SmPC) is now approved in EU, propose to delete this sentence or rephrase accordingly.	This has been now deleted.
13	273	Novartis	Please add dose of daunorubicin and cytarabine: **Previous text** "RATIFY was a randomised phase III study of induction (daunorubicin/cytarabine) and consolidation (high-dose cytarabine) chemotherapy combined with midostaurin or placebo in treatment-naive patients with FLT3-mutated AML." **Recommended new text** "RATIFY was a randomised phase III trial of standard "7 + 3" regimen induction (cytarabine 200 mg/m2/day, administered for 7 days, plus daunorubicin 60 mg/m2, administered for 3 days) and, for patients who achieved CR after induction, consolidation (high-dose cytarabine at a dose of 3 g/m2 every 12 hours) chemotherapy combined with midostaurin or placebo in newly diagnosed patients with FLT3-mutated AML."	We agree on the contents of MAHs suggestion but we prefer not to report too much detail in summary section. Recommended text has not been implemented into text.
13	278	Novartis	Please change the tense to present because the IIT is still ongoing and still recruiting patients: „...is an ongoing single-arm phase II trial involving 145 patients (18-70 years, interim CSR from 30 April 2016, with a data-cut of 31-Dec-2015) receiving midostaurin with standard induction and consolidation therapy."	The tense has been changed to present as suggested but we do not prefer to add too much detailed information into summary section and therefore details in parentheses has not been Added as suggested.
13	278	Novartis	Please add study number to the investigator-initiated trial "AMLSG 16-10 / CPKC412DE02T"	Added as suggested.

Page	Line	Organisation	Comment	Reply from author
13	282	Novartis	Please add study detail here, as recommended in PRISMA Extension Statement (which states that for each study the characteristics of the study for which data are extracted should be given: study size, PICOS, follow-up period) **Previous text** "The UK NCRI AML17 trial compared standard chemotherapy with daunorubicin 60 mg/m2 to high-dose daunorubicin. The results of the subgroup analysis (n=200) of this study were applied only to the indirect comparisons related to OS." **New text** "The UK NCRI AML17 trial was terminated prematurely due to a significantly higher 60-day mortality rate observed in the 90 mg/m2 vs 60 mg/m2 daunorubicin group (10% vs 5%, respectively, p=0.02). Due to the early termination, the trial randomised 1206 patients rather than the planned 1700. Patients were either newly diagnosed AML or high-risk MDS (aged 16-72 years) and were treated with a "10 + 3" regimen first induction cycle of cytarabine (administered for 10 days) plus daunorubicin 60 mg/m2 or 90 mg/m2 (administered for 3 days). After a risk assessment, all patients were re-randomised to a second induction cycle. Those patients eligible for the lower dose of daunorubicin 50 mg/m2 and with FLT3-positive disease (n=130) were re-randomised to daunorubicin 50 mg/m2 + lestaurtinib (CEP-701) 40-80 mg bid or to daunorubicin 50 mg/m2 + placebo. Patients were further randomised to receive one or two courses of high-dose cytarabine (3 g/m2 12-hourly). The results from the post-hoc exploratory subgroup analysis for FLT3-ITD-positive patients (n=200) from a median of 28 months follow-up were applied to the indirect comparisons related to OS.	We agree in principle on the comment (at least partly) but as mentioned previously, we do not prefer to add such detailed descriptions into summary. However, we added a few more important details of this study into the text.
13	299	Novartis	In alignment with approved SmPC, please add here outcome of secondary endpoints which is currently missing: "..., however, a treatment benefit was observed in females in all secondary efficacy endpoints." **Previous text** A difference in OS effect was observed for men versus women in a prespecified subgroup analysis (HR=0.53 [95% CI: 0.39–0.72] for men and HR=1.01 [95% CI: 0.76–1.34] for women). **Recommended new text** A difference in OS effect was observed for men versus women in a prespecified subgroup analy-sis (HR=0.53 [95% CI: 0.39–0.72] for men and HR=1.01 [95% CI: 0.76–1.34] for women). Treatment benefit was observed in females in all secondary efficacy endpoints.	Even though this is not directly related to OS results, it is basically true as suggested. We have added a sentence that "This heterogeneity in effect was not observed in other efficacy endpoints".

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13	302	Novartis	Novartis recommends to describe the treatments for the indirect comparison more completely, and to add a summary of the limitations: **Previous text** Indirect results comparing midostaurin with high-dose daunorubicin used during induction showed no difference between the treatments in terms of OS (DA 90 mg/m2 vs. midostaurin/DA 60 mg/m2: HR=0.84 [95% CI: 0.54–1.31]). However, several limitations (also severe by nature) apply to this indirect comparison. **Recommended new text** Indirect results comparing daunorubicin 90 mg/m2 in the first induction cycle ("10 + 3" regimen) followed by a second course and consolidation versus midostaurin plus standard induction ("7 + 3" regimen) and consolidation, showed no difference between the treatments in terms of OS (HR=0.84 [95% CI: 0.54–1.31]). However, several serious methodological limitations apply to this indirect comparison, including limited similarity of the treatments in the 'common' reference arm, risk of bias at study and outcome level, and questions as to the validity of transitivity and proportional hazards assumptions.	We partly agree and information about the regimens has been added. Since we are reporting results here (and not discussion), we did not add specific details on the limitations here. These are discussed elsewhere in the report.
14	333	Novartis	In order to interpret this statement about grade 3-4 AEs the comparison needs to be made versus the control arm. Otherwise please remove the statement.	Comparison added and sentence clarified.
14	341	Novartis	change "increased AST and renal failure in " to "increased AST, decreased neutrophil count, and renal failure in"	Changed accordingly.
14	342	Novartis	change "febrile neutropaenia in the placebo group" to "febrile neutropaenia, decreased neutrophil count and decrease platelet count in the placebo group"	Changed accordingly.
14	342	Novartis	change " 21 (6.1%) " to " 23 (6.7%) "	Changed since MAH has updated some of the safety results.
14	343	Novartis	change "15 (4.5%)" to "17 (5.1%)"	Changed since MAH has updated some of the safety results.

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15	352	Novartis	Please change Comments entry in second row in Table 1 to, "Indirect results comparing daunorubicin 90 mg/m2 in the first induction cycle ("10 + 3" regimen) followed by a second course and consolidation versus midostaurin plus standard induction ("7 + 3" regimen) and consolidation, showed no difference between the treatments in terms of OS (HR=0.84 [95% CI: 0.54–1.31]). However, several serious methodological limitations apply to this indirect comparison, including limited similarity of the treatments in the 'common' reference arm, risk of bias at study and outcome level, and questions as to the validity of transitivity and proportional hazards assumptions."	We have now specified some details and information about the limitations in to the text in table 1.
15	352	Novartis	Please specify in Comments column on right side of Table 1 that ‚deaths on treatment' includes those occurring within 30 days of discontinuation of treatment	Specified.
16	360	Novartis	Novartis recommends to remove the word "standard" from "(ii) standard induction and consolidation chemotherapy", because although daunorubicin 90 mg/m2/day for induction is recommended in the Norwegian guideline, it is far from the standard "7 + 3" regimen used across Europe and it is not recommended in the ELN2017 guideline.	'standard' has been removed.
16	379	Novartis	Novartis acknowledge this gap, however, this statement might be too strong bearing in mind that long-term OS data are available. Furthermore, we recommend EUnetHTA to discuss the feasibility of QoL data collection in this patient population, particularly during induction and high-dose consolidation chemotherapy. **Previous text** No data on the health-related quality of life or disease-specific quality of life were available, which is a severe evidence gap. [D0001] **Recommended new text** No data on the health-related quality of life or disease-specific quality of life were available, however, quality of life data are being collected in the IIT and will become available once the study is completed.	We have added a sentence on the upcoming QoL data. However, this is currently still considered as a severe evidence gap.

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16	381	Novartis	**Previous text** **"**There was no relevant heterogeneity in the effect on OS observed in the subgroup analyses, except for a difference between males and females. This difference was not fully discussed in the submission file. [D0001]" In our submission file, we indicated that further analyses can be found in the NEJM 2017 publication by Stone et al (Ref Nr 4). In order to provide a more balanced view on the value of midostaurin on females, we would recommend the following: **Recommended new text** "There was no relevant heterogeneity in the effect on OS observed in the subgroup analyses, except for a difference between males and females. Further analyses can be found in the NEJM 2017 publication by Stone et al (Ref Nr 4). However, a treatment benefit was observed in females in all secondary efficacy endpoints."	We have mentioned that heterogeneity in the effect was not observed in other efficacy outcomes (except OS).

16	384	Novartis	Novartis recommends to follow best practice guidelines on reporting of indirect comparisons (ICs). According to the PRISMA Extension statement, the discussion of the indirect comparison should include alongside the summary of main findings discussion of the strength of the evidence for the outcome, limitations at study and outcome level, limitations at review level (reporting bias, incomplete retrieval), validity of assumptions and concerns about network geometry. We include below a suggested text to replace the paragraph in rows 384-389. **New text** The EUnetHTA authors performed an indirect comparison of high-dose (90 mg/m2) daunorubicin with induction chemotherapy ("10 + 3" regimen) followed by a second course and consolidation chemotherapy versus midostaurin in combination with standard induction ("7 + 3" regimen) and consolidation chemotherapy, which showed no difference between the treatments in terms of OS (HR=0.84, 95% CI: 0.54–1.31). Drawing conclusions from this indirect comparison should be cautioned against because of several serious methodological limitations that raise questions about the IC's validity: 1) The 'common' reference arm differed between the two trials: in RATIFY the reference arm was standard induction with daunorubicin 60 mg/m2/day plus cytarabine ("7 + 3" regimen) and consolidation chemotherapy, whereas in AML17 the reference arm was induction with daunorubicin 60 mg/m2/day plus cytarabine ("10 + 3" regimen) followed for FLT3 patients by a second course of daunorubicin 50 mg/m2 +/- lestaurtinib and one or two courses of consolidation chemotherapy. Since the reference arms act as the anchor for the IC, these differences challenge the validity of the IC; 2) The strength of the evidence for the FLT3-ITD patients in AML17 is weak because of the high risk of bias for the OS data (derived from a post-hoc exploratory subgroup analysis). Selective reporting bias may be underestimated. Further, the AML17 trial publications do not state that correction for multiplicity was made; 3) The proportional hazards assumption does not appear to hold for the AML17 trial for the FLT3-ITD subgroup - because after 6 months the Kaplan-Meier curves cross, a key indicator of non-proportional hazards. The HR reported, therefore, may not be valid, and hence, any IC based on the HR is compromised in its validity. 4) In a valid and unbiased IC, the transitivity assumption requires that the trials have been conducted similarly and that the characteristics of patients in the studies are, on average, similar. Further, characteristics that may modify the treatment effect must be similar. As the characterisation of the FLT3-ITD subgroup patients in the AML17 trial has not been reported, it is not possible to establish whether the transitivity assumption holds. An important feature of the FLT3-positive subgroup analysis from the AML17 trial was that all patients were FLT3-ITD, whereas in RATIFY patients were either ITD or TKD. The impact of this difference is not known. Furthermore, the 90 mg/m2/day dose of daunorubicin used during induction in the AML17 trial does not represent the gold standard of treatment across Europe.	We have now specified some details and information about the limitations related to indirect comparison.

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17	438	Novartis	In line with the previous comment about the comparability of midostaurin vs daunorubicin 90 mg/m2, ["There was insufficient evidence to determine whether midostaurin treatment was more beneficial than high-dose daunorubicin (90 mg/m2) used during induction in terms of OS"] Novartis is proposing to replace this sentence with the following text: "The comparison between midostaurin and high-dose daunorubicin 90 mg/m2 is based on an indirect comparison with several serious methodological limitations and, therefore, no conclusions can be drawn regarding the treatments' relative effectiveness."	We have also added a note that this is based on indirect comparison with serious limitations.
19	458	Novartis	Change "after achieving CR. CIR is measured at 12 months." to "after achieving CR."	Changed.
19	458	Novartis	Change "less than 5% blasts occurring on or before day 60" to "less than 5% blasts"	Changed.
19	458	Novartis	Change "on or before 60 days of initiation of protocol therapy;' to "during induction"	Changed.
26	553	Novartis	Please remove the word "standard" from "standard induction", as discussed previously	Removed.
29	638	Novartis	Novartis recommends to add "in Norway" after this sentence, i.e. "be used during induction phase in Norway"	We are referring now that it has been recommended for example in Norway but we do not restrict this comparator to Norway only.
33	720	Novartis	**Previous text** Midostaurin gained the first regulatory approval worldwide from the US Food and Drug Administration (FDA) on 28th April 2017 and from Swissmedic on 4th May 2017 followed by Health Canada approval on 24th July 2017. The FDA approval was restricted to the induction and consolidation phase. The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on 20th July 2017**.** Novartis recommends to replace this paragraph with the following: **Recommended new text** "Midostaurin gained the first regulatory approval worldwide from the US Food and Drug Administration (FDA) on 28th April 2017 and from Swissmedic on 4th May 2017 followed by Health Canada approval on 21st July 2017 and EU approval (EC decision) on 18th September 2017. While the FDA and Health Canada approvals were restricted to the induction and consolidation phase, the EMA and Swissmedic approvals included induction, consolidation and the maintenance phases."	Changed as recommended.
34	732	Novartis	change "FL3" to "FLT3" in table	Changed.

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40	935	Novartis	Please adapt from "de novo" to „...newly diagnosed“ in alignment with the approved SmPC and other sections of the document.	Not changed as de novo (recurrent translocations AML) is referring to aethiolgy rather than whether is newly diagnosed patients.
40	944	Novartis	For consistency, please add „...adult patients...“, to the sentence "approximately 30% of all adult patients with AML)" since the prevalence in pediatric patients is different.	Added as suggested.
41	976	Novartis	Please add „..ongoing single-arm..“ since patients are currently being recruited.	Added as suggested.
41	976	Novartis	Change "on older patients" to "on older patients (based an on interim report in April 2016)."	Added as suggested.
41	978	Novartis	Please remove the word "standard", as discussed previously	Removed.
42	1003	Novartis	Please change this bullet point to "• Maintenance (up to 12 cycles): midostaurin monotherapy OR placebo"	Changed accordingly.
44	1023	Novartis	Please adapt „The IIT is an ongoing single-arm study..“	Adapted.
44	1026	Novartis	Please add: „The total number of patients analysed was 145 at the time of the interim CSR, with a data cut-off on 31-Dec-2015.”	Added as suggested.
45	1055	Novartis	Please replace "MAL" with "AML"	Replaced as suggested.
45	1067	Novartis	Please change to: "Furthermore, no details of the baseline characteristics of patients with FLT3-ITD mutated AML are not available for assessing the similarity of the patient groups compared in the indirect analysis."	Rephrasing has been made but not exactly as suggested.
46	1084	Novartis	Change "one-fifth of patients (22.2% and 19.3%, respectively) " to "one-fifth of patients"	No changes were made based on this comment since we are reporting important facts of SCT rates.
48	1119	Novartis	Novartis recommends revision to interpretation of indirect comparison as follows: **Previous text** Consequently, there is no evidence that midostaurin treatment would be more beneficial than high-dose daunorubicin used in induction, or vice versa. Several limitations apply to this indirect comparison, which are discussed in Section 8. **New text** Drawing conclusions from this indirect comparison should be cautioned against because of several serious methodological limitations that raise questions about the IC's validity. These limitations are discussed in Section 8.	No changes were made. This section reports results only and not interpretations of the results. We have added some further issues related to IC but we are not reporting them here but in sections where IC is discussed.
52	1189	Novartis	Please add: „...from the interim CSR, with a data cut-off of 31-Dec-2015“	Detail added.

Page	Line	Organisation	Comment	Reply from author
52	1194	Novartis	Please change "Kaplan–Meyer " to "Kaplan–Meier "	Changed accordingly.
54	1214	Novartis	Please add a footnote to Research question table to indicate that "death as SAE" refers to "death on treatment, within 30 days of discontinuation".	This table refers to original research questions. Such details are not included into this assessment element table. No changes were made on this. However, we have specified this in the relevant section concerning death as SAE.
54	1239	Novartis	Please change "patients receiving midostaurin" to "both treatment groups, however, a mechanistic explanation for this observation was not found."	No changes has been made based on this comment.
54	1245	Novartis	Please add a footnote to the table to indicate that "Numbers updated as per PKC412A2301 CSR Amendment 1"	We agree on this and checked the information. The table is now updated. We have referred to this CSR amendment in the beginning of section 6.2. (included studies). Footnotes were not inserted.
55	1252	Novartis	Please change 'monotherapy' to 'maintenance'	Maintenance monotherapy has been added.
55	1256	Novartis	Please change 'Monotherapy phase' to 'Maintenance phase' in Table 19	Changed as suggested.
60	1363	Novartis	To this statement, "This difference was not seen in subgroup analyses of EFS." Novartis proposes to add "or in any other secondary efficacy endpoints"	Addition made.
60	1379	Novartis	Suggest revision to interpretation of indirect comparison as follows: **Previous text** "Consequently, there is no evidence that midostaurin treatment would be more beneficial than high-dose daunorubicin used during induction, or vice versa. Indirect comparisons were conducted by authors." **New text** "Drawing conclusions from this indirect comparison should be cautioned against because of several serious methodological limitations that raise questions about the IC's validity. These limitations are discussed below.	Not changed. Limitations are discussed right below this paragraph.

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60	1382	Novartis	Please add/incorporate to the list of limitations the following: 1) The 'common' reference arm differed between the two trials:in RATIFY the reference arm was standard induction with daunorubicin 60 mg/m2/day plus cytarabine ("7 + 3" regimen) and consolidation chemotherapy, whereas in AML17 the reference arm was induction with daunorubicin 60 mg/m2/day plus cytarabine ("10 + 3" regimen) followed for FLT3 patients by a second course of daunorubicin 50 mg/m2 +/- lestaurtinib and one or two courses of consolidation chemotherapy. Since the reference arms act as the anchor for the IC, these differences challenge the validity of the IC; 2) The strength of the evidence for the FLT3-ITD patients in AML17 is weak because of the high risk of bias for the OS data (derived from a post-hoc exploratory subgroup analysis). Selective reporting bias may be underestimated. Further, the AML17 trial publications do not state that correction for multiplicity was made; 3) The proportional hazards assumption does not appear to hold for the AML17 trial for the FLT3-ITD subgroup - because after 6 months the Kaplan-Meier curves cross, a key indicator of non-proportional hazards. The HR reported, therefore, may not be valid, and hence, any IC based on the HR is compromised in its validity. 4) In a valid and unbiased IC, the transitivity assumption requires that the trials have been conducted similarly and that the characteristics of patients in the studies are, on average, similar. Further, characteristics that may modify the treatment effect must be similar. As the characterisation of the FLT3-ITD subgroup patients in the AML17 trial has not been reported, it is not possible to establish whether the transitivity assumption holds. An important feature of the FLT3-positive subgroup analysis from the AML17 trial was that all patients were FLT3-ITD, whereas in RATIFY patients were either ITD or TKD. The impact of this difference is not known.	We have added more details of the limitations and added a sentence "drawing conclusions from this indirect comparison should be cautioned.' (because of these limitations)
62	1455	Novartis	Please change, "and approximately 75% of patients in both groups reported at least one grade 3–4 AE considered related to treatment" to "and 78% and approximately 75% of patients in the midostaurin and placebo groups, respectively reported at least one grade 3-4 AE considered related to treatment"	Changed as applicable.
62	1460	Novartis	Please note the following important correction. Please correct the following sentence, "The most frequent treatment-related grade 3–4 adverse events were thrombocytopaenia, neutro-paenia, anaemia and febrile neutropaenia." to "The most frequent grade 3–4 adverse events regardless of relationship to study drug were thrombocytopaenia, neutropaenia, anaemia and febrile neutropaenia."	True. Corrected as suggested.
62	1461	Novartis	Please note the following correction. Please correct the following sentence, "The events leading to discontinuation in more than one patient were dermatitis exfoliative, increased ALT, increased AST and renal failure in the midostaurin group and febrile neutropaenia in the placebo group." to "Grade 3-4 adverse events leading to discontinuation in more than one patient were dermatitis exfoliative, increased ALT, increased AST, decreased neutrophil count and renal failure in the midostaurin group and	Suggested addition has been made.

