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Single Technology Appraisal (STA)

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

Section A: Clarification on effectiveness data

Literature searching

1. **(Priority question) Please provide details regarding the identification and selection of studies of telaprevir, used as the historical comparisons for 3D/2D regimens (for example search criteria, screening methods, and a flow chart explaining reasons for excluded studies).**

Having contacted our global development team who designed our phase III studies, AbbVie can confirm that data from similar subpopulations in the phase III telaprevir trials discussed in detail in the US prescribing information (USPI) and the EPAR from EMA were used to derive the thresholds for the various subpopulations studied in the six AbbVie Phase III studies. Meta-analytic methods were used only to combine the rates in a properly weighted method when the same subpopulations were enrolled in multiple telaprevir trails. The clinical development team obtained agreement on using these SVR thresholds to show non-inferiority and superiority in consultation with both the US FDA and CHMP. There was no intention to conduct a formal meta- analysis including systematic literature review to identify the studies used to estimate the telaprevir SVR rates used as the historical controls in our phase III trials.

In this way, AbbVie was able to power its phase III program to detect non-inferiority and subsequent superiority vs. the SVR data for telaprevir matched at the aggregate level by cirrhosis/non-cirrhosis status, previous treatment experience and sub-genotype. For example, please see the following excerpt from Table 26, page 72 of AbbVie's evidence submission for the calculation of the telaprevir SVR data and the subsequent powering of the two SAPPHIRE studies (Table 1 below):

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Table 1: Calculation of historical telaprevir SVR data to power study number for the SAPPHIRE trials

<table>
<tr><th>SAPPHIRE-I</th><th>SAPPHIRE-II</th></tr>
<tr>
<td>The primary efficacy analyses assessed non-inferiority and superiority with respect to the rate of sustained virologic response at post-treatment week 12 associated with 3D + RBV by comparing it with a calculated historical control rate of 78% (95% confidence interval [CI], 75 to 80). This control rate was based on response rates among previously untreated patients without cirrhosis who received telaprevir and PegIFN/RBV – i.e. a similar patient population to SAPPHIRE-I (Feld et al supplementary appendix):

SVR Rates for Telaprevir-Based Therapy in Treatment-Naïve Subjects

<table>
<tr><th></th><th>ADVANCE</th><th>ILLUMINATE</th><th>Meta Analysis</th></tr>
<tr><th>Telaprevir Studies</th><th>T12/PR n/N (%)</th><th>T12/PR n/N (%)</th><th>T12/PR % [95% CI]</th></tr>
<tr><td>Treatment-naïve subjects without cirrhosis[1]</td><td>270/342 (79)</td><td>367/479 (77)</td><td>78 [75, 80]</td></tr>
<tr><td>Treatment-naïve GT1a subjects</td><td>162/217 (75)</td><td>273/388 (70)</td><td>72 [68, 75]</td></tr>
<tr><td>Treatment-naïve GT1b subjects</td><td>119/142 (84)</td><td>112/149 (75)</td><td>80 [75, 84]</td></tr>
</table>

GT1a = genotype 1a; GT1b = genotype 1b

To establish that the rate of SVR at post-treatment week 12 associated with the active regimen was non-inferior to the historical control rate, the lower boundary of the 95% confidence interval for the rate of SVR at post-treatment week 12 in group A had to exceed the upper boundary of the 95% confidence interval for the control rate minus 10.5 percentage points (70%). To establish that the rate of sustained virologic response at post-treatment week 12 associated</td>
<td>The primary efficacy analyses assessed the non-inferiority and superiority of the rate of sustained virologic response at post-treatment week 12 with 3D + RBV as compared with a calculated historical control rate of 65% (95% confidence interval [CI], 60 to 70). This control rate was based on response rates among patients with HCV genotype 1 infection and no cirrhosis who had previously been treated with PegIFN/RBV and who received retreatment with telaprevir and PegIFN/RBV – i.e. a similar patient population to SAPPHIRE-II. The control rate was weighted for the proportions of patients with a prior relapse, partial response, or null response that were expected in SAPPHIRE-II (Zeuzem et al supplementary appendix):

Estimated SVR Rates for Telaprevir-Based Therapy in Treatment-Experienced, Without Cirrhosis

<table>
<tr><th></th><th colspan="3">REALIZE[a]</th></tr>
<tr><th></th><th>All T12/P48[b] n/N (%)</th><th>Projected Enrollment in Study M13-098 (%)</th><th>Population-Based Weighted Average % [95% CI]</th></tr>
<tr><td>Prior relapsers</td><td>198/229 (86)</td><td>30</td><td>65 [60, 70]</td></tr>
<tr><td>Prior partial responders</td><td>46/65 (71)</td><td>35</td><td></td></tr>
<tr><td>Prior null responders</td><td>40/97 (41)</td><td>35</td><td></td></tr>
</table>

To establish that the rate of sustained virologic response with 3D + RBV was non-inferior to the historical rate, the lower boundary of the 95% confidence interval for the rate among patients receiving the active regimen during the double-blind period had to exceed the upper</td>
</tr>
</table>

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with the active regimen was superior to the historical control rate, the lower boundary of the 95% confidence interval for the rate in group A had to exceed the upper boundary of the confidence interval for the historical rate (80%). The two-sided 95% confidence intervals were calculated with the use of the normal approximation to the binomial distribution.	confidence boundary of the control rate minus 10.5 percentage points (60%). To establish that the rate of sustained virologic response with 3D + RBV was superior to the historical rate, the lower boundary of the 95% confidence interval for the rate among patients receiving the active regimen during the double-blind period had to exceed the upper confidence boundary of the historical rate (70%).

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2. (Priority question) Please clarify how studies were identified and selected to derive the sustained virological response rates (SVR) presented in Table 58 of the submission.

Table 58 in AbbVie's evidence submission illustrates the treatment-specific impact of certain disease characteristics on the ability to achieve SVR across different treatment regimens for HCV GT1. Again, there was no formal systematic literature review to identify studies to inform these estimates. For the comparator regimens, AbbVie used the manufacturer submissions (MS) and associated ERG reports submitted to NICE because all the regimens included in the table with the exception of PegIFN/RBV were assessed under the STA process and therefore include a great deal of data that have been sufficiently disaggregated to be able to inform Table 58. In addition, the EPARs for each of the regimens also contain SVR data stratified by disease characteristics such as fibrosis status, previous treatment experience and sub-genotype, which corroborated the data identified in the manufacturer submissions.

Therefore, whilst no formal systematic literature review was conducted, AbbVie relied upon the fact that the manufacturer for each of the comparator regimens had identified all relevant trials for their own regimens. For example, for simeprevir + PegIFN/RBV, in a comprehensive systematic literature review, the manufacturer identified two phase III trials in treatment naïve patients, QUEST-1 and QUEST-2. Table 58 utilises pooled data from these two trials that were presented in the manufacturer's submission. For the null responder population, the systematic literature review only identified one trial, the ATTAIN study, as the other treatment experienced trial, PROMISE, was conducted only in prior relapsers. The reason 'n' numbers are not included in Table 58 is because the graph showing SVR data in the manufacturer submission only presented percentages.

AbbVie reviewed the data for each of the other regimens following a similar system of review. For example, for boceprevir + PegIFN/RBV the manufacturer of this agent identified one phase III trial in treatment naïve HCV GT1 patients in a comprehensive systematic literature review conducted for its STA submission, SPRINT-2 (page 38 of the boceprevir MS) – the data for which have been used in Table 58.

For AbbVie's own regimen, pooled data for licensed arms from across the phase III programme for the appropriate sub-groups have been used. For clarity, and so the ERG can replicate the analysis, the data sources are shown in Table 2 as follows and all the SVR data for these sub-groups can be found in Section 6.5.1.1 to 6.5.1.6 of the evidence submission:

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Table 2: Data sources for SVR data presented in Table 58 of AbbVie's submission for 3D - derived from licensed arms of phase III trials

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 (n=100) • GT1b tx naïve patients from PEARL-III receiving 3D (n=209)
GT1 naïve, cirrhotics (F4)	75/78 **(96.2)**	• GT1a tx naïve patients from TURQUOISE-II receiving 3D + RBV 24 week treatment duration (n=56) • GT1b tx naïve patients from TURQUOISE-II receiving 3D + RBV 12 week treatment duration (n=22)
GT1 null responders, no cirrhosis (F0-F3)	115/119 **(96.6)**	• GT1a patients from SAPPHIRE-II receiving 3D + RBV (n=87) • GT1b patients from PEARL-II receiving 3D (n=32)
GT1 null responder cirrhotics (F4)	64/67 **(95.5)**	• GT1a patients from TURQUOISE-II receiving 3D + RBV 24 week treatment duration (n=42) • GT1b patients from TURQUOISE-II receiving 3D + RBV 12 week treatment duration (n=25)

3. **(Priority question) The submission lists Hezode *et al* 2014 and Pol *et al*. as the primary study references for the PEARL-I trial (in Table 25,) but neither of these has been supplied to the ERG and the full reference for Pol *et al* is not listed in the reference list. Please supply these references.**

Apologies, these are now included in a separate file marked 'additional references'. Please note that these are interim analyses presented at congresses as either posters or oral presentations. For example, Hezode *et al* does not have SVR12 data, instead it presents interim efficacy data such as RVR and the end of treatment rates (EOTR). For all data, specifically SVR12 response rates, please refer to the CSR which has also been included in the folder marked 'additional references'.

4. **Reference 37 for the M14-103 study 'Integrated Summary of Efficacy (ISE). AbbVie data submission to EMA 2014' has not been included with the other references. Please supply this reference.**

Apologies, these are now included in a separate file marked 'additional references.'

5. **Please provide a flow chart showing the inclusion and exclusion of clinical effectiveness studies of 3D/2D, and provide reasons for exclusion of studies.**

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A flow chart showing the inclusion and exclusion of clinical effectiveness studies identified in the systematic literature review has been included in the answer to question 8. Therefore, please see AbbVie's response to question 8.

6. Please provide the full reference for the ILLUMINATE telaprevir study.

Apologies, the web link for this study in the reference list does contain all the information we are referring to in the main text of the submission and we also use the EPAR which is on the EMA website, however we have provided the full reference in a separate file marked 'additional references' as requested.

Quality assessment

7. **(Priority question) The detailed quality assessment for the study 'PEARL I' is missing (Appendix 10, p126). Please provide this.**

Please see Table 3 below for the missing quality assessment for PEARL-I.

Table 3: Quality assessment for the PEARL-I randomised controlled trial

Study ID or acronym: PEARL I		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Patients were randomly assigned via the Interactive Response Technology (IRT) system. Treatment-naïve, HCV GT4-infected subjects were randomised in a 1:1 ratio to receive 2D for 12 weeks or 2D plus RBV for 12 weeks (i.e., Groups 1 and 4, respectively). The randomisation schedule was stratified by IL28B genotype (CC versus non-CC). Treatment-experienced, HCV GT4 subjects were enrolled and assigned to receive 2D plus RBV for 12 weeks (i.e., Group 6).	Yes
Was the concealment of treatment allocation adequate?	It was an open label study.	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Characteristics across the groups were similar for baseline demographics and disease characteristics. The group of treatment-experienced subjects had a lower percentage of subjects who were genotype CC (12.2% in Group 6) than the groups of treatment-naïve subjects (27.3% in Group 1; 26.2% in Group 4), otherwise there were no significant differences between groups.	Yes

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Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	It was an open label study.	N/A
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Limited data have been published so far, more data including SVR data will be presented in a peer reviewed journal.	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy, safety and demographic analyses were performed on all subjects who received at least one dose of study drug i.e. intention-to-treat analysis. HCV RNA values were selected for analysis based on the defined visit windows. When there was no HCV RNA value in a defined visit window, the closest values before and after the window were used for flanking imputation, regardless of the value chosen for the subsequent and preceding window. For flanking imputation, if a subject had a missing HCV RNA value at a post-baseline visit but with undetectable or unquantifiable HCV RNA levels at both the preceding value and the succeeding value, the HCV RNA level was considered undetectable or unquantifiable, respectively, at this visit for this subject. Subsequent to this flanking imputation, if a subject was missing a value for the visit window associated with the analysis, the subject was imputed as a failure (i.e., not undetectable or unquantifiable) for analyses of RVR.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

8. Please provide details of the study screening, data extraction, quality assessment processes, and measures taken for quality control of the systematic review (for example whether the data extraction was undertaken by more than one reviewer, did reviewers carry out these tasks independently of each other, whether there was any protocol for identifying and resolving disagreements)?

For the systematic literature review, a first reviewer (JM) conducted the literature search which was deliberately kept quite broad (see Appendix 10.2.4 for details of the search terms). It should be noted that AbbVie was aware of all the phase III trials that were either ongoing or had just completed at the time of the literature search because the 3D/2D regimens are new chemical entities and AbbVie is the sponsor of all the studies, particularly

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as the regimens did not have marketing authorisation at the time of the literature search. We therefore knew we were in possession of more data then would be identified in a systematic review, and as such the stringencies normally observed for this type of review when there is a wealth of data from different trial sponsors were not necessary.

Nevertheless, the first reviewer JM performed two search strings, the first to identify any phase II or III clinical trials of 3D or 2D; and the second string as a 'catch-all' to identify any other studies of 3D or 2D not identified as phase II or III clinical trials, with all duplicates to the first string removed. Both of the broad search strings performed by JM identified only 15 citations in each string fulfilling the search criteria. JM performed this analysis independently of the 2nd reviewer (KB).

A second reviewer (KB), hand searched each of the 15 citations identified in both strings of the literature review (all the citations have been included in Appendix 10.2.7). In the first string, of the 15 relevant citations, two citations refer to the same phase II study, AVIATOR, and were combined; two citations refer to the same liver post-transplant study, CORAL-I, and again were combined for data extraction; two of the citations refer to the same cirrhotic study, TURQUOISE-II, and were combined; two citations refer to the PEARL-II study in treatment experienced HCV GT1b patients, and were combined; two citations refer to SAPPHIRE-I and two additional citations refer to the treatment-experienced study - SAPPHIRE-II. Finally, single citations refer to PEARL-III, PEARL-IV, and PEARL-I in HCV GT4 subjects. A total of 9 studies were therefore identified and considered relevant to the decision problem; subsequently full manuscripts were obtained where these existed. In the absence of full manuscripts, conference abstracts were used. In addition, the CSRs for all the studies were used to provide any more detailed data where necessary. Data abstraction was performed by KB, there were no disagreements requiring a third reviewer to intervene.

In the second search string, which looked at any other publications of 3D/2D other than the clinical trial publications found in the first string, the first reviewer (JM) identified 15 potentially relevant citations. The second reviewer (KB) subsequently and independently hand searched all 15 citations and found 11 citations referring to different analyses of the phase II dose finding study AVIATOR, data from which had already been identified and extracted in the first search string. A study of 2D in Japanese HCV GT1b patients was identified, but was excluded at this stage as the proposed licence in HCV GT1b patients is for 3D and not 2D, so this regimen is outside of the licence. Similarly, another citation was found for PEARL-I but for the HCV GT1b arms which again uses the 2D dose regimen which is outside of the licence. Finally, a phase IIa dose finding study was identified but used ombitasvir as monotherapy initially followed by off-licence doses of varying combinations of paritaprevir and/or dasabuvir. Therefore, of the 15 potential citations identified in the second search, none were considered relevant to the decision problem.

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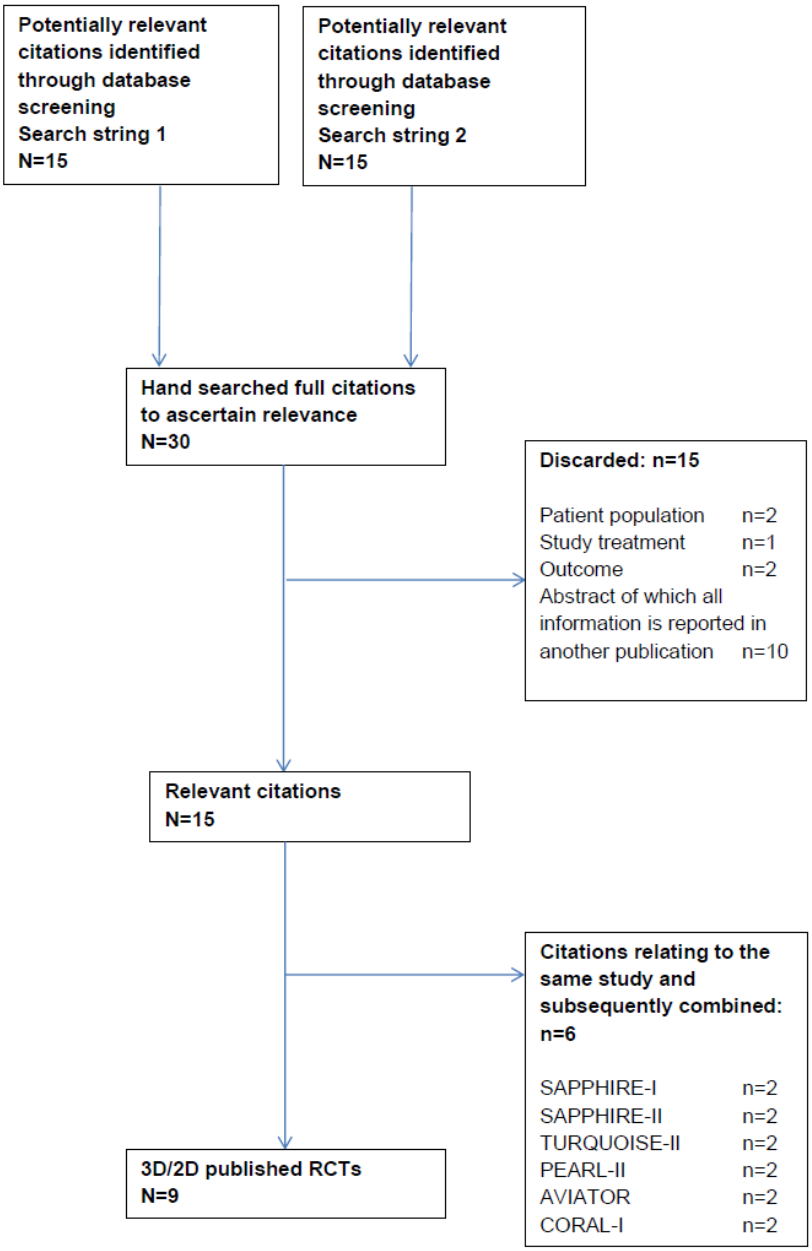
It should be noted that neither string in the literature review identified any data from the opioid replacement study (M14-103) or the HCV/HIV co-infection study (TURQUOISE-I), which AbbVie included in the submission. Therefore, data from 11 RCTs are included in the submission but the systematic literature review only identified 9 of them (see Figure 1 for the flow-chart of clinical effectiveness studies).

Figure 1: flow chart showing the inclusion and exclusion of clinical effectiveness studies of 3D/2D identified in the literature review



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Clinical trials and evidence synthesis

9. (Priority question) Please provide baseline characteristics of participants in the studies included for the estimation of sustained virological response (SVR) with telaprevir and used as historical control rates for comparison with 3D/2D regimens (such as ADVANCE, ILLUMINATE and REALIZE). Please comment on any similarities and/or differences to the populations in the 3D/2D studies.

As mentioned in the answer to question 1, AbbVie's HCV GT1 phase III trials were designed to determine the safety and efficacy of 3D vs. historical telaprevir SVR rates from the telaprevir phase III clinical trial programme grouped at an aggregate level by the following specific disease characteristics: cirrhosis/non-cirrhosis status, previous treatment experience and sub-genotype. Baseline demographics such as sex, age, ethnicity and other disease characteristics such as IL-28B genotype, baseline HCV RNA levels, baseline HP-10 levels, etc. were not matched. (Note – this only applies to 3D and not 2D as telaprevir is only licensed for GT1 not GT4).

Baseline demographic and clinical characteristic data for the telaprevir phase III RCTs are discussed in more detail in 9.1 below. It was not possible to examine the baseline characteristics for the specific matched historical control rates as baseline data for telaprevir are not available at this disaggregated level. However, it appears that the distribution of baseline characteristics at least across the studies examined, other than cirrhosis status and the type of previous treatment-experience, are broadly similar between the telaprevir studies and the 3D SAPPHIRE studies. Furthermore, by selecting comparisons based on disease characteristics such as cirrhosis status and previous treatment experience, other characteristics associated with these prognostic factors e.g. increased age, higher baseline RNA level, will actually be correlated as well.

Given that it has not been possible to properly analyse the baseline characteristics for the historical telaprevir cohorts vs the baseline characteristics in the AbbVie studies, we have also provided data from the MALACHITE studies in section 9.2. These head-to-head, randomised, open-label, phase III studies are ongoing, and aim to evaluate the safety and efficacy of 3D +/- RBV vs. telaprevir in treatment naïve (MALACHITE-I) and PegIFN/RBV experienced (MALACHITE-II) HCV GT1 patients, results of which will be presented at EASL in April 2015. Data from the MALACHITE studies show a good balance in demographics and disease characteristics between the 3D and telaprevir arms. Importantly, the SVR rates for both 3D and telaprevir in the head-to-head trials are comparable to the SVR data reported for 3D and the historical telaprevir control rates used in the phase III programme discussed in detail in the submission.

9.1 Comparison of ADVANCE and REALIZE to AbbVie's 'equivalent' phase III GT1 trials – SAPPHIRE-I and SAPPHIRE-II

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As discussed in detail in the submission, AbbVie has six completed phase III RCTs in HCV GT1. The PEARL studies were conducted in specific sub-genotypes, either treatment naïve (GT1b - PEARL-III and GT1a -PEARL-IV) or treatment experienced (GT1b - PEARL-II), and the TURQUOISE-II study was conducted in a wholly cirrhotic population, so distribution of sub-genotype, cirrhosis status, and previous treatment experience are obviously different in these studies compared to the telaprevir studies. The most similar 3D studies to the telaprevir phase III trials are the SAPPHIRE studies, which comprise a mixture of GT1a and GT1b subjects.

ADVANCE is the main randomised, controlled treatment naïve telaprevir study (n=363) with a mixed population of HCV GT1a and 1b patients, however there were 21 (6%) cirrhotic patients also included in this study. The closest similar 3D study to ADVANCE would be SAPPHIRE-I, a double-blind, randomised, controlled phase III trial in treatment naïve HCV GT1 patients (comprising a mixture of GT1a and 1b), but excluding cirrhotic patients (see Table 4). REALIZE is the main randomised, controlled study of telaprevir in treatment-experienced HCV GT1 patients, and includes 72 (27%) cirrhotic patients. The closest similar 3D study to REALIZE would be SAPPHIRE-II, a double-blind, randomised, controlled phase III trial in treatment-experienced HCV GT1 patients (mixture of GT1a and 1b), but that excludes cirrhotic patients and also, and purposefully, has a much higher proportion of null responders (see Table 5). Regardless, Table 4 and Table 5 show that baseline characteristics are broadly similar between these 3D and telaprevir studies.

Table 4: Comparison of baseline characteristics in HCV GT1 tx naïve patients between 3D (SAPPHIRE-I) and telaprevir (ADVANCE)

Baseline characteristic	**SAPPHIRE-I 3D + RBV N=473**	**ADVANCE T12/PR N=363**
Age, mean (SD)	49.4 (10.98)	46.5 (10.8)
Male sex, n (%)	271 (57.3)	214 (59.0)
Ethnicity – Hispanic/Latino, n (%)	27 (5.7)	35 (9.6)
BMI, mean (range)	25.7 (18.0-38.4)	26.3 (18.0-47.0)
HCV RNA $\geq$ 800,000 IU/mL, n (%)	369 (78.0)	281 (77.4)
HCV GT1a sub-genotype	322 (68.1)	217 (59.8)
Baseline HCV RNA log10IU/mL, mean (SD)	6.40 (0.62)	6.3 (0.7)
Cirrhosis, n (%)	0 (0)	21 (6)

Table 5: Comparison of baseline characteristics in HCV GT1 tx-experienced patients between 3D (SAPPHIRE-II) and telaprevir (REALIZE)

Baseline characteristic	**SAPPHIRE-II 3D + RBV**	**REALIZE T12/PR48**

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	N=297	N=266
Age, mean (range)	51.7 (19-71)	51 (23-69)
Male sex, n (%)	167 (56.2)	183 (69)
Ethnicity – Hispanic/Latino, n (%)	22 (7.4)	25 (9.4)
BMI, mean (SD)	26.3	28 (5.0)
HCV RNA ≥ 800,000 IU/mL, n (%)	255 (85.9)	238 (89)
HCV GT1a sub-genotype	173 (58.2)	136 (52)
Baseline HCV RNA log10IU/mL, mean (SD)	6.55 (0.54)	6.6 (0.548)
Cirrhosis, n (%)	0 (0)	72 (27)
Previous treatment response		
Null responder	146 (49.2)	72 (27)
Partial responder	65 (21.9)	49 (18.4)
Relapser	86 (29.0)	145 (54.5)

AbbVie acknowledges that this is only an analysis of the SAPPHIRE studies, and does not look at baseline data across all the AbbVie trials. Furthermore, unfortunately this analysis is looking at summary statistics for the individual trial arms and not for the exact population that was used to generate the historical telaprevir SVR data - in the absence of disaggregated telaprevir baseline data being available. However, it is likely that a similar distribution of characteristics would have been observed for the grouped subpopulations. It is also important to note that there are certain baseline demographics and disease characteristics that are not independent of prognostic factors like cirrhosis status, previous treatment experience, and sub-genotype like age, baseline HCV RNA level, IL28B genotype etc. For example, a cirrhosis patient who has failed therapy with PegIFN/RBV is likely to be older with a higher baseline RNA than a treatment naïve mild patient. This is reflected in the baseline characteristics of SAPPHIRE-I vs. TURQUOISE-II, where the average age and proportion of patients with baseline HCV RNA ≥ 800,000 IU/mL in the treatment naïve population was 49.4 years and 78%, respectively, vs. 57.1 years and 89% in the cirrhotic patient population, respectively.

Therefore, given that the main clinical characteristics known to affect the likelihood of response: cirrhosis status, sub-genotype and type of previous treatment experience were matched to the 3D population in the calculation of the historical SVR rates for telaprevir, and these appear to be correlated with other disease characteristics, AbbVie considers that the methodology used to calculate the SVR rates for telaprevir in the 3D clinical trial programme qualify as a 'historical control'. This methodology was agreed with the US FDA and EMA.

9.2 Data from the MALACHITE studies - head-to-head trials of 3D vs. telaprevir

The MALACHITE studies are ongoing head-to-head, randomised, open-label, active-controlled trials comparing the safety and efficacy of 3D +/- RBV vs. telaprevir +

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PegIFN/RBV. Data for the primary endpoint were released end December 2014 and will be presented at EASL in April 2015. Tables 6 and 7 below show comparable baseline characteristics between 3D and telaprevir for treatment naïve patients (MALACHITE-I, Table 6) and PegIFN/RBV treatment experienced patients (MALACHITE-II, Table 7). Note, the MALACHITE studies excluded cirrhotic patients as part of the eligibility criteria for the trials.

Table 6: Baseline demographics and disease characteristics in treatment naïve HCV GT1 patients - MALACHITE-I

	Treatment Group						
Characteristic n (%)	**Arm A (GT1a , 3D+RBV)**	**Arm B (GT1a, TPV/PR)**	**Arm C (GT1b, 3D+RBV)**	**Arm D (GT1b, 3D)**	**Arm E (GT1b, TPV/PR)**	**Total**	***P* value**
Sex, Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Race, White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Ethnicity , Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Geographic region, South America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Canada	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Australia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
IL28B genotype, CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
HCV RNA Level, < 800,000 IU/mL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
≥ 800,000 IU/mL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Fibrosis stage, F0 - F1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
F2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
F3 or higher	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Age, years Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BMI, kg/m^2 Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

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Table 7: Baseline demographics and clinical characteristics in tx-experienced patients – MALCHITE-II

	Treatment Group			
Characteristic, n(%)	**Arm A (3D+RBV)**	**Arm B (TPV/PR)**	**Total**	***P* value**
Sex, Female	[redacted]	[redacted]	[redacted]	
Male	[redacted]	[redacted]	[redacted]	
Race, White	[redacted]	[redacted]	[redacted]	
Ethnicity, Hispanic or Latino	[redacted]	[redacted]	[redacted]	
Geographic region, South America	[redacted]	[redacted]	[redacted]	
Europe	[redacted]	[redacted]	[redacted]	
Australia	[redacted]	[redacted]	[redacted]	
HCV RNA genotype 1 subtype, 1a	[redacted]	[redacted]	[redacted]	
1b	[redacted]	[redacted]	[redacted]	
IL28B genotype, CC	[redacted]	[redacted]	[redacted]	
CT	[redacted]	[redacted]	[redacted]	
TT	[redacted]	[redacted]	[redacted]	
HCV RNA Level, < 800,000 IU/mL	[redacted]	[redacted]	[redacted]	
≥ 800,000 IU/mL	[redacted]	[redacted]	[redacted]	
Fibrosis stage, F0 - F1	[redacted]	[redacted]	[redacted]	
F2	[redacted]	[redacted]	[redacted]	
F3 or higher	[redacted]	[redacted]	[redacted]	
Type of response to previous pegIFN/RBV treatment, n (%)				
Null responder	[redacted]	[redacted]	[redacted]	
Partial responder	[redacted]	[redacted]	[redacted]	
Relapser	[redacted]	[redacted]	[redacted]	
Age year Mean ± SD	[redacted]	[redacted]	[redacted]	
BMI, kg/m^2 Mean ± SD	[redacted]	[redacted]	[redacted]	

The following tables show the SVR12 rates reported from the MALACHITE studies:

Table 8: SVR12 rates from MALACHITE-I in HCV GT1 treatment naïve patients

	GT1a		GT1b		
	3D+RBV	**TPV/PR**	**3D+RBV**	**3D**	**TPV/PR**
SVR 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
***p* value (3D regimens vs. TPV/PR)**	[redacted]		[redacted]	[redacted]	

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Table 9: SVR12 rates from MALACHITE-II in HCV GT1 treatment experienced patients

	3D+RBV	TPV/PR
SVR 12	[redacted]	[redacted]
***p* value (3D+RBV vs. TPV/PR)**	[redacted]	

Table 10 below compares SVR rates reported from the MALACHITE studies to the pooled analysis for 3D and the historical telaprevir data used to power the 3D trials. As mentioned above, the MALACHITE trials excluded patients with cirrhosis (F4), as a result the pooled analysis and the historical telaprevir SVR rates in Table 10 below also exclude cirrhotic patients to allow for a like-for-like comparison. In addition, the proportion of null responders, relapsers and partial responders in the MALACHITE studies was similar to the phase III trials, again allowing for a like-for-like comparison of the data.

Table 10: Comparison of SVR rates for 3D and telaprevir from the MALACHITE studies and AbbVie's phase III HCV GT1 trial programme

	Pooled SVR rate for 3D from HCV clinical trial programme % (n/N) *	[redacted]	[redacted]	[redacted]
GT1, tx naïve,	97.3% (613/630)	[redacted]	[redacted]	[redacted]
GT1, tx-experienced,	97.3% (257/264)	[redacted]	[redacted]	[redacted]

* See Table 14 of Viekirax SPC.

To conclude, the data in Table 10 show that the SVR rates seen in AbbVie's extensive phase III HCV GT1 clinical trial programme, for both 3D and the calculation of the historical telaprevir controls, are replicable in head-to-head trials of the two agents.

10. Please provide information about the dosing regimens used in the above mentioned telaprevir studies (question 9).

AbbVie used pooled SVR data using telaprevir as per the dosing used in the phase III trials to calculate the historical SVR rates. For example, to calculate the historical telaprevir SVR rate for the powering of SAPPHIRE-I, AbbVie used pooled data from ADVANCE and ILLUMINATE – see Table 11 below. The T12/PR dosing regimen arm from both ADVANCE and ILLUMINATE was used, both of which include an option for response guided therapy i.e. either T12/P24 or T12/P48. A total of 363 patients were enrolled in the telaprevir arm of the ADVANCE trial, of which 21 were cirrhotic and excluded from the calculation of the historical control leaving n=342. In ILLUMINATE, a total of 540 patients received study drug of which 61 were cirrhotic and excluded from the calculation of the historical control, such that the SVR12 rate including patients with cirrhosis was 74% and this was uplifted to 77% in the

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calculation of the historical control as per the EPAR reported SVR data for telaprevir by fibrosis status.

Table 11: SVR rates for telaprevir in treatment naïve patients used to determine the power for SAPPHIRE-I

SVR Rates for Telaprevir-Based Therapy in Treatment-Naïve Subjects

	ADVANCE	ILLUMINATE	Meta Analysis
Telaprevir Studies	**T12/PR n/N (%)**	**T12/PR n/N (%)**	**T12/PR % [95% CI]**
Treatment-naïve subjects without cirrhosis[1]	270/342 (79)	367/479 (77)	78 [75, 80]
Treatment-naïve GT1a subjects	162/217 (75)	273/388 (70)	72 [68, 75]
Treatment-naïve GT1b subjects	119/142 (84)	112/149 (75)	80 [75, 84]

GT1a = genotype 1a; GT1b = genotype 1b

11. Please provide the clinical study reports for all the 2D and 3D trials included in the submission.

Apologies, these are included in a separate file marked 'additional references.' Please note, we haven't provided any interim reports e.g. for CORAL-I and TURQUOISE-I, as they are not final analyses; and the data contained within them do not feature in the economic modelling.

12. Please explain whether a network meta-analysis was considered for comparators where complete networks existed?

Yes, we considered using a network meta-analysis for comparators where complete networks existed. Unfortunately, even if we had included an NMA for comparators where complete networks existed, we still would not be able to connect the network to include AbbVie's regimens so we still wouldn't have been able to obtain estimates of the relative effectiveness of 3D or 2D vs. other treatment regimens for HCV, which is particularly important given this is an STA evaluating AbbVie's HCV regimens.

As discussed in detail in Section 6.7 of the submission, AbbVie encountered a number of insurmountable problems that meant that the results from the disconnected NMA could not be considered robust (see Section 6.7.1 and 6.7.2). Subsequently, AbbVie looked at implementing the output from other published networks in this disease area to inform the estimates for comparator regimens. In particular, AbbVie looked at using the MTC developed by the manufacturer of simeprevir to inform estimates of simeprevir, telaprevir, boceprevir, and PegIFN/RBV.[1]

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Firstly, it is worth re-iterating that it is well documented that there are known predictive factors that affect the probability of achieving an SVR like HCV GT1 sub-genotype, type of response to prior treatment, or the cirrhotic status of a patient. Furthermore, the magnitude of the impact the specific characteristic has on achieving an SVR varies across treatments making any network meta-analysis very challenging in this disease area. A treatment effect model (as performed by the manufacturer of simeprevir) will mitigate the impact of some of these characteristics, particularly for characteristics that have a common effect on all treatments, as the calculation of relative effectiveness will cancel out the impact a common covariate has on the probability of response. However, in HCV many of the predictive factors lead to a treatment specific effect, such that in an indirect comparison, trials of treatments with a high proportion of favourable characteristics may artificially appear to have superior SVR rates, when in fact the difference in efficacy estimates are attributable to the difference in the spread of treatment specific characteristics across the trials.

In the MTC performed by the manufacturer of simeprevir, the manufacturer stated that characteristics such as sub-genotype, percentage of cirrhosis patients, type and percentage of treatment experience, as well as a host of other characteristics were broadly similar across the included trials in the MTC. However, upon examination of the baseline characteristics of the included trials in the manufacturer's submission, it appears that the proportion of cirrhotic patients in the different trials varies from around 4% up to 30%, and the percentage of GT1b patients varies from 23% up to 72% of the total trial population. In the ERG critique of the manufacturer's MTC, the ERG stated that some form of meta-regression would have been beneficial to account for the differences in clinical characteristics across the different trials and the impact these differences may have on the ability to achieve SVR. AbbVie has already explained in Section 6.7.2 of the submission why covariate adjustment is difficult in this disease area, so can understand why it was not performed in this MTC.

Therefore, no covariate adjustment was performed in the simeprevir MTC, but the clinical characteristics known to affect treatment response are not spread equally across the studies. This wouldn't necessarily be an issue if the clinical characteristics conferred a common effect across all treatments, but unfortunately and as evidenced by Table 58 in the submission (reproduced here as Table 12), these characteristics are treatment-specific and the magnitude of the impact the specific characteristic has on achieving an SVR varies across treatments. Table 12 shows that AbbVie's licensed regimens are not affected by any of these characteristics, with 96.8% HCV GT1 treatment naïve non-cirrhotic patients achieving an SVR and 95.5% HCV GT1 cirrhotic prior null responders also achieving an SVR.

However, for all the other agents, one or more of these disease characteristics considerably affect the SVR data but to differing degrees i.e. the effects are treatment specific. For example, it appears that having compensated cirrhosis leads to a 25% reduction in SVR for PegIFN/RBV (44.4% to 33.3%), compared to telaprevir or simeprevir which show about an

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18% (75.4% to 61.9%) to 26% (81.9 to 60.4%) relative reduction in SVR; or compared to boceprevir where being cirrhotic appears to lead to a 52.5% relative reduction in SVR (65.9% to 31.3%). Similarly, for null responders, it appears that there is a dramatic 12-fold reduction in SVR for PegIFN/RBV (91.6% reduction, 44.4% to 3.7%), a 53.8% and 38.6% reduction for telaprevir (75.4% to 34.8%) and simeprevir (81.9% to 50.3%) respectively; and a 0.2% reduction for AbbVie's 3D (96.8% to 96.6%).

Therefore, AbbVie concludes that unless like-for-like can be accurately compared, or there are considerable treatment specific adjustments made to any analyses, then all NMAs in this disease area should be interpreted with caution.

Table 12: Treatment-specific impact of certain disease characteristics on ability to achieve SVR for different HCV GT1 regimens

	SVR n/N (%)					
Treatment	**3D +/- RBV**	**PegIFN/RBV**	**TPV + PegIFN/RBV**	**BOC + PegIFN/RBV [a]**	**SOF + PegIFN/RBV [b]**	**SIM + PegIFN/RBV**
GT1 naïve, no cirrhosis (F0-F3)	611/631 **(96.8)**	151/340 **(44.4)**	258/342 **(75.4)**	222/337 **(65.9)**	220/240 **(91.7)**	377/460 **(81.9)**
GT1 naïve, cirrhotics (F4)	75/78 **(96.2)**	7/21 **(33.3)**	13/21 **(61.9)**	5/16 **(31.3)**	42/52 **(80.8)**	29/48 **(60.4)**
GT1 null responders, no cirrhosis (F0-F3)	115/119 **(96.6)**	1/27 **(3.7)**	16/46 **(34.8)**	-	-	**(50.3)**
GT1 null responder cirrhotics (F4)	64/67 **(95.5)**	1/10 **(10.0)**	5/26 **(19.2)**	-	-	**(24.6)**

[a] boceprevir + PegIFN/RBV was not studied in HCV GT1 null responders.
[b] sofosbuvir + PegIFN/RBV was not studied in treatment-experienced HCV GT1 patients.

Data for 3D are pooled for the relevant sub-group across all trials.
Data for PegIFN/RBV for naïve and experienced patients from PegIFN/RBV arms of the telaprevir trials ADVANCE (NEJM, Jacobson et al, 2011) and REALIZE (NEJM, Zeuzem et al, 2011), respectively.
Data for telaprevir for naïve patients and experienced patients from ADVANCE (NEJM, Jacobson et al, 2011) and REALIZE (NEJM, Zeuzem et al, 2011), respectively.
Data for boceprevir from SPRINT-2 (NEJM, Poordad et al, 2011).
Data for sofosbuvir from NEUTRINO (NEJM, Lawitz et al, 2013).
Data for simeprevir for naïve patients from QUEST-1 (Lancet, Jacobson et al, 2014) and QUEST-2 (Lancet, Manns et al, 2014), and data for treatment-experienced patients from ATTAIN (Figure 15, page 56 of MS submission to NICE).

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13. In section 6.6 of the submission (regarding meta-analysis), only random effect estimates are presented. Please provide the corresponding fixed effects estimates (Figure 17-19).

As discussed in Section 6.6 of the submission, the only software available we could find that is able to deal with single-arm studies is called Meta-Analyst (see Wallace et al for discussion on attributes of different meta-analysis software),[2] as the usual software like RevMan and STATA aren't able to deal with the study design of AbbVie's HCV clinical trials. In initial work on the meta-analysis, we managed to run an analysis using a fixed effects model using the data set for Figure 17. This analysis showed a higher DIC then we found when using a random effects model – this is unsurprising, as the high level of heterogeneity in the AbbVie clinical trial programme had already been discussed. Given that random effects models better account for heterogeneity between trials by increasing the variance and are not overtly precise in the estimates we considered this to be a more conservative approach as well as a better fit. We therefore provided all analyses using a random effects model.

We have tried to re-run the datasets using the fixed effects approach as requested by the ERG but unfortunately we have been unable to rerun the fixed effects analysis due to issues with the software crashing. Therefore, unfortunately we cannot provide the above requested analysis.

14. Section 6.5.1.7 of the submission (page 175) states that only arms G and L of the AVIATOR trial used treatment regimens of 3D that are relevant to the proposed marketing authorisation. The regimen used in arm E also seems relevant to the proposed marketing authorisation (for genotype 1b non-cirrhotic patients) – please clarify why the company does not consider arm E relevant.

The ERG is correct that Arm E is relevant for any genotype 1b non-cirrhotic patients, but not relevant for genotype 1a, as 3D is given as monotherapy without ribavirin. Of the 79 patients enrolled in arm E, only 25 (31.6%) were genotype 1b non-cirrhotic patients – therefore the data for this arm weren't included in the submission. AbbVie presented SVR rates for whole arms of AVIATOR and M14-103 in the evidence submission, but didn't present the data sub-divided by sub-genotype because the numbers of patients for each arm were already very small, without dividing them further into sub-genotype. However, given the ERG's question 15 below - the data have now been included for arm E (and the other arms of interest) stratified by sub-genotype.

15. Please provide the SVR rates (% achieving SVR) for GT1a and GT1b in the AVIATOR trial who received regimens E, G and L. Please also provide SVR rates for GT1a and GT1b patients in the M14-103 trial.

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Table 13 below presents the percentage of patients achieving SVR from arms E, G and L of the phase II, dose-finding study AVIATOR, and also the phase II study in patients receiving stable opioid therapy - study M14-103. As previously mentioned, the sample sizes are quite small and some of the arms include unlicensed regimens of 3D. For clarity AbbVie has greyed out the text where this is the case, so the data are still presented but it is clear that the reported SVR rates are outside of the licence.

Table 13: SVR rates for arms E, G and L from AVIATOR and M14-103 stratified by sub-genotype

Trial	**SVR12 or 24***	
	Genotype 1a	**Genotype 1b**
AVIATOR		
Tx naïve - Arm E (3D)	[redacted]	[redacted]
Tx naive - Arm G (3D + RBV)	[redacted]	[redacted]
Null responders - Arm L (3D + RBV)	[redacted]	[redacted]
M14-103	[redacted]	[redacted]

* AVIATOR used SVR24, whereas M14-103 used SVR12 as the primary outcome measure.

16. Please clarify the exact doses of each drug used in the 3D + RBV treatment regimen in the M14-103 trial.

All patients in this single arm, open-label study received the following 3D + RBV regimen:

- Paritaprevir/ritonavir/ombitasvir (ABT-450/r/ABT-267) 150 mg/100 mg/25 mg QD
- Dasabuvir (ABT-333) 250 mg BID
- RBV weight based, 1,000 mg or 1,200 mg daily divided BID per label(e.g., < 75 kg = 1,000 mg daily divided BID or ≥ 75 kg = 1,200 mg daily divided BID)

Furthermore, patients had to have been on stable opioid replacement therapy of methadone (n=19, 50%) or buprenorphine (n=19, 50%) + naloxone for at least 6 months prior to screening. The exact dose of opioids varies per patient dependent on the stage of titration they are at and the level of opioid required at baseline.

Section B: Clarification on cost-effectiveness data

Literature searching

17. (Priority question) The base case analysis uses non-treatment-specific transitional probabilities as described in Shepherd et al. (2007) which were based on the economic evaluation undertaken alongside the UK Mild hepatitis C Trial (Wright et al. 2006).It is not clear whether any general or targeted searches were conducted to identify new evidence to update these transition probabilities. Please state whether any such searches were undertaken. If so please provide details.

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No literature searches were specifically conducted to identify new evidence for the non-treatment specific transition probabilities (TPs). As noted by the ERG, AbbVie's base case cost-effectiveness analysis sourced TPs for the natural history of liver disease from the previously published economic evaluation by Shepherd et al. (2007). However, a systematic review of the literature on cost-effectiveness studies of various chronic Hep C treatments was undertaken by AbbVie to primarily identify sources for healthcare resource use, unit costs and utilities. Full publications that were considered relevant to inform AbbVie's economic evaluation were also inspected for values and evidence on transition probabilities to model the natural history of progressive liver disease. AbbVie did not identify any sources of TPs deemed more appropriate than those reported in the economic evaluation by Shepherd et al. (2007), undertaken alongside the UK Mild Hep C Trial (Wright et al. 2006). As a result, disease progression transition probabilities adopted for the model base case were the same as those used in Shepherd et al. (2007), Hartwell et al. (2011) and consistent with many subsequent NICE appraisals of different pharmacological treatments for chronic Hep C.

Model validation

18. **(Priority question) Please provide a full description of the independent, technical and internal model validation exercise carried out by the company, as referred to in section 7.8.1.**

Independent, technical and internal model validation exercises were performed as follows:

AbbVie contracted an independent consultancy (Medicus Economics) to develop the model; the Principal Investigator leading that work was Scott Johnson, Ph.D., who has developed models for NICE review previously. The model structure, underlying assumptions, and disease model input values were reviewed by a modelling team led by Uwe Siebert, Ph.D., Professor of Public Health (UMIT) and Adjunct Professor of Health Policy and Management (Harvard University). Prior to the submission, Medicus Economics also presented findings to the UMIT modelling team, to assess whether the model results were clearly presented, and to assess how changes in disease model parameters affected results in a face validity test.

The model's treatment inputs including SVR, adverse event, treatment duration, and quality of life effect were extracted from clinical trial publications, EPARs or CSRs by Medicus Economics, who developed slide decks demonstrating the extraction of the data from these sources. A second independent firm, Snell Communications Inc., audited the treatment inputs, including all information on the tab called "Treatment Library" and the regimen inputs sheets.

When the model was complete, it was completely reviewed from beginning to end by a third independent firm, RTI Health Solutions, specifically by a team led by Josephine Mauskopf. The RTI team performed a comprehensive internal model validation, including reviewing all

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model inputs for accuracy and validity, proximal model calculations (formulae), model operations, VBA programming, and model output. The derivation of figures from output was also checked. Labelling was also checked.

External validation has been described in Section 7.8 of the submission. The model's predicted 20-year cirrhosis rates were compared with estimates published in the clinical literature and previously developed models.

Resource use and costs

19. (Priority question)The submission states that the treatment costs for all treatment regimens were based on mean treatment duration from selected clinical trials, using data on treatment discontinuation. Did these estimated treatment costs include all potential stopping rules (including response-guided treatment for telaprevir and boceprevir as well as futility-based stopping rules for pegylated interferon plus ribavirin)?

Yes, this is correct. Treatment costs for telaprevir (TPR), boceprevir (BOC) and pegylated interferon and ribavirin (PR) regimens were calculated on the basis of their mean treatment duration derived from selected clinical trials, incorporating trial rules on treatment continuation or discontinuation. Based on the available trial efficacy data for telaprevir, boceprevir and PR, AbbVie incorporated a set of pre-defined response-guided treatment (RGT) continuation or discontinuation rules integral to the design of the clinical trials including: 1) rules allowing for shortening of treatment duration when an adequate response is reached at pre-defined time points (note: incorporated for telaprevir and boceprevir regimens, but not for PR alone) 2) futility (stopping) rules to discontinue treatment in patients who did not achieve adequate response (note: incorporated for telaprevir, boceprevir and pegylated interferon plus ribavirin regimens).

Telaprevir:

For example, stopping rules for telaprevir implemented in our model are based on the ADVANCE and REALIZE trials to discontinue treatment in patients who did not have an adequate early response. In addition, a response-guided treatment rule was employed in ADVANCE based on extended rapid virologic response (RVR - defined as undetectable HCV RNA at weeks 4 and 12) so that patients in the T12PR group who met the response criteria received only 12 additional weeks of PR alone, leading to a shortened treatment duration. This is in line with telaprevir's SPC.

PegIFN/RBV:

Pre-defined futility rules for PR in genotype 1 treatment-naïve and -experienced patients are based on the PR arms of the ADVANCE and REALIZE trials respectively. These stopping

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rules are aligned with those that are denoted in peginterferon and ribavirin SPCs. However, the ADVANCE trial did not allow for the RVR discontinuation rule for treatment naïve patients, unlike the SPCs (patients with undetectable HCV RNA level at week 4 and week 24 during treatment could discontinue further treatment) and as such this response guided stopping rule was not factored into AbbVie's analysis.

Boceprevir:

Response-guided treatment continuation and discontinuation rules for boceprevir are implemented in our model based on the SPRINT-2 and RESPOND-2 trials. For example, in the RGT arm of SPRINT-2, patients with undetectable HCV RNA at weeks 8 and 24 received additional 24 weeks of boceprevir + PR for total treatment duration of 28 weeks when the treatment was considered complete. Patients with detectable HCV RNA between weeks 8 and 24, but undetectable at week 24, stopped BOC at week 28, but then continued PR alone for a subsequent 20 weeks for a total treatment duration of 48 weeks. Treatment was discontinued for reasons of futility if HCV RNA level was detectable at week 24. In RESPOND-2, HCV RNA levels were assessed for stopping rule at week 12 and failure to achieve an undetectable HCV RNA level resulted in discontinuation of all treatment and advancement to follow-up. Boceprevir's SPC however recommends that if a patient has hepatitis C virus RNA results greater than or equal to 1,000 IU/mL at treatment week 8, then the treatment should be discontinued. This stopping rule was not factored into AbbVie's analysis as it was not implemented in the clinical trials.

