**Single Technology Appraisal**

**Sofosbuvir – Chronic Hepatitis C**

**NICE Clarification Letter – Gilead Sciences Response**

**12th March 2014**

## Section A: Clarification on clinical effectiveness data

A1. **Priority Question**: **Please explain the eligibility criteria or system used to define the inclusion and exclusion criteria for the phase 2 and phase 3 trials (as described in Table 8, manufacturer's submission p. 53).**

Phase II and III study were initially identified by the phase stated by the publication authors. If no phase was reported in the publication, the study was included and a note was made in the data extraction that study phase was 'not reported'. Studies that did not mention the phase but stated that it was a pilot, animal or other study design listed in the inclusion criteria were excluded. When possible the study names (e.g., FUSION) were used to confirm further details about the study phase.

A2. **Priority Question: Please provide critical appraisal of the four included phase 2 randomised controlled trials (QUANTUM, SPARE, ATOMIC, and ELECTRON) using the same table that was used for the quality assessment of the phase 3 trials (Table 20, manufacturer's submission p. