National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C [ID731]

ERG response to AbbVie factual inaccuracies check

24th March 2015

You are asked to check the ERG report from Southampton Health Technology Assessments Centre (SHTAC), University of Southampton to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **16th March 2015** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Suggestion that 3D HCV GT1 programme based on observational data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 14, 15 and 30, the ERG report refers to the 3D HCV clinical trial programme as "*essentially observational studies (i.e. individual trial arms, rather than randomised comparisons) and subgroup analyses within trials arms*." Whilst AbbVie can understand why the ERG might state this, the fact is that the 3D HCV GT1 clinical trial programme comprised large, well-conducted randomised controlled trials in over 2,000 HCV patients, not observational studies. The reason for the historical comparison was due to the paradigm shift in treatment to a completely interferon-free regimen, and was agreed by EMA and the US FDA. Further, the same historical trial design has also been employed by other interferon free regimens in this disease area. On page 15 the ERG states, "*Overall the ERG considers that the SVR12 outcomes may be subject to bias due to the data essentially being observational data*,"	AbbVie proposes the wording is amended from: *"…the SVR12 estimates are mainly derived from what are essentially observational studies (i.e. individual trial arms, rather than randomised comparisons) and subgroup analyses within trials arms."* to the following: ***"… although the SVR12 estimates are derived from RCTs, there are limitations with the data i.e. individual trial arms are used, rather than randomised comparisons, and subgroup analyses within trials arms.*** *And from:* "*Overall the ERG considers that the SVR12 outcomes may be subject to bias due to the data essentially being observational data*," to the following: ***Overall the ERG considers that the SVR12 outcomes could be subject to bias because of the limitations with the RCTs in terms of trial design"***	The implication from the ERG is that the clinical trial programme is made up of observational studies, which are perceived to be less robust then RCTs. This is factually inaccurate and implies the SVR12 results are uncertain. Given that the SVR12 results were repeatedly and consistently circa 97%, with tight confidence intervals, across a broad spectrum of over 2,000 HCV GT1 patients suggest that the SVR12 results are robust. This is further supported by the results of a head-to-head RCT of 3D vs. telaprevir provided to the ERG during clarification questions (MALACHITE I and II).	The ERG acknowledges that use of the phrase "observational studies" in the ERG report may imply to the reader that the data were derived from observational studies rather than RCTs. Therefore the ERG has changed this to read "observational data" instead on p. 14 and additionally on p. 133 where we have also used the phrase "observational studies". The ERG already uses the phrase "observational data" on p. 15 and on p. 30. The ERG has not otherwise changed the text to that suggested by the company, as both the ERG's original text and the company's suggested changes make the same point.

Issue 2 Suggestion of bias in 3D SVR12 rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 15 of the ERG report it states *"There were higher proportions of patients with mild fibrosis (e.g. fibrosis scores of F0 and F1) in the 3D studies than the historical comparator telaprevir studies, which may have biased the SVR estimates in favour of 3D."* Results from head-to-head RCTs of 3D vs. telaprevir (MALACHITE I and II), which only became available end December 2014, replicated the superior SVR12 results of 3D vs the historical telaprevir controls discussed in the submission. Therefore, is it likely that the results from the RCTs do not bias the estimates in favour of 3D as the ERG states.	None - just a point to note that the ERG's statement isn't really justified based on the available data.	N/A.	No change requested.

Issue 3 Suggestion of limited data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 15 of the ERG report it states, *"There were limited data available in the submission about SVR12 outcomes and other outcomes for the subgroups of patients specified to be of interest in the scope and decision problem: those with cirrhosis, HIV co-infection and patients who are post-liver transplant. In particular, no studies were identified that had been conducted in patients with HCV GT4 who had cirrhosis, who would be treated with 2D + RBV for 24 weeks, according to the licensed indication. Therefore, no data for this licensed indication are available."* First and foremost, the data for cirrhotics are not limited. AbbVie is the first company to conduct a trial entirely in HCV GT1 cirrhotic patients (n=390). In comparison, data for comparator regimens in cirrhosis are limited e.g. boceprevir in tx naïve patients n=13 or for telaprevir n=93 combining patient numbers from both ADVANCE (n=21) and REALIZE (n=72).	AbbVie considers that this statement should be removed entirely. Or at the very least any reference to cirrhosis should be removed, given that the HIV co-infection and post-transplant data are derived from interim analyses - this could constitute "limited data".	The ERG is stating that the data for 3D in cirrhotics are limited. This implies that the SVR data in cirrhotics are based on a small sample size, and there is therefore greater uncertainty in the SVR12 data as a result. AbbVie believes this statement is unjustified, particularly when the sample size in TURQUOISE-II (the 3D cirrhosis trial) far exceeds the sample size for any of the comparator regimens.	The ERG has not changed the original text in the ERG report about these limited data, as the ERG's opinion is that the SVR estimates provided in the CS as based on small sample sizes for these subgroups (as we explain in the next paragraphs in this response). Instead, we have clarified the nature of the data (e.g. whether it was from an interim or subgroup analysis) and sample sizes in the text on p. 15 to make it clear why we consider the data limited. While the TURQUOISE II TRIAL of people with GT1 HCV and compensated cirrhosis included 380 patients, the ERG notes that (as is shown in the ERG report on p. 33) only subgroup analyses from this trial provide data that is relevant to the licensed indications for patients with HCV GT1a and GT1b. Therefore, data from a total of 189 patients are available to inform SVR rates for the licensed indications (for the

In relation to GT4 and cirrhosis, AbbVie deliberately modelled tx naïve and tx experienced patients excluding cirrhosis because there aren't any data. We have not made any claim for the cost-effectiveness of 2D in this patient group. With regards to HIV co-infection we provided data for n=63 (more than some comparator regimens have in cirrhotic patients) and for post-transplant we provided interim data for n=34 patients.			GT1a licensed indication the n = 121, and for the GT1b licenced indication the n = 68). The ERG believes that the data for patients with cirrhosis is also limited as none is available for patients with HCV GT4 with cirrhosis. The ERG also considers the available sample sizes for people with HIV co-infection (n = 63) and people who are post-transplant (n = 34) to also be small and thus the data are limited.

Issue 4 IFN eligibility status

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 15 and 24 of the ERG report it states, "*No efficacy data for people who are intolerant to or ineligible for interferon treatment were presented, which meant no efficacy data for this subgroup were available to inform the economic model. Instead, the company used the same efficacy data as for IFN-eligible patients for this subgroup in the model, but did not provide a justification for*	Wording could be amended to the following: ***"No efficacy data for people who are intolerant to or ineligible for interferon treatment were presented, which meant no efficacy data for this subgroup were available to inform the economic model. This is because 3D and 2D are IFN-free regimens and there was therefore no need to stratify patients at baseline in the trials by their interferon eligibility status. Instead, the company used the same efficacy data as for IFN-eligible patients for this subgroup in the***	To reflect the fact that 3D is an IFN-free regimen and it was not a requirement of our trials designs, rather than an implication that we did not have any data.	The ERG acknowledges and understands that it would not be a requirement of the trials to stratify patients at baseline by their interferon status. However, it is possible that interferon ineligible patients could differ to those who are interferon eligible in a way that may affect outcomes. Given that there are no data in the CS for this group, this possibility in

why this was considered appropriate." As discussed at the decision problem meeting, this is not a sub-group analysis AbbVie considered to be relevant to 3D or 2D, but was included as part of the scope based primarily on previous appraisals of other regimens that have an option to have co-administered interferon e.g. 12 weeks sofosbuvir + PegIFN/RBV vs. 24 weeks sofosbuvir + RBV; or 12 weeks simeprevir + PegIFN/RBV vs. 12 weeks simeprevir + sofosbuvir. AbbVie's regimens are entirely interferon-free and there was therefore no need to stratify patients at baseline in the trials by their interferon eligibility status. One could further argue that null responders, a sub-group of patients AbbVie ensured were well represented in its trials, would equate to the IFN ineligible or intolerant group. SVR12 rates for 3D in null responders were 96.65% (115/119). (Table 58 of the CS)	***model, but did not provide a justification for why this was considered appropriate."***		relation to the 3D and 2D regimens remains unknown. The ERG therefore has not changed the original text.

Issue 5 Suggestion of limited data in cirrhosis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 24 of the ERG report it states, "*There are also limited data available on SVR rates for patients with cirrhosis, as the majority of the trials excluded patients with cirrhosis. Only one completed study (TURQUOISE II) focussed solely on patients with cirrhosis, and one ongoing study (of patients co-infected with HIV; TURQUOISE I) included patients with (n = 6) and without cirrhosis (n = 25) and provided subgroup analyses of SVR by cirrhosis status.*" As mentioned in Issue 3 above, this is incorrect. The data in cirrhosis are not limited. AbbVie questions why the sample size for TURQUOISE-II isn't included but the sample sizes for TURQUOISE-I are? AbbVie is the first company to conduct a trial entirely in HCV GT1 cirrhotic patients (n=390) – not a small number of patients. In comparison, data for comparator regimens in cirrhosis are limited e.g. boceprevir in Tx naïve patients n=13 or for telaprevir n=93 combining patient numbers	Remove statement.	The ERG is stating that the data for 3D in cirrhotics are limited. This implies that the SVR data in cirrhotics are based on a small sample size, and there is therefore greater uncertainty in the SVR12 data as a result. This isn't fair, particularly when the sample size in TURQUOISE-II (the 3D cirrhosis trial) far exceeds the sample size for any of the comparator regimens.	The ERG believes that the data for patients with cirrhosis are limited for the regimens in line with the licensed indications in the TURQUOISE-II trial, due to small sample sizes of the subgroup analyses providing data for these patients with cirrhosis treated with the licensed regimens (please see our response to Issue 3 above). The ERG has not removed the statement, as suggested by the company, but has instead clarified that subgroup analyses provided data for these patients for the licenced regimens, and clarified the sample sizes in the text on p. 24, to make it clear why we consider the data limited. The ERG has amended the text as follows: "*Only one completed study (TURQUOISE II[17]) focussed solely on patients with cirrhosis. This RCT included 380 people with GT1 HCV and compensated cirrhosis; however, only subgroup analyses provided data that is*

from both ADVANCE (n=21) and REALIZE (n=72).			*relevant to the licensed indications for patients with HCV GT1a and GT1b. Therefore, data from a total of 189 patients are available to inform the SVR rates for the licensed indications: for the licensed indication for patients with HCV GT1a and compensated cirrhosis the n = 121, and for the licensed indication for patients with HCV GT1b and compensated cirrhosis the n = 68."*

Issue 6 Feasibility of NMA for comparator regimens

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 47 of the ERG report it states, *"In terms of populating the economic model, the ERG considers that the company could have done an NMA for the comparators, even if an NMA for the 3D and 2D regimes was not possible"* As reiterated in the company clarification questions, AbbVie does not consider that a robust NMA could have been done for the comparators unless treatment specific covariate adjustments could be applied to	Unless treatment specific covariate adjustment can be undertaken, an NMA for the comparator regimens should be interpreted with caution.	To illustrate why AbbVie considers a robust NMA cannot be performed in HCV GT1, we have calculated the SVR rates from the odds ratios the ERG used in their mini MTC for F4 patients (cirrhosis) for the comparators, and compared those to the actual SVR rates reported in the HCV GT1 treatment naive trials for those comparators: **Actual SVRs in F4's from RCTs** / **SVRs predicted from ERG MTC** SMV: 60.4% / 70.7% TVR: 61.9% / 65.4%	Response noted, but not a factual error. No change made to the text It is a matter of opinion whether it may be better to use data from external sources (subject to uncertainty and other caveats) or to provide no cost effectiveness estimates for comparators included in the NICE scope.

the different comparators to account for the different proportions of baseline characteristics across the trials.		BOC 31.3% 63.9% As anticipated, using ORs to predict SVRs without properly adjusting for differences overestimates the effect of the comparator regimens in cirrhotics.	

Issue 7 Telaprevir not licensed in GT4 patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 64 of the ERG report it states, "*In contrast to the phase III trials in HCV GT1 participants there was no planned historical comparison with telaprevir in the PEARL I study.*" AbbVie would like to clarify that this is because telaprevir is not licensed for HCV GT4.	None.	N/A	No change required.

Issue 8 Incorrect percentage of GT1a patients in Malachite I trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 72 and 74 of the report in discussion about the MALACHITE-II baseline characteristics, the ERG states, [redacted]	Amend percentage in text.	Incorrect percentage of patients.	Yes, the company is correct, this should be [redacted]. The ERG has now amended this on p. 72 and p. 73. (NB this relates to pages 73 and 74 and not page 72.)

[redacted]			

Issue 9 Company's review of published economic evaluations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states: *"The objectives for the review (Table 67 on pages 224 to 225 of the CS) list the included comparators as telaprevir+PegIFN+RBV and boceprevir+PegIFN+RBV and make no reference to sofosbuvir, simeprevir or PegIFN+RBV dual therapy."*	The wording should be revised to read as: *"The objectives for the review (Table 67 on pages 224 to 225 of the CS) list the included comparators as telaprevir+PegIFN+RBV, boceprevir+PegIFN+RBV and* ***PegIFN+RBV dual therapy*** *and make no reference to sofosbuvir or simeprevir".*	This wording needs amending as dual therapy with PegIFN+RBV is mentioned in Table 67 of the CS under the Interventions and comparators considered in the review.	Accepted - the ERG has amended the text on page 80

Issue 10 Patient Group and choice of subgroup analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84 of the ERG report states that: *"It is not clear whether the decision to sub-divide genotype-1 is driven by evidence of significant differences in efficacy or disease progression, or*	Although differences in efficacy of 3D have been observed between subgenotypes 1a and 1b, these differences are not significant. In addition, AbbVie does not agree that there is any evidence of significant differences in disease progression between subgenotypes 1a and 1b, nor it indicates this in the submission. It is therefore unclear as to	In the NICE final scope, under section "Other considerations" it is stated that "If evidence allows the following **subgroups** will be considered": 1. Genotype	Noted, but not a factual error. No change made to the text

primarily due to difference in treatment combination (3D alone for GT1b and 3D+RBV GT1a non-cirrhotic patients and for cirrhotic patients in both subgroups) and duration (24 weeks for GT1a cirrhotic patients versus 12 weeks for all others) for the intervention."	why the ERG arrived to this opinion. In section 7.9.1 of the CS, it was highlighted that in order to maximise treatment outcomes of patients treated with AbbVie's Regimen, sub-genotyping will have to be performed as this would ensure that patients are matched to appropriate combinations of DAAs indicated to treat either GT1a or GT1b. In addition, NICE final scope for ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C requested the analysis to be presented by sub-genotype (see justification in the right hand column). <u>AbbVie therefore proposes that the wording of the paragraph outlined in the left hand column is revised to read:</u> *"It is not clear whether the decision to sub-divide genotype-1* ***may be*** *driven by evidence of differences in efficacy or disease progression,* ***however it is more likely that this decision was*** *primarily* ***made*** *due to difference in treatment combination (3D alone for GT1b and 3D+RBV GT1a non-cirrhotic patients and for cirrhotic patients in both subgroups) and duration (24 weeks for GT1a cirrhotic patients versus 12 weeks for all others) for the intervention."*	AbbVie has interpreted this as a request to provide the analysis on genotype subgroups and has in turn presented data for sub-genotypes 1a and 1b.	