The above response-guided treatment continuation and discontinuation rules including futility are described in more detail in section 7.3.1 of the submission. In summary, AbbVie's economic evaluation modelled the aforementioned rules applied in the selected clinical trials rather than those specified in the SPCs. This was done on the basis that the SVR rates informing efficacy inputs in the model are the ones reported in those trials and are linked to the same response-guided and futility rules. The rules are however broadly similar to those stated in the SPCs. Minor differences are not expected to have a significant impact on the overall ICERs. Section 7.5.1 of the submission details how these trial based rules are fed into the calculation of the mean treatment costs for each regimen.

20. Please clarify whether all potential stopping rules (including response-guided treatment for telaprevir and boceprevir) were included in the calculation of treatment costs in the probabilistic sensitivity analysis? If so please explain how.

As detailed in question 19, 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 within the SPCs or 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

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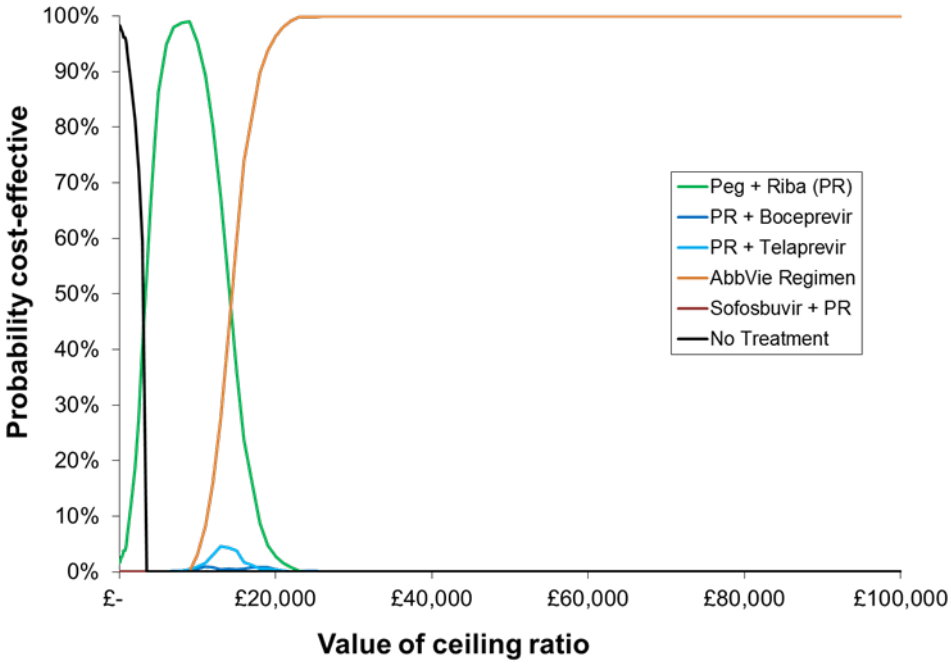
discontinued treatment for futility. As such we modelled all regimens exclusively as per their trials and did not sample regimen costs probabilistically in the submission.

However in response to this question by the ERG, we made an adaptation to the model to vary the probability of meeting a stopping rule when in the boceprevir or telaprevir arms, based on a beta distribution and using the observed percentage of stopping and sample size as input parameters. The assumption was made in this sensitivity analysis that SVR, adverse event rate, and treatment-related health utility were not affected by a patient's likelihood of meeting a stopping criterion (see prior paragraph regarding our perspective on this assumption). We ran a PSA including the stochastic stopping rule addition, and calculated the below CEAF (see Figure 2). The results in Figure 2 show the CEAF for HCV GT1 naïve patients; the results of which are essentially identical to Figure 38 in the original submission. In both the original submission and revised analysis, the AbbVie Regimen is the optimal therapy at a willingness-to-pay threshold of more than £15,000/QALY. At a willingness-to-pay threshold of less than £15,000/QALY, PR or no treatment are optimal. The reason for the new change is that the potential for lower costs resulting from a stopping rule is relatively low, such that both the boceprevir and telaprevir arms provide relatively low value compared to the other treatments.

Figure 2: Cost-effectiveness Acceptability Curve, GT1, treatment-naïve (IFN-eligible) patients, Revised Model including stochastic stopping rule in the boceprevir and telaprevir arms



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Modelling of treatment effect and uncertainties

21. (Priority question) Please provide details on how the SVR was calculated in the probabilistic sensitivity analysis. Please clarify whether methodological uncertainty arising from the assumption of the proportionate difference in SVRs by fibrosis stage and sub-genotypes (section 7.3.1), is captured in the probabilistic sensitivity analysis.

For the purpose of the probabilistic sensitivity analysis (PSA), SVR rates were calculated using Briggs et al. (2003) methodology (explained in detail in section 7.6.2 of the submission). On inspection of the clinical trial efficacy and adverse event data (reported in section 7.3.1 of the submission), it was noted that there were patient segments across AbbVie's and competitor trials in which either the observed SVR rate or AE rate was equal to 100% or 0% respectively. In order to generate variance for these model parameters in the PSA and specify distributions to represent uncertainty in their estimation, AbbVie utilised Bayesian methodology advocated by Briggs et al. (2003). By applying this method, it is inferred that for example the observed 100% SVR rates are imprecisely measured (in a sense that a patient could fail to have an SVR) and that these point estimates have uncertainty around them. This uncertainty can be formally expressed through the prior distribution. By adopting this approach, minimally informative prior distributions are used to generate variance around 100% or 0% parameters so that the problem of observing 100% or 0% counts is overcome. However, in order to avoid a systematic bias against segments where the observed SVR (AE) rate equals 100% (0%), this method has been uniformly applied to all regimens and their SVR (AE) rates, irrespective of whether they were 100% (0%) or not. Therefore, the Briggs et al. method changes the observed trial point estimates for SVRs or AEs for all regimens in the PSA. As AbbVie applied this methodology uniformly across all patient segments and all regimens, the proportionate difference in SVR rates by fibrosis stage and sub-genotypes observed in the clinical trials was maintained in the PSA.

22. Please provide further detail on the approach to sampling SVRs for parameter uncertainty in the probabilistic sensitivity analysis. The description in section 7.6.3 refers to using beta distributions and suggests that these were sampled between imputed lower and upper bounds (derived for the deterministic sensitivity analysis), while tables in section 7.3.1 report number with SVR and sample size for trials (n/N) and also imputed values for those subgroups where data were not available.

- **Please clarify exactly how variation for the SVRs was estimated and how the values were sampled in the probabilistic sensitivity analysis.**

Section 7.6.3 of the submission highlights that the SVR and AE rates derived from the clinical trials are subsequently recalculated for the PSA using the Briggs et al. (2003) methodology

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(described in the above answer). A conservative prior distribution for regimens' SVR rates was assumed for each patient segment, assuming that the first patient observation is a failure. Then we effectively added the observations from the trials into the model and computed standard errors assuming they take on a binomial distribution. Equally, to impute uncertainty into the AEs measurement (where the observed trial AEs were 0%), we assumed that the prior distribution was based on one patient who had an AE. Both parameters are then assumed to follow beta distribution in the PSA characterized by the trial segment sample size and percentage with SVR and AE respectively.

Briggs et al. methodology is also the basis for the SVR and AE variation in the deterministic sensitivity analysis allowing variation for parameters otherwise not possible (100% or 0% counts). In other words, the model will run the tornado diagram with Briggs et al. "switched on" to get the imputed lower and upper bound values (CIs) on SVRs and AEs. This is not to be mixed with the imputation that we describe in section 7.3.1 of the submission which refers to the extrapolation of observed clinical trial outcome data ("unadjusted" efficacy data), namely SVR rates for subgroups (e.g. sub-genotype and/or compensated cirrhosis) when such efficacy results were not reported in the publications, using simple calculations and assumptions.

- **Please clarify whether correlation between SVR for each treatment regimen, stratified by fibrosis stage and/ or sub-genotype, was included in the probabilistic sensitivity analysis. If so please explain how.**

No, correlations between SVR for each treatment regimen, stratified by fibrosis stage and/or sub-genotype, were not included in the probabilistic sensitivity analysis. The quantitative value of such correlations is not known, and we are unaware of data that could be used for their estimation. Had a network meta-analysis been possible in this disease area, we might have been able to generate the data to inform the correlations. At least by omitting such correlations, the model is conservative in the sense that the stochastic variation is greater than would be the case if the treatment regimens' therapeutic effects were positively or negatively correlated (in which case they would tend to cluster together).

<u>Utility values</u>

23. Section 7.4.7 of the company's submission states that "for health states beyond compensated cirrhosis, such as DCC [decompensated cirrhosis] and HCC [hepatocellular carcinoma], we extrapolate the decrement observed in Wright et al. (2006) between mild health state and DCC and HCC onto the EQ-5D scores of mild Hep C patients collected in our trails [sic] to derive utility values for DCC and HCC". However Table 100 in section 7.3.6 states the sources for utility values beyond compensated cirrhosis as Grieve et al. (2006); Wright et al. (2006);

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Shepherd et al. (2007); Hartwell et al. (2011). Please clarify the source for the utilities used for health states beyond compensated cirrhosis.

Table 100 (section 7.3.6 of the submission) details utility values for the initial fibrosis stages (mild, moderate and compensated cirrhosis) and stages beyond compensated cirrhosis (DCC, HCC, LT) that have been used in AbbVie's model base-case. Although we list multiple references for these utilities, the primary source referred to in our submission as well as utilised in all other listed references is Wright et al. (2006). This is consistent with assumptions around utility used in other cost-effectiveness analyses recently appraised by NICE.

In section 7.4.7 of the submission, we describe one of the scenario analyses where we substitute utilities for mild, moderate and compensated cirrhosis health states sourced from Wright et al. (2006) with the utilities collected in AbbVie's clinical trials. AbbVie's clinical trials however only studied chronic Hep C patients with mild fibrosis, moderate fibrosis and compensated cirrhosis, and did not enrol patients with more severe stages of the disease, e.g., patients with DCC, HCC and LT. Therefore in this aforementioned scenario analysis, for health states beyond compensated cirrhosis we continue to source the data from Wright et al. (2006). However, to be conservative, rather than applying the absolute utility values for DCC, HCC and LT (as we do in the model base case), we calculate the difference (decrement) between the utility for mild HCV reported in Wright et al. and the utilities for DCC, HCC and LT respectively (thereby increasing the health utility of these states from the base case), and further apply this difference to the mild fibrosis utility scores derived from AbbVie's clinical trials to derive new estimates for DCC, HCC and LT. We would argue that this scenario analysis could be biased if we used health utilities for the mild, moderate and CC states from the patient population in the clinical trials (which appear higher than in the Mild HCV cohort) and health utilities from a community cohort for the HCC, DCC and LT states; doing so could potentially exaggerate the absolute numeric difference in health utility between the two sets of health states. However, please be aware that this was only done in one scenario analysis and is not the base case.

24. The submission presents EQ-5D-3L utilities (calculated using the UK cross-walk to EQ-5D-5L) in Tables 104 and 105 for each trial separately.

- **Did the company consider pooling utility values from comparable populations?**

Yes, the company did consider pooling the data and has done so where appropriate. AbbVie appreciates that this was not obvious from Tables 104 and 105 in the submission document where the baseline utilities as well as end-of treatment utilities were presented separately for each trial. However in the cost-effectiveness model that was submitted, data for comparable populations were pooled. For example, utility data for mild and moderate GT1a, treatment naïve patients were pooled from SAPPHIRE-I and PEARL-IV clinical trials to yield an overall

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mean utility for these respective patient populations. AbbVie initially also considered pooling utilities across GT1a and GT1b mild and moderate patients, however, we ultimately decided against it given that patients infected with GT1a and GT1b chronic Hep C received different regimens of 3D (i.e. patients infected with GT1a require 3D + RBV, while GT1b patients receive 3D without ribavirin). Given the possibility that ribavirin-induced side effects may have negatively impacted treatment-related health utilities, it was decided that we would analyse utilities for GT1a and GT1b patients separately. On post-hoc inspection of the utility data in patients receiving ribavirin over 12 weeks vs. those who did not, we noted differential impact on utility. However, as the model was already structured to analyse the groups separately, we maintained the initial approach. Separation of patients according to treatment history (treatment naïve or treatment experienced), and the treatment duration (12 or 24 weeks of 3D + RBV) was appropriate as differences in mean annualised on-treatment disutilities were observed.

- **Please provide further information on the justification for applying the UK cross-walk to responses from non-UK participants.**

As mentioned in Section 7.4.3 of the submission, AbbVie applied the UK crosswalk function to the EQ-5D-5L responses elicited from the entire patient sample that participated in AbbVie's trials, including responses from non-UK participants in order to generate utility values for EQ-5D-5L descriptions. There are several reasons as to why we have done so. First of all, as discussed in the submission, the UK patients constituted only 5.7% of the total enrolled trial subjects. For utility analysis AbbVie wanted to preserve the largest sample size (n) possible and therefore utilised the EQ-5D-5L response data from the entire patient pool. Second, regardless of the fact that the responses were generated by patients originating in different countries, AbbVie was not interested in how respondents in each respective country felt about chronic hepatitis C. Rather, AbbVie was solely interested in the UK general population perceptions of health profiles and the level of health reported by chronic hepatitis C patients, irrespective of their country of origin. We thus used the EQ-5D-5L responses from all patients, but have analysed them by applying the UK crosswalk. Lastly, by applying country-specific weights to their participants' EQ-5D-5L descriptions (with extrapolation of data for countries whose county-specific weights are not available) and then combining them into a single preference-based health utility index, the overall utility would be confounded by country specific tariffs and would thus be challenging to interpret. Therefore AbbVie deemed it would be more appropriate to apply the UK crosswalk uniformly to all EQ-5D-5L responses.

- **Separately for each trial, please provide a summary of baseline and end of treatment EQ-5D-3L estimates using the UK crosswalk from the EQ-5D-5L collected exclusively from the UK participants (accepting there are likely to be very small numbers or zero counts for some cells).**

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As requested, here is the summary of baseline and end of treatment EQ-5D-3L estimates using the UK crosswalk from the EQ-5D-5L collected exclusively from the UK participants. Please note that UK patients were only recruited in to 4 out of the 6 phase III HCV GT1 trials and no UK patients participated in the HCV GT4 study, PEARL-I.

Table 14: Utility data from the UK sample of AbbVie's phase III clinical trial programme

All patients-baseline utilities

STUDY IDENTIFIER	N Obs	N	Mean	Std Dev	Minimum	Maximum
Sapphire1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sapphire 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Turquoise II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pearl IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

All patients-final treatment visit

STUDY IDENTIFIER	N Obs	N	Mean	Std Dev	Minimum	Maximum
Sapphire1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sapphire 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Turquoise II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pearl IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

All patients-post-treatment week 12

STUDY IDENTIFIER	N Obs	N	Mean	Std Dev	Minimum	Maximum
Sapphire1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sapphire 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Turquoise II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pearl IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As can be seen from Table 14 above, the utilities derived from the UK only sample are broadly similar at baseline and at the end-of-treatment visit to those calculated from the entire pool of patients across multiple countries using the UK cross-walk.

25. The company's submission states that EQ-5D-5L utility values, derived from the clinical trials, were not suitable for use in the model as only 5.7% of the total enrolled adult population were UK patients. Please clarify whether the utility decrements applied for adverse events, derived from the clinical trials (Table 110, section 7.4.8) were based on all patients or the sub-group of UK patients.

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Utility decrements applied for adverse events, derived from clinical trials (Section 7.4.8, Table 110 for unannualised or Table 112 for annualised decrements) were based on the total enrolled patient population as opposed to sub-group of UK patients.

Additionally, just to clarify, Section 7.4.7 of the submission states that AbbVie decided not to use clinical trial utilities in the model base-case as we were unsure how representative these were of UK patients suffering with chronic Hepatitis C. However, a scenario analysis using the clinical trial utilities was performed to evaluate the impact a different source of utilities has on the base-case results. For further details, please refer to scenario analysis number 20 in section 7.7.9 of the submission.

Section C: Textual clarifications and additional points

26. Please explain the term "historical control" used in the submission. The ERG understands this to mean an analysis of matched patient-level data. However the historical control used in the submission (and to calculate power of the trials) appears to be the overall SVR reported from telaprevir trials, where matching has only been attempted at the aggregate level (in terms of genotype and degree of fibrosis [non-cirrhosis versus cirrhosis]). Please clarify.

Please see AbbVie's responses to question 1 and question 9 for clarification of the historical controls. But to summarise: as agreed with the US FDA and EMA, the telaprevir data termed "historical control" in the submission utilises SVR rates from the telaprevir trials by selecting equivalent subpopulations at an aggregate level by sub-genotype e.g. 1a vs. 1b (not genotype as the question above states), cirrhosis status, and also previous treatment experience – treatment naïve, null responder to PegIFN/RBV, relapser to PegIFN/RBV or partial responder to PegIFN/RBV. All of these clinical characteristics are well documented to have an impact on the probability of achieving an SVR. The ERG is correct in that patient level matching for multiple characteristics was not performed. It should be noted that the term 'historical control' in regards to the telaprevir SVR data used to power the 3D phase III trials has also been employed in all the regulatory documents submitted to EMA, and supplied by EMA, and also in the NEJM trial publications.

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