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			decreased platelet count, febrile neutropaenia and decreased neutrophil count in the placebo group."	
62	1463	Novartis	Please correct the following sentence, "Overall, 21 (6.1%) patients in the midostaurin group and 15 (4.5%) patients in the placebo group discontinued therapy because of grade 3–4 AEs." to "Overall, 23 (6.7%) patients in the midostaurin group and 17 (5.1%) patients in the placebo group discontinued therapy because of grade 3–4 AEs."	Changed since MAH has updated some of the safety results.
62	1470	Novartis	Please add "Grade" to "3-4 AEs were high"	Added as suggested.
62	1473	Novartis	Please change " patients receiving midostaurin. " to "both treatment groups, however, a mechanistic explanation for this observation was not found"	We added a note that mechanistic explanation for the observation was not found. Other changes were not conducted based on this comment.
63	1486	Novartis	Novartis proposes the following amendment to reflect EUnetHTA's statement in the discussions section in lines 417-421. "Midostaurin in combination with standard induction and consolidation chemotherapy is considered more effective than standard induction and consolidation chemotherapy alone in terms of improved OS in adult patients who are considered suitable for intensive chemotherapy."	Word "intensive" has been added. Other changes has not been made based on this comment.
63	1493	Novartis	Please change this statement in line with our recommendations to line 386. **Previous text** There was insufficient evidence to determine whether midostaurin treatment was more beneficial than high-dose daunorubicin (90 mg/m2) used during induction in terms of OS. **Recommended new text** Drawing conclusions from the indirect comparison of the relative treatment effects of midostaurin versus high-dose daunorubicin (90 mg/m2) during induction in terms of OS should be cautioned against because of several serious methodological limitations that raise questions about the indirect comparison's validity	We have modified the text but not directly as suggested.
63	1502	Novartis	Please change "patients receiving midostaurin" to "both treatment groups, however, a mechanistic explanation for this observation was not found."	No changes has been made based on this comment.

Page	Line	Organisation	Comment	Reply from author
63	1505	Novartis	Novartis agrees that further research is needed and that is one of the reasons why the IIT was initiated and is ongoing. Therefore, we propose the following modification: **Previous text** Further research is required on the effects of midostaurin in the older population. **Recommended new text** „Further research is ongoing to gain a better understanding of the effects of midostaurin in the older population.”	We have modified this sentence but not exactly as suggested.
64	1550	Novartis	Please add full reference as follows: *Haematologica*, 2016 101 Supplement 1 (325)	Full ref details added as suggested.