Input from manufacturer on the 2nd draft assessment "CRIZANLIZUMAB FOR THE PREVENTION OF RECURRENT VASO-OCCLUSIVE CRISES IN SICKLE CELL DISEASE PATIENTS AGED 16 YEARS AND OLDER"

Project ID: PTJA10

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 crizanlizumab for the prevention of recurrent vaso-occlusive crises in sickle cell disease patients aged 16 years and older was open to review by the manufacturer Novartis between **05/10/2020 and 09/10/2020**.

Comments received from:

Market Authorisation Holder
Novartis

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 [Novartis]

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9	218 (871)	**Text from EUnetHTA assessment:** "Only in patients receiving HU/HC and patients with 5-10 VOC prior to randomisation, a statistically significant reduction in annualised VOC rate was seen (Table 0.2)." **Novartis comment:** SUSTAIN was not powered to assess statistical significance in subgroups; it is therefore incorrect and misleading to focus on the lack of statistical significance in some subgroups. **Proposed amendment:** "The analyses by subgroups of relevant disease characteristics on the primary and secondary endpoints related to VOC show a consistent trend in favour of crizanlizumab 5mg/kg over placebo."	1	This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check. Nevertheless, we do agree with the comment of Novartis and added the following sentence to prevent potential focussing on statistically significant differences in subgroups: "Results should, however, be interpreted with caution, since SUSTAIN was not powered to assess statistical significance in subgroups."
11	258 (1054)	**Text from EUnetHTA assessment:** "Results for all outcomes were recalculated using negative binomial regression, imputation method M6, and investigator-adjudicated VOC data without patient 124-002 (Table 0.3). No statistically significant difference was seen between crizanlizumab and placebo in the annualised VOC rate (primary outcome) nor in the annualised rate of days hospitalised (key secondary outcome)." **Novartis comment:** The recalculated analysis is a supplementary analysis supporting the original result, as reflected in the EU SmPC and the CHMP assessment report. This analysis is based on a combination of approaches that despite being voluntarily conservative against crizanlizumab, continue to show a clinically relevant difference vs placebo. The statistical significance for such supplementary analysis should not be expected to replace the formal analyses planned by protocol. It should further be noted that the calculated relative risk (RR) for all analyses requested by the CHMP does not vary significantly, thus suggesting	1	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. We did made it more clear that these findings were based on sensitivity analyses.

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		that the results were not dissimilar. **Proposed amendment:** "Results for all outcomes were recalculated via a scenario using negative binomial regression, highly conservative imputation method M6, and investigator-adjudicated VOC data without patient 124-002 (Table 0.3). The re-analysis showed a reduction in the predicted number of VOCs leading to healthcare visits of 26% for crizanlizumab 5 mg/kg vs placebo (RR=0.74, 95% CI [0.52, 1.06]). The provided re-analysis showed a 28% reduction of the predicted number of days hospitalised due to VOC on crizanlizumab 5 mg/kg compared to placebo (RR=0.72, 95% CI=[0.36, 1.45]). Although not statistically significant, the results show a positive numerical trend in favour of crizanlizumab 5 mg/kg over placebo in line with the protocol-planned analyses."		
12	288 (1039)	**Text from EUnetHTA assessment:** "Due to the large dropout rate of 35%, the question arises whether the 288 study is still powered enough to detect differences in efficacy and safety results between the treatment 289 arms." **Novartis comment:** Novartis consider it important to highlight that the observed dropout rates in SUSTAIN were similar to rates reported in other recent placebo-controlled trials in patients with SCD (Niihara Y, Smith WR, Stark CW. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. N Engl J Med 2018;379:1880), and that there were no unexpected imbalances in dropouts between groups and reasons for dropouts appear to be similar across treatment groups.	1	This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check. Nevertheless, the comment is considered relevant by the Authoring Team and added to the Discussion section of the main document (not the Summary).
12	296	**Text from EUnetHTA assessment:** "Analysing data on VOC frequency in a different way with regards to the statistical method and imputation method for handling missing data gave different results, leading sometimes to different conclusions (i.e. statistically significant results lost significance). The lack of	1	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