Issue 11 Intervention and comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 87, ERG report states: *"For GT1 IFN-eligible patients, included*	<u>This paragraph should be amended to read as</u>: *:"For GT1 IFN-eligible patients, included*	In GT1, treatment naïve patients, a comparison to sofosbuvir +	Accepted - the ERG has amended the text on page

comparators are telaprevir+PegIFN+RBV, boceprevir+PegIFN+RBV and PegIFN+RBV and are modelled in line with their respective marketing authorisations."	*comparators are* ***sofosbuvir+PegIFN+RBV****, telaprevir+PegIFN+RBV, boceprevir+PegIFN+RBV and PegIFN+RBV and are modelled in line with their respective marketing authorisations."*	PegIFN+RBV was included. Please refer to page 256 of the CS.	87
On Page 87 ERG report states: *"The CS states (in section 2.7 page 45) that boceprevir+PegIFN+RBV and PegIFN+RBV are not widely used for HCV GT1 in current UK clinical practice. The implication (though not explicitly stated in the CS) of the statement (that boceprevir+PegIFN+RBV and PegIFN+RBV are not widely used for HCV GT1 in current UK clinical practice) is that telaprevir+PegIFN+RBV would be the current standard of care for the majority of protease inhibitor-tolerant GT1 HCV patients receiving anti-viral treatment in the UK. The ERG clinical advisors agree that PegIFN+RBV dual therapy would not be used in GT1 patients unless there was a reason not to include a protease inhibitor in the treatment regimen. However the ERG clinical advisors suggest that boceprevir would be used as frequently as telaprevir in GT1 patients."*	It is factually incorrect that boceprevir+PegIFN+RBV regimen is used as frequently as telaprevir+PegIFN+RBV in clinical practice in England. Based on the analysis conducted by the IMS on the real world prescribing of the first generation protease inhibitors in the NHS England, it is well known that far greater proportion of patients are being prescribed telaprevir-based regimen compared to boceprevir. In addition to the clinical expert opinion received with regard to the standard of care for the majority of protease inhibitor-tolerant GT1 HCV patients in England (referred to in section 7.3.5 in the CS), this analysis is the basis for AbbVie's statement that boceprevir+PegIFN+RBV and PegIFN+RBV dual therapy are not widely used for HCV GT1 in current UK clinical practice. <u>The proposed change to the wording is as follows:</u> *"The CS states (in section 2.7 page 45) that boceprevir+PegIFN+RBV and PegIFN+RBV are not widely used for HCV GT1 in current UK clinical practice. The implication (though not explicitly stated in the CS) of the statement (that boceprevir+PegIFN+RBV and PegIFN+RBV are not widely used for HCV GT1 in current UK*	Analysis of hospital prescribing data by the IMS (real world evidence on treatment pathways in England) has shown that the majority of protease inhibitors-tolerant GT1 HCV patients are treated with telaprevir based regimen compared to boceprevir based regimen.	Noted. It appears that the clinical experts we approached disagree with those approached by the company. However we have correctly stated the opinion of the experts we approached.

	clinical practice) is that telaprevir+PegIFN+RBV would be the current standard of care for the majority of protease inhibitor-tolerant GT1 HCV patients receiving anti-viral treatment in the UK. The ERG clinical advisors agree that PegIFN+RBV dual therapy would not be used in GT1 patients unless there was a reason not to include a protease inhibitor in the treatment regimen. The ERG clinical advisors suggest that boceprevir would be used as frequently as telaprevir in GT1 patients. ***However the advice received by AbbVie's clinical advisors and the IMS prescribing data seem to reflect that boceprevir+PegIFN+RBV and PegIFN+RBV are not as widely used to treat protease inhibitor-tolerant GT1 HCV patients compared to telaprevir+PegIFN+RBV."***		

Issue 12 Clinical effectiveness and SVR rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 91 of the ERG report states: *"As stated in the CS, the same level of information (number of trial participants and number experiencing SVR) is not reported for the Q80K negative population in the simeprevir trials, as is reported for other included comparators. However the mixed treatment comparison (MTC) outputs for the Q80K negative population are available in the*	Whilst AbbVie agrees with the ERG that the most appropriate way to derive estimates of relative effectiveness for comparator regimens would have been via a network of evidence, AbbVie wishes to reiterate issues associated with the MTC conducted by Janssen (see section X page X of CS) and also highlighted in the ERG report prepared by SHTAC during simeprevir's appraisal (page 36 within the ERG report of the simeprevir submission) with regards to the same MTC that was now used by SHTAC in the assessment of AbbVie's regimens (Table 35 in	Whilst the MTC would have been considered ideal to derive estimates of relative effectiveness to ensure consistency in the evidence base for comparator regimens, the limitation of the MTC conducted by Janssen in the appraisal of simeprevir, raised by the ERG and supported in full by AbbVie (highlighted in the middle column) was the primary reason as to why AbbVie did not use it to this	Response noted, but not a factual error. No change made to the text As noted previously, it is a matter of opinion whether it is appropriate to use data from external sources (subject to uncertainty and other caveats) or to provide no cost effectiveness estimates for comparators included in the

simeprevir CS Table 30 (page 83) and Table 85 (page 145). The MTC results report odds ratios, with 95% credible intervals, for three treatment regimens (telaprevir, boceprevir and simeprevir each in combination with PegIFN+RBV) compared with PegIFN+RBV. The ERG has estimated fibrosis-stage precific SVRs for simeprevir using the PegIFN+RBV SVRs from ADVANCE RCT (which are used in the CS model) and the odds ratio for simeprevir relative to PegIFN+RBV (4.83) reported in the CS for simeprevir (see Table 35)."	the ERG report of AbbVie's submission) to estimate SVR rates for comparator regimens. In the appraisal of simeprevir, the ERG commented that *"Some differences in baseline characteristics of the included trials (MS Table 20 p. 68-69 and MS Table 21 p.70) can be observed. In particular for both the treatment-naïve patient trials and the treatment-experienced trials* ***variability was observed in the proportion of HCV genotype 1a patients*** *(range 38% to 67% and 35% top 62% respectively),* ***Black patients*** *(range 1% to 27% and 2% to 15% respectively)* ***and Metavir 4 score*** *(range 0 to 13% and 10% to 27%)…****Meta-regression could have been undertaken to determine what effect the variations in the baseline characteristics noted above would have on the results.****"* The ERG further summarises the key caveats to the MTC as follows: • *The low number of trials available to inform the network of evidence with the majority of connections informed by only one trial;* • *The MTC for treatment-experienced patients considered all treatment-experienced participants together: prior relapsers, null and partial responders, and SVR is likely to differ in these subgroups;* • *Variations in some patient characteristics that were not further investigated e.g. by*	purpose. In addition, it is important to point out that simeprevir CS used different definitions of mild and moderate fibrosis compared to other CSs, namely patients with mild fibrosis were defined as having Metavir score of F0-F2 whilst patients with moderate fibrosis as having Metavir score of F3. In other CSs (including AbbVie's), mild fibrosis was defined as having Metavir score of F0-F1 whereas moderate fibrosis as having Metavir score F2-F3. Therefore further caution has to be applied when interpreting results of the MTC given that these definitions vary.	NICE scope.

	meta-regression; • *The exclusion of patients with HCV genotype 1a who were Q80K positive from simeprevir arms for the analysis of SVR breaks randomisation, but this is in line with treatment recommendations in the SPC"* <u>Proposed amendment to the highlighted paragraph in the left hand column:</u> *"As stated in the CS, the same level of information (number of trial participants and number experiencing SVR) is not reported for the Q80K negative population in the simeprevir trials, as is reported for other included comparators.* ***The ERG agrees that the company's rationale for excluding these comparators is reasonable.*** *However the mixed treatment comparison (MTC) outputs for the Q80K negative population are available in the simeprevir CS Table 30 (page 83) and Table 85 (page 145). The MTC results report odds ratios, with 95% credible intervals, for three treatment regimens (telaprevir, boceprevir and simeprevir each in combination with PegIFN+RBV) compared with PegIFN+RBV. The ERG has estimated fibrosis-stage specific SVRs for simeprevir using the PegIFN+RBV SVRs from ADVANCE RCT (which are used in the CS model) and the odds ratio for simeprevir relative to PegIFN+RBV (4.83) reported in the CS for simeprevir (see Table 35)."* ***Although the ERG used this source to derive estimates of relative effectiveness for simerpevir+PR, telaprfevir+PR and boceprevir+PR, it must be noted that based***		

	on the critique and limitations of this MTC highlighted in the ERG report of simeprevir's appraisal (page 36 within the ERG report of the simeprevir submission) , the MTC results should be interpreted with caution."		
Page 93 of the ERG report states: *"The CS does not state explicitly where the efficacy data for the interferon-ineligible subgroups have been derived from, nor do they discuss the appropriateness of applying a natural history model that was developed and populated for evaluating interferon-containing regimens to an interferon-ineligible population…The ERG feels that this assumptions should have been highlighted in the CS and that some justification is needed to support this assumption."*	It is factually incorrect to state that previously developed natural history models for chronic hepatitis C (one of them also applied in AbbVie's submission) have been specifically developed and populated for evaluating interferon-containing regimens. These models have been developed to evaluate the natural history of chronic hepatitis C without any specific reference to criteria of interferon-suitability or unsuitability. It just so happens that the first regimens that have populated these models have been interferon-containing. AbbVie is further unaware of any literature discussing or suggesting that modelling the natural history of disease for interferon-ineligible patients should be any different to that of interferon-eligible. In addition, AbbVie's approach to modelling of chronic hepatitis C is no different to the approach taken by other manufacturers of IFN-sparing regimens that have already been reviewed and approved by NICE. <u>AbbVie therefore proposes that the highlighted paragraph is reworded into</u>: ***"The CS does not state explicitly where the efficacy data for the interferon-ineligible subgroups have been derived from The ERG feels that these assumptions should have been highlighted in the CS and that some***	Further to the explanation provided in the middle column, natural history model that was originally developed and subsequently adapted by AbbVie and other manufacturers has not been developed specifically for treatment-experienced patients with enrolment criteria distinguishing between IFN-eligible and -ineligible patients. Rather, the same model was used and populated for treatment-naïve patients where it was impossible to specify a-priori patients who were interferon-ineligible (i.e. subsequent null responders). However at no point was the model questioned for its appropriateness in modelling of treatment-naïve cohort. Therefore, AbbVie further challenges factual accuracy of the statement made by the ERG.	Response noted, but not a factual error. No change made to the text The ERG do not state that using the model for interferon ineligible patients is inappropriate, but that the CS should have discussed the appropriateness of the model for this population. Without a clear definition of what makes patients ineligible for interferon it is not clear whether the existing model structure and baseline risks are appropriate for this group of patients.

	justification is needed to support this assumption."		

Issue 13 Treatment duration

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 94 of the Erg report states: *"However the ERG is concerned that these trial-based estimates may not fully capture treatment-futility stopping rules for PegIFN-based treatment regimens or response-guided treatment durations indicated for patients treated with telaprevir and boceprevir. For telaprevir, the approach taken to estimating treatment duration appears not to have taken account of patienst discontinuing study drugs (either telaprevir alone or all treatment) during the first twelve weeks of treatment (referred to as the "telaprevir or placebo phase" for which data are reported by Jacobson and colleagues, but is based on overall discontinuations reported at the end of the trial.* *The publication reporting the SPRINT-2 trial used to populate the model with clinical data for boceprevir reports less*	This is factually incorrect as the proportion of patients who discontinue TPR during the so called "telaprevir" or "placebo" phase has been accounted for in the model. The details of the patients that discontinue during the said phase are available within the 'TPV+PR sheet tab' in the electronic model. The statement concerning the publication of the SPRINT-2 trial is further considered factually incorrect as the trial publication provided sufficient data to model treatment discontinuations. AbbVie would also find it helpful if the ERG provided a recommendation as to any other alternative source which would be deemed a suitable basis for adjustment to modelled treatment duration for boceprevir+PegIFN+RBV treatment. <u>AbbVie therefore wishes the highlighted paragraph be reworded as:</u> ***"However the ERG is concerned that these trial-based estimates may not fully capture treatment-futility stopping rules for PegIFN-based treatment regimens or response-guided treatment durations indicated for patients treated with telaprevir and boceprevir."***	In addition to the explanation provided in the middle column, AbbVie provided a full clarification on treatment continuation and discontinuation rules applied in the model in the manufacturer's response to the ERG clarification questions (see response to the priority question 19). As discussed in the response, AbbVie modelled all regimens as per their phase III trials. As such, any response-guided or futility rules utilised in the trials were also implemented in the calculation of the base case treatment costs. In the absence of efficacy data corresponding to the rules contained in the real life, alternative data to inform efficacy estimates (SVR rates) were not calculable. AbbVie was reluctant to make assumptions on the alternative proportion of patients that would have either achieved rapid viral response or discontinued treatment for futility. As such the model integrated all	Comments noted, but not a factual inaccuracy. Examination of the electronic model indicates that discontinuation for telaprevir is based on figures reported in Figure 1 of the ADVANCE trial publication (Jacobson et al, NEJM 2011;364:2405-2416). These figures (15/210 for T12PR24 and 80/153 for T12PR48 refer to discontinuations of all study treatment at any phase during the planned treatment duration). The ERG noted that the "SAFETY" section of the ADVANCE trial publication provides more information on treatment discontinuations, including the proportion of patients who discontinued telaprevir only (7% in the T12PR group). The ERG checked the

information on discontinuations and would not provide a suitable basis for similar adjustment to modelled treatment duration."		futility and response-guided treatment rules for patients treated with telaprevir and boceprevir regimens as per their registration trials.	SPRINT-2 trial publication (Poordad et al NEJM 2011;364:1195-1206), but could not find similar detail. Hence the statement that there was less information regarding discontinuations in the latter publication.

Issue 14 Adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 96 of the ERG report states: *"The adverse event incidences are drawn from the same sources as the SVRs (see Table 38). The CS is not explicit regarding the grade of included adverse events included in the model."*	AbbVie considers this statement to be factually incorrect as it is explicitly specified in the Tables generated within section 7.3.1 of the CS (for example, please refer to the Table 75 of CS) that only Grade 3-4 neutropenia and thrombocytopenia were modelled. Further, as indicated by the references for the data sources in the CS, incidences of all other treatment-emerging AEs were modelled where they occurred in >5% of patients. Therefore although not explicitly stated, the references for the modelled AEs are clearly stated. <u>The proposed amendment of the language would be</u>: *"The adverse event incidences are drawn from the same sources as the SVRs (see Table 38). The CS is not explicit regarding the grade of included adverse events in the mode* ***except for the neutropenia and thrombocytopenia****."*	Tables specifying AEs included in the model for AbbVie's regimen and all comparator regimens within 7.3.1 of the CS explicitly provide grading of neutropenia and thromboicytopenia. In addition, all Tables include references to the trial sources providing descriptions of AEs.	Accepted - the ERG has amended the text on page 96