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		consistent results lowers the confidence in a robust treatment effect of crizanlizumab." **Novartis comment:** Novartis do not consider that the provided re-analyses lead to different conclusions. All sensitivity analyses performed in the submission dossier, and provided during the review, resulted in a treatment effect estimate for the frequency of VOCs leading to healthcare visits, that was systematically and consistently in favour of crizanlizumab over placebo. This trend was true whether using the negative binomial or Hodges-Lehmann method, adjudicated vs investigator VOCs and regardless of the assumptions adopted for the imputation of missing data. The robustness and certainty around the magnitude of benefit demonstrated in the primary outcome is further fully supported by the consistent results observed in the secondary outcomes demonstrated by: - A greater than two-fold increase in the proportion of patients with no VOC in patients receiving crizanlizumab 5 mg/kg compared to placebo - A three-fold longer Kaplan-Meier estimated median time to first VOC compared with placebo - A reduction in the frequency of uncomplicated VOC versus placebo, and - A reduction in the VOC frequency on-treatment compared to baseline **Proposed amendment:** "All treatment effect estimates for the primary and secondary endpoints are systematically in favour of crizanlizumab and the observed favourable trends for the 5 mg/kg crizanlizumab dose are of a magnitude considered clinically relevant for SCD patients. Supplementary analyses, taking into account different statistical methodology and no crisis adjudication, continued to support a beneficial effect of 5mg/kg crizanlizumab on the risk of VOC occurrence compared to placebo. The use of investigator reported VOCs (excluding one outlier patient) instead of adjudicated VOCs had		scope of a fact check. In our view, we gave a well-balanced overview of the pre-specified analyses as well as the post-hoc sensitivity analyses. Nevertheless, as the sensitivity analyses are based on the appropriate statistical test, use a conservative but appropriate imputation method, and used the more reliable investigator-adjudicated data, confidence in this treatment effect is high. The fact that these analyses show no significant difference between crizanlizumab and placebo whereas the pre-specified analyses did, questions the robustness of the treatment effect of crizanlziumab.

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		very little impact on the results of the primary endpoint. Further, it was only under the most conservative imputation method that statistical significance could no longer be reached. The consistency of the results improves confidence in a robust treatment effect of crizanlizumab."		
12	301	**Text from EUnetHTA assessment:** "VOCs managed at home were not counted. This does not necessarily mean that VOCs managed at home are less severe than those managed in the hospital. Other reasons mentioned for not seeking medical support include a previous poor experience at hospital and the perception that medical professionals do not understand SCD. It is therefore an important limitation of the SUSTAIN trial that information on the total rate of VOC is lacking." **Novartis comment:** As stated on line 301, VOCs managed at home are not necessarily less severe than those managed in the hospital. The fact that the SUSTAIN trial does not capture home treated VOC events is a limitation. However, it remains clinically plausible that home-treated VOCs could also be reduced by crizanlizumab meaning that the reduction in VOCs reported in SUSTAIN may be an underestimate of the true benefit of crizanlizumab, as a reduction in home-treated VOCs was not recorded. The decision to record only those VOCs requiring a health care visit in the SUSTAIN trial was made in order to increase the objectivity of the primary endpoint and thereby increase certainty in the results of the primary outcome. Collection of VOCs leading to HC visit was considered more reliable because of the HC visit documentation, than the collection of patient reported accounts of VOC they managed at home.	1	This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check. In addition this is not considered accurate to include in the assessment report. However, the reason why the company choose to use only data of VOCs that lead to a healthcare visit in the first place is added to the Discussion of the main text (not the summary).
12	311 (1098)	**Text from EUnetHTA assessment:** "Based on the randomised, double-blind, placebo-controlled phase II SUSTAIN trial, crizanlizumab did not reduce the annualised rate of VOCs (primary outcome) compared to placebo, in addition to best	1	The MAH was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy

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		supportive care with or without HU/HC treatment." **Novartis comment:** This statement does not reflect the primary outcome of the trial based on the pre-specified statistical analysis plan. Given the aforementioned positive trend in the outcomes of the supplementary analysis of the primary endpoint submitted to the EMA in support of the robustness of the magnitude of benefit of the primary outcome, there is no reason to expect that the true magnitude of benefit is reflected by the analysis incorporating the most conservative assumptions. Indeed, the re-analyses of the primary endpoint requested by the CHMP consistently showed a reduction of the predicted number of VOCs leading to healthcare visits. Even for the analysis utilising the most conservative assumptions biased against crizanlizumab, a clinically relevant reduction of VOCs of 26% was observed in favour of crizanlizumab 5 mg/kg vs placebo (RR=0.74, 95% CI [0.52, 1.06]). The lack of significance of this analysis could be explained by the highly conservative, reference-based imputation for around a third of patients who discontinue before the end of the trial. This conclusion also seems to ignore the findings of the planned analysis including annual rate of VOCs, time to first VOC and % of patients VOC-free, which all show clinically relevant differences in favour of crizanlizumab over placebo. Furthermore, preliminary efficacy data from the ongoing study A2202, showed a median reduction from baseline of 1 VOC per year, consistent with that observed in SUSTAIN. A reduction of 1 VOC per year is considered to be a highly clinically relevant outcome. Results of A2202 further confirm that the magnitude of benefit of crizanlizumab 5mg/kg vs SOC demonstrated by the primary outcome is robust.		and is, therefore, outside the scope of a fact check. Although not considered a fact check, we made the conclusion more balanced by showing the findings of both the pre-specified analyses and the sensitivity analyses.

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		Proposed amendment: "Based on the randomised, double blind, placebo controlled phase II SUSTAIN trial, crizanlizumab reduced the annualised rate of VOCs compared to placebo in addition to SOC with or without HU/HC treatment. Supplementary analyses using a conservative approach to manage early discontinuations, using a different statistical methodology and removing the requirement for crisis adjudication showed a numerical beneficial effect on the risk of VOC occurrence in the 5 mg/kg crizanlizumab group compared to placebo. Whilst statistical significance was lost in this highly conservative analysis, potentially due to the conservative, reference-based imputation for around a third of patients who discontinued before the end of the trial, the clinically significant reduction in VOC rate is supportive of the efficacy of crizanlizumab vs SOC."		
12	319 (1107)	**Text from EUnetHTA assessment:** "Further, different statistical analyses and imputation methods led to different results, thereby questioning the robustness of the treatment effect of crizanlizumab." **Novartis comment:** Novartis consider this statement (i.e. "led to different results") misleading. As discussed above, in all sensitivity analyses performed in the submission dossier, and provided during the review, the treatment effect estimate for frequency of VOC leading to healthcare visits is systematically in favour of crizanlizumab over placebo, whether using the negative binomial or Hodges-Lehmann method, investigator or adjudicated VOCs and regardless of the assumptions adopted for the imputation of missing data. **Proposed amendment:** "Supplementary analyses taking into account the issues regarding statistical methodology and crisis adjudication show a beneficial effect	1	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. In our view, the sensitivity analyses most closely resemble the treatment effect of crizanlizumab in real life (effectiveness), as it uses the appropriate statistical test, the most appropriate though conservative imputation method and the more reliable investigator-adjudicated data. Furthermore, a non-significant

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		on the risk of VOC occurrence with crizanlizumab 5 mg/kg compared to placebo. The use of investigator reported VOC (excluding one outlier patient) instead of CRC-adjudicated VOC affected the results only marginally. Under the most conservative imputation method, statistical significance could no longer be reached. However, all treatment effect estimates for the primary and secondary endpoints are systematically in favour of crizanlizumab and the observed favourable trends for the crizanlizumab 5 mg/kg dose are of a magnitude considered clinically relevant for SCD patients." 		result differs from a significant result and therefore the statement that different ways of analyzing the data led to different results is misleading is in our opinion not correct.
12	223	**Text from EUnetHTA assessment:** "QoL did not differ between patients that received crizanlizumab vs placebo in addition to standard care." **Novartis comment:** Whilst this is a true statement, further examination of the study methodology indicates that the lack of difference in HRQoL likely has little to do with the efficacy of crizanlizumab. Fixed sampling of questionnaires resulted in an exceptionally low number of responses in either treatment arm during a crisis event. As the SUSTAIN trial was established essentially to measure the absence of VOC, a 7-day recall period in combination with the fixed sampling time points and the relatively short trial duration means that it is highly unlikely that the trial would have shown a benefit in favour of either intervention. Instead of measuring the impact of decreased crisis rates on HRQoL, the methodology employed really only captured the HRQOL of patients between VOC. It is highly plausible that 12 months was not a sufficient period to really capture the impact of reducing VOC in the short term.	2	This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check. In the Discussion section of the main text, we slightly adapted the hypothesis of the MAH for not finding an improved HRQoL in the crizanlizumab arm compared to placebo.
13	Table 0.4	**Novartis comment:** It is unreasonable to present the efficacy analysis only for the sensitivity analysis and not for the results of the pre-specified primary analysis. The sensitivity analyses were requested by EMA to test the robustness of the primary outcome and were never intended as a	1	The authoring team does not agree with the MAH that the sensitivity analyses are used as the only source of evidence. Throughout the assessment

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		replacement for the primary outcome or results of the trial. Consequently, they should not be used as the primary or only source of evidence upon which to make a conclusion in the report.		report we consistently showed both the results of the pre-specified analyses and the results of the sensitivity analyses. Only for GRADE we had to make a decision between the two type of analyses. Since the sensitivity analyses were based on the appropriate statistical test, calculated with the most appropriate though conservative imputation method, used the more reliable investigator-adjudicated data, and included more easily to interpreted ratios, these results were used to rate the quality of evidence.
19	Table 1.1	**Text from EUnetHTA assessment:** "Hypersensitivity to the active substance or to any of the excipients (Sucrose, Sodium citrate (E331), Citric acid (E330), Polysorbate 80 (E433))." **Novartis comment:** The list of contra-indications for crizanlizumab should be aligned with the full list available in the current draft SmPC and provided in the company submission. **Proposed amendment:** "Hypersensitivity to the active substance or to any of the excipients (Sucrose, Sodium citrate (E331), Citric acid (E330), Polysorbate 80 (E433), water for injections)."	2	This comment is considered a fact check and is therefore updated in the final assessment report.
19 onward	Table 1.1	**Novartis comment:**	1	We agree with the comment of

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	Table 1.2	Crizanlizumab will not replace the use of HU/HC in clinical practice and therefore HU/HC should not be considered a comparator. On the contrary, crizanlizumab, as per CHMP recommendation, can be given as an add-on therapy to HU/HC or as monotherapy in patients for whom HU/HC is inappropriate or inadequate. In this way, the benefit of crizanlizumab observed in the SUSTAIN trial is an additive benefit above and beyond that already being provided by SOC with or without HU/HC. Thus, the most appropriate comparator is SOC with or without HU/HC as outlined in Table 2.1 of the report (pg. 23)		the MAH that HU/HC is not a comparator on its own. This is also clearly written in section 1.3 of the assessment report and shown in the PICO table. Nevertheless, HU/HC is a major component of the treatment strategy of VOC prevention. Therefore, we choose to include it in tables 1.1 and 1.2.
25	Table 3.1 (Exclusion Criteria)	**Text from EUnetHTA assessment:** "Population did not include patients < 16 years with SCD." **Novartis comment:** The exclusion criterion for the SLR is currently stated incorrectly. **Proposed amendment:** "Population did not include patients ≥ 16 years with SCD."	2	This comment is considered a fact check and deemed correct by the authors. It is therefore updated in the final assessment report.
30	639	**Text from EUnetHTA assessment:** "This study was initiated to assess the comparability between the formulation of crizanlizumab used in the SUSTAIN study (SelG1) and the to be commercialised compound of crizanlizumab (SEG101)." **Novartis comment:** The primary objective of SOLACE-adults is not to assess comparability of SelG1 and SEG101, but to characterise PK and PD of crizanlizumab-SEG101 (https://clinicaltrials.gov/ct2/show/NCT03264989). **Proposed amendment:** "The purpose of SOLACE-adults is to characterise the PK and PD of SEG101/crizanlizumab at 5 mg/kg and to evaluate the safety and	1	This comment is considered a fact check and verified on clinicaltrials.gov. Since the comment by the MAH is deemed correct by the authors, it is changed in the final assessment report.

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		efficacy of SEG101/crizanlizumab in SCD patients."		
30	652	**Text from EUnetHTA assessment:** "SUCCESSOR was a retrospective cohort study of patients who completed SUSTAIN. However, none of the patients received treatment with crizanlizumab during the SUCCESSOR study period." **Novartis comment:** Novartis would like to emphasise that the importance of the SUCCESSOR study lies in supporting the effect of crizanlizumab by demonstrating increased VOC rates following crizanlizumab discontinuation. The results of this study support the pre-specified analysis outcome that crizanlizumab reduced VOCs vs SOC.	2	This comment is not deemed relevant by the authors, since this part of the assessment report describes why the SUCCESSOR study is excluded from the main analysis.
31	665	**Text from EUnetHTA assessment:** "Patients were stratified by concomitant HU use (yes/no) and by the number of VOCs prior to randomisation (2-4 vs 5-10)." **Novartis comment:** The current description of the stratification performed in SUSTAIN should include the additional information provided below for correctness. **Proposed amendment:** "Patients were stratified by concomitant HU/HC use (yes/no) and by the number of VOCs in the year prior to randomisation (2-4 vs 5-10)."	2	This comment is considered a fact check. Since the proposed amendment is correct, the text is updated in the final assessment report.
34	682	**Text from EUnetHTA assessment:** "A total of 329 patients were screened for eligibility, of which 198 patients were included in the study. Reasons for not being included in the study were 'not meeting eligibility criteria' (n=131; not specified which exclusion criteria) and 'declined to participate' (n=18)." **Novartis comment:** The numbers stated in the context of patient disposition/flow in	2	This comment is considered a fact check. Since the proposed amendment is checked by the authors and considered correct, the text is updated in the final assessment report.

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		SUSTAIN should be corrected in line with the company submission. **Proposed amendment:** "A total of 329 patients were screened for eligibility, of which 198 patients were included in the study. Reasons for not being included in the study were 'not meeting eligibility criteria' (n=118; not specified which exclusion criteria) and 'declined to participate' (n=13)."		
34	691	**Text from EUnetHTA assessment:** "The vast majority was black (91.9%), followed by white (4.6%) and other (3.5%)." **Proposed amendment:** "The vast majority was black (91.9%), followed by white (4.5%) and other (3.5%)."	2	This comment is considered a fact check. Since the proposed amendment is checked by the authors and considered correct, the text is updated in the final assessment report.
37	749	**Text from EUnetHTA assessment:** "However, in the SUSTAIN trial, Good Clinical Practice (GCP) inspectors did not recommend accepting these data due to many uncertainties. The most outstanding one relates to the 2-week rule, in which VOCs that occurred within 14 days were not counted as separate events. This rule was not mentioned in the study protocol and it is unclear if it is applied during the entire study. " **Novartis comment:** In order to avoid misunderstandings regarding this critical point, the wording should be more closely aligned with the statement provided in the draft CHMP assessment report. **Proposed amendment:** "However, in the SUSTAIN trial, Good Clinical Practice (GCP) inspectors did not recommend accepting these data due to remaining uncertainties. In particular, a major uncertainty pertains to the 2-week rule (VOCs that occurred within 14 days were not counted as a separate event) as this timeframe was not (pre)defined in the study	1	This comment is considered a fact check. Since the proposed amendment is verified in the European Public Assessment Report (EPAR) and deemed correct, the text is updated in the final assessment report.

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		protocol and it cannot be followed whether it was consistently applied during the entire study."		
37	749	**Text from EUnetHTA assessment:** "The rationale behind excluding those patients is the fact that being on a chronic blood transfusion programme would prevent VOCs and therefore would confound the results on the efficacy of crizanlizumab. " **Novartis comment:** The wording on the exclusion of chronic blood transfusions in SUSTAIN should be more closely aligned with the rational stated in the company submission. **Proposed amendment:** "The rationale behind excluding those patients is the fact that there are only limited relevant data for the efficacy of blood transfusions for the prevention of VOC specifically, a direct comparison of crizanlizumab to a standard of care comprising of regular blood transfusions is therefore not possible."	2	This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check. Nevertheless, we did align the rationale of excluding patients on chronic blood transfusions more closely with the rationale stated in the company submission.
39	Table 4.9	**Text from EUnetHTA assessment:** Uncomplicated VOC – standard median (placebo): 2.98 **Proposed amendment:** Uncomplicated VOC – standard median (placebo): 2.91	2	This comment is considered a fact check. Since the proposed amendment is verified with the Common Technical Document and deemed correct, the text is updated in the final assessment report.
39	Table 4.9	**Text from EUnetHTA assessment:** Complicated VOC **Novartis comment:** This outcome should be removed from the table, as it is no clear where these specific data have been obtained from.	1	This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check. However, since we agree with the MAH and Table 4.10 also shows

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				information on complicated VOCs, we deleted this part of Table 4.9.
42	Table 4.13	**Text from EUnetHTA assessment:** HU/HC use, yes – standard median (range) for placebo: 2.98 (0, 24.3) **Proposed amendment:** HU/HC use, yes – standard median (range) for placebo: 3.58 (0, 13.5)	2	This comment is considered a fact check. Since the proposed amendment is verified against the EPAR and deemed correct, the text is updated in the final assessment report.
44	955	**Text from EUnetHTA assessment:** "No statistically significant difference was seen between crizanlizumab and placebo in the annualised VOC rate (primary outcome). The certainty of the evidence was graded as low due to a serious risk of bias and serious imprecision of the treatment effect." **Novartis comment:** As previously stated, Novartis believe that the bias in all of these additional analyses is *against* crizanlizumab – meaning that the results of the analyses are more confirmatory of the benefit, rather than suggesting that the results are likely biased against SOC. In order to provide a more accurate statement, Novartis would request to include the original statement from the CHMP assessment report. **Proposed amendment:** "Under the most conservative (worst-case) imputation method, statistical significance could no longer be reached. However, all treatment effect estimates for the primary and secondary endpoints are systematically in favour of crizanlizumab and the observed favourable trends for the 5 mg/kg crizanlizumab dose are of a magnitude considered clinically relevant for SCD patients."	1	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. This is not considered a fact check. Furthermore, this is also not the conclusion that the authoring team and the dedicated reviewers draw from these supplementary analyses. Therefore, we did not update the text with the proposed amendment.
44	958	**Text from EUnetHTA assessment:**	1	This comment is not related to

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		"Since the primary outcome is non-significant, positive findings for secondary outcomes are only considered to be hypothesis-generating." **Novartis comment:** The protocol-planned primary efficacy analysis was both clinically relevant and statistically significant. As such, all secondary endpoints can be taken into account as relevant. Deciding to exclude these patient relevant analyses due to the unwavering focus on the highly conservative M6 assessment is not considered reasonable.		a factual inaccuracy and is, therefore, outside the scope of a fact check. Nevertheless, we agree with the MAH that the primary outcome of the pre-specified analyses was indeed statistically significant and consequently secondary outcomes from the sensitivity analyses can be taken into account in the assessment report. The sentence was removed.
46	Table 4.147	**Text from EUnetHTA assessment:** ADRs by SOC – grades ≥3 **Novartis comment:** Novartis would suggest to exclude grade ≥3 ADRs (by SOC) from this table as it is not clear where these data have been obtained from – instead, it may be more accurate to refer to the wording in the company submission: "The majority of the ADRs were mild to moderate (grade 1 to 2), with severe events (grade ≥3) observed for pyrexia and arthralgia (1 case [0.9%] each)."	1	This part of the table is not removed, but changed to NR (not reported).
50	1069	**Text from EUnetHTA assessment:** "It is unclear when a reduction in VOC is perceived as clinically relevant [...] Since VOCs are extremely painful and can trigger severe complications such as ACS and stroke, every VOC that is prevented can be seen as a clinically relevant effect. Nevertheless, using the analyses requested by the CHMP, no reduction in annualised VOC rate was identified." **Novartis Comment:** The M6 analysis still demonstrates an absolute reduction of 1 VOC compared to SOC. The lack of statistical significance associated with	1	This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check. The Authoring Team also does not agree with the comment of the MAH that the M6 analysis demonstrates an absolute reduction of 1 VOC, for the difference between the two treatment arms is not statistically

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		this analysis has been previously explained and it is important to note again that the analysis is conservatively biased against crizanlizumab. Given the highly consistent reduction of at least 1 VOC for all submitted supplementary analysis, supporting the outcome from the primary, pre-specified analysis, it is clear that the impact of crizanlizumab on reducing the overall VOC burden for a patient is clinically relevant.		significantly different (and therefore not all patients will experience a reduction in VOC frequency).
50	1075	**Text from EUnetHTA assessment:** "Nevertheless, using the analyses requested by the CHMP, no reduction in annualised VOC rate was identified." **Novartis comment:** This statement as part of the discussion should provide additional context in line with statements included in the CHMP assessment report. **Proposed amendment:** "Using the most conservative (worst-case scenario) analyses requested by the CHMP, no statistically significant reduction in annualised VOC rate was identified even if there is still a numerical difference in favour of crizanlizumab. However, all treatment effect estimates for the primary and secondary endpoints are systematically in favour of crizanlizumab and the observed favourable trends for the 5 mg/kg crizanlizumab dose are of a magnitude considered clinically relevant for SCD patients."	1	This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check. Nevertheless, we changed the wording slightly so that the text gives a more complete and accurate view of the findings.
50	1080	**Text from EUnetHTA assessment:** "The used outcomes were of clinical relevance and supported by patient organisations. However, since the study duration was only 1 year, the SUSTAIN trial did not capture long term outcomes to determine the impact of crizanlizumab on mortality and SCD complications (such as acute chest syndrome)." **Novartis comment:**	1	This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check. Nevertheless, a part of the proposed amendment does provide more context and its addition to the final assessment report is