Issue 15 Patient Outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 98 of the report states: *"It is not clear whether this end-of-treatment assessment refers to scheduled or actual end-of-treatment – if it is the former, then the on-treatment disutility is likely to be under-estimated as observations would be missing for patients who prematurely discontinued (including those who discontinued due to adverse events)."*	Although unclear to the ERG, the explanation was provided on page 293 of the CS where it was highlighted that subjects who prematurely discontinued the Treatment Period (week 12 or 24 respectively) should have returned to the site to complete the premature D/C visit procedures. Therefore the end-of-treatment assessment refers to the actual rather than the scheduled visit. <u>AbbVie proposes the following amendment to the wording:</u> *"It is not clear whether this end-of-treatment assessment refers to scheduled or actual end-of-treatment – if it is the former, then the on-treatment disutility is likely to be under-estimated as observations would be missing for patients who prematurely discontinued (including those who discontinued due to adverse events).* ***However it is likely to be the latter given the description noted on page 293 of the CS****."*	The justification for the requested amendment is provided on page 293 of the CS.	Response noted, but not a factual error. No change made to the text
Page 99 of the ERG report states: *"The CS does not discuss the reasoning behind estimating different disutilities for each fibrosis stage or genotype sub-*	Although AbbVie did not explicitly discuss the reasoning behind estimating different disutilities for each fibrosis stage or genotype sub-group in the submission document, AbbVie provided full clarification and its rationale as part of the ERG clarification questions.	The response to clarification question 24 details the reasoning behind estimation of disutilities for each fibrosis stage or genotype sub-group.	Response noted. The ERG has amended the text on page 99 to recognise that further detail on reasons for stratifying disutilities by fibrosis stage and

group or appear to consider clinical meaningfulness or statistical plausibility of differences identified."	<u>Proposed amendment to the paragraph wording:</u> *"The CS does not discuss the reasoning behind estimating different disutilities for each fibrosis stage or genotype sub-group in the submission,* ***however it does provide the reasoning in the response to ERG clarification questions.*** *The company also does not appear to consider clinical meaningfulness or statistical plausibility of differences identified,* ***however it must be acknowledged that the studies were not powered to assess such differences."***		genotype subtype was supplied following a request for clarification. No further discussion on plausibility of differences was provided so no change was made in response to the second comment.
Page 99 of the ERG report further discusses that *"Furthermore the CS does not discuss the plausibility of including positive values (i.e. an assumption which appears to apply for a number of the groups that patients are better on-treatment than off it) – for example GT1b patients with mild and moderate fibrosis have positive utility decrements while on-treatment as do GT4 patients with mild and moderate fibrosis."*	Whilst it is true that in some instances disutilities appear to have either a positive or a negative "sign", the difference between them is unlikely to be meaningful as the absolute values do not differ significantly from 0. <u>Proposed amendment to the wording</u>*:* *"Furthermore the CS does not discuss the plausibility of including positive values (i.e. an assumption which appears to apply for a number of the groups that patients are better on-treatment than off it) – for example GT1b patients with mild and moderate fibrosis have positive utility decrements while on-treatment as do GT4 patients with mild and moderate fibrosis.* ***However these findings must be interpreted with caution given the absolute values of the noted changes in utilities between the baseline and end-of-treatment are likely to simply be variance around zero and thus unlikely to be clinically different from one another****."*	In addition to the justification for amendment provided in the middle column, AbbVie wishes to state that given 3D and 2D are IFN-free therapies with much improved side-effect profiles, the probability that these regimens would cause a "true" decrement in patients' quality-of-life whilst on therapy is low.	Response noted, but not a factual error. No change made to the text

Issue 16 Resource use

Description of problem	Description of proposed amendment	Justification for amendment	
Page 100 of the ERG report states: *"The CS does not explicitly state assumptions over dosing, frequency, or location of treatments that underlie the acquisition costs of the intervention or comparators."*	This statement is not entirely factually correct as the assumptions surrounding AbbVie's regimens dosing and frequency of treatment are provided within section 1 of the CS. The proposed amendment to the wording: ***"The CS does not explicitly state assumptions over dosing, frequency, or location of treatments that underlie the acquisition costs of the comparators."***	Please refer to Table 21 of the CS for details on AbbVie's assumptions over dosing, dosing frequency and the cost per treatment course (12 or 24 weeks) for both 3D and 2D.	Response noted, but not a factual error. No change made to the text The ERG chose to use the word "explicit" to make clear that the CS does not directly state basis of the acquisition costs applied in the model.
Page 101 of the ERG report state: *"It is particularly unclear regarding the dosage of RBV included in any treatment regimen (including 3D and 2D regimens where appropriate)."*	Whilst the ERG is right in that the dose of RBV assumed for either AbbVie's regimens or the comparators wasn't specifically discussed in the text of the CS document, these assumptions are reported in Table 118 of the CS. Proposed amendment to the text: *"It is particularly unclear regarding the dosage of RBV included in any treatment regimen (including 3D and 2D regimens where appropriate),* ***however cost per dose and cost per day have been presented in Table 118 of the CS****."*	Very few economic evaluations explicitly cite average patient weight in cost calculations of RBV. In CS, AbbVie assumed an average daily dose of 1000mg of RBV will be consumed on an average body weight of 66Kg to 80Kg. It is further stated in CS (page 375) that given more than one Ribavirin was available in the UK, market share estimates of Copegus and Rebetol were based on UK budget impact analysis by Thorlund et al., 2012.	Response noted, but not a factual error. No change made to the text