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		This statement as part of the discussion should provide additional context in line with the CHMP assessment report and company submission. **Proposed amendment:** "The used outcomes were of clinical relevance and supported by patient organisations. Deaths and the occurrence of other serious complications in SUSTAIN were rare, balanced between treatment arms and the assessment that none were considered treatment-related can be followed. However, since the study duration was only 1 year, the SUSTAIN trial did not capture long term outcomes to determine the impact of crizanlizumab on mortality and SCD complications (such as acute chest syndrome)."		therefore deemed relevant by the authors.
50	1080	**Text from EUnetHTA assessment:** "There may be a relationship between the frequency of VOC and the occurrence of these longer-term outcomes, but this is unknown based on the short duration of SUSTAIN." **Novartis comment:** This statement as part of the discussion should provide additional context in line with the company submission. **Proposed amendment:** "There may be a relationship between the frequency of VOC and the occurrence of these longer-term outcomes, as indicated by additional database analyses presented as part of the company submission, but this could not be demonstrated in SUSTAIN due to the short study duration."	1	This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check. Nevertheless, it does provide more context and its addition to the final assessment report is therefore deemed relevant by the authors.
52	1103	**Text from EUnetHTA assessment:** "Based on the randomised, double-blind, placebo-controlled phase II SUSTAIN trial, crizanlizumab did not reduce the annualised rate of VOCs (primary outcome) compared to placebo, both in addition to best supportive care with or without HU/HC treatment."	1	Although this comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check, we made the conclusion more balanced

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		Novartis comment: This statement as part of the conclusion should provide additional context to accurately reflect the conclusion of the CHMP assessment report. **Proposed amendment:** "Based on the randomised, double-blind, placebo-controlled phase II SUSTAIN trial (pre-planned primary analysis) crizanlizumab reduced statistically significantly and clinically relevantly the annualised rate of VOCs, in a population already receiving best supportive case, with or without HU/HC. In a supplementary conservative post-hoc analysis of the primary endpoint, although statistical significance could not be reached, the treatment effect estimates for the primary and secondary endpoints are systematically in favour of crizanlizumab over placebo. The lack of significance could be explained by the conservative, reference-based imputation for around a third of patients who discontinue before the end of the trial. Considering the totality of evidence, efficacy has been established."		by showing the findings of both the pre-specified analyses and the sensitivity analyses.
52	1103	**Text from EUnetHTA assessment:** "No data on mortality was available." **Novartis comment:** This statement as part of the conclusion should provide additional context in line with the company submission. **Proposed amendment:** "Due to the duration of the trial, differences in long-term outcomes, such as mortality, or relatively uncommon complications such as ACS, could not be detected. However, supplementary long-term evidence for the association between VOC rates and mortality as well as other complications was available from additional database analyses and has been presented as part of the submission."	1	This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check. Nevertheless, we did incorporate the first sentence of the proposed amendment as it provides more context and is deemed relevant by the authors.

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68	Appendix 5	**Text from EUnetHTA assessment:** Safety Pool Analysis including SOLACE-adults **Novartis comment:** Footnotes for the definition of asterisk-based annotations in the table are missing.	2	This comment is considered a fact check. The footnotes are added to the table in Appendix 5.
68	Appendix 5	**Text from EUnetHTA assessment:** Exposure (SOLACE – A2202): 64.7 weeks **Novartis comment:** As safety data from SOLACE-adults for 35.4 weeks (in line with the CTD) are presented in the table, the stated exposure should be aligned accordingly. **Proposed amendment:** Exposure (SOLACE – A2202): 35.4 weeks	2	This comment is considered a fact check. Since the proposed amendment is verified against the EPAR and deemed correct, the text is updated in the final assessment report.
68	Appendix 5	**Text from EUnetHTA assessment:** ADRs by System Organ Class **Novartis comment:** The mention of ADRs should be removed from this table, as it is not clear where these data have been obtained from.	1	This comment is considered a fact check. ADRs should be AEs and is changed accordingly in the final assessment report.
71 onward	All research questions	**Text from EUnetHTA assessment:** Ongoing studies – STAND trial (A2301; NCT03814746): started July 2019; estimated completion December 2027. **Novartis comment:** Novartis would request that the planned date for primary analysis results from A2301 is included (across the entire table), in line with the CHMP assessment report. **Proposed amendment:**	1	This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check. Nevertheless, the authors agree with the addition of the planned date for primary analyses, as this is in line with the EPAR.

Page	Line	Comment	Character of comment	Reply from author
		Ongoing studies – STAND trial (A2301; NCT03814746): started July 2019; planned results of primary analysis in December 2025.		