Issue 17 Costs

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 104, Table 41 'Cost per week of component treatments of intervention and comparators' in the ERG report states:
<table>
<tr><th></th><th>Cost per pack (£)</th><th>Quantity / pack</th><th>Unit dose</th><th>Frequency</th></tr>
<tr><td>2D (Viekirax)</td><td>10,733.33</td><td>56</td><td>125/75/50mg</td><td>2 per day</td></tr>
<tr><td>3D (Exviera)</td><td>933.33</td><td>56</td><td>250 mg</td><td>2 per day</td></tr>
</table>
</td>
<td><u>Proposed amendment to the first and 5th column in the Table 41:</u>
<table>
<tr><th></th><th>Frequency</th></tr>
<tr><td>2D (Viekirax)</td><td>2 tablets once daily</td></tr>
<tr><td>Exviera</td><td>1 tablet twice daily</td></tr>
</table>
</td>
<td>Please note that 3D is composed of Viekirax (2D) + Exviera. Viekirax (2D) is taken once per day whereas Exviera is taken twice per day.</td>
<td>Noted, but this change would not materially change the estimated treatment cost. No change made to the text</td>
</tr>
<tr>
<td>Page 105, Table 42 'Drug acquisition costs' in the ERG report assumes the following costs for Ribavirin:
<table>
<tr><th></th><th>Genotype</th><th>Fibrosis stage</th><th>Tx naïve/ experienced</th><th>Treatment duration (weeks)</th><th>Ombitasvir/ paritaprevir/ ritonavir</th><th>Dasabuvir</th><th>Ribavirin (1200mg/day)</th></tr>
<tr><td>3D+RBV</td><td>GT1a</td><td>Non-cirrhotic</td><td>either</td><td>12</td><td>32,199.99</td><td>2,799.99</td><td>964.14</td></tr>
</table>
</td>
<td>Very few economic evaluations explicitly cite average patient weight in cost calculations of Ribavirin and therefore AbbVie assumed a daily dose of 1000mg based on an average body weight of 66Kg to 80Kg.

Therefore the <u>cost of Ribavirin should be amended to read as</u>:

"Ribavirin (1000mg/day)</td>
<td>In addition to the Table 118 in the CS detailing cost per dose and cost per day for Ribavirin, a detailed breakdown of Ribavirin cost is available in the electronic model for the ERG to access and</td>
<td>Accepted - the ERG has amended Table 42 page 105</td>
</tr>
</table>

	£888.72 This cost is for 12 week regimens requiring RBV. The cost for 24 weeks should be amended accordingly.	review.	

Issue 18 Assessment of uncertainty

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 108 of the ERG report states: *"The parameters of 49 one-way sensitivity analyses, which are common to all comparisons are presented in table 128 (page 397 to 398) of the CS."*	Proposed text amendment: *"The parameters of 49 one-way sensitivity analyses, which are common to all comparisons are presented in table 128 (page **394 to 395**) of the CS."*	N/A	Accepted - the ERG has amended the text on page 108

Issue 19 Scenario Analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 109 of the ERG report states: *"The scenario analyses are presented as tabulations (up to four tables for each scenario, resulting in a total of 39 tables) with no accompany narrative or*	This statement is not entirely factually correct as AbbVie presented a narrative for some scenario analyses such as scenarios concerning baseline patient characteristics, indirect costs, alternative transition probabilities based on Grishchenko et al (2009), alternative efficacy for PR and alternative health state utilities.	Please refer to pages 389 to 393 of the CS for more information.	Response noted, but not a factual error as the narrative referred to on pages 389 to 393 of the CS describes the methodology and input data for the scenario analysis and not the results. The ERG have amended the

discussion."	AbbVie therefore proposes the following amendment to the text: *"The scenario analyses are presented as tabulations (up to four tables for each scenario, resulting in a total of 39 tables) with* ***a limited*** *narrative or discussion."*		text on page 109 to clarify this as follows: "The scenario analyses are presented as tabulations (up to four tables for each scenario, resulting in a total of 39 tables) with no **accompanying** narrative or discussion **of the results**."

Issue 20 Threshold analysis on effectiveness of 3D and 2D

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 127 of the ERG report states: *"When effectiveness of 3D is reduced to 92.5%, sofosbuvir+PegINF+RBV is no longer excluded by extended dominance leading to more marked increases in the ICER for 3D…"*	Whilst AbbVie appreciates that the ERG ran threshold analysis on the effectiveness of 3D and 2D, AbbVie wishes to highlight that a scenario where the SVR rate for 3D would actually drop to 92.5% in GT1, treatment-naïve non-cirrhotic patients (as detailed in Table 59 of the ERG report, p.126) is highly implausible. This is supported by the tight 95% confidence interval observed for 611/631 GT1, non-cirrhotic, Tx-naïve patients achieving SVR across AbbVie's trials (**95%CI 95.16 to 97.94**). Proposed amendment of the wording: "*When effectiveness of 3D is reduced to 92.5%, sofosbuvir+PegINF+RBV is no longer excluded by extended dominance leading to*	**Treatment** / **3D +/- RBV** / **Source** **GT1 naïve, no cirrhosis (F0-F3)** / 611/631 **(96.8)** / • GT1a Tx naïve patients from SAPPHIRE-I receiving 3D + RBV (n=322) • GT1a Tx naïve patients from PEARL-IV receiving 3D + RBV	Response noted, but not a factual error. No change made to the text

	*more marked increases in the ICER for 3D…**The probability of such scenario occurring is very low**."*			(n=100) • GT1b Tx naïve patients from PEARL-III receiving 3D (n=209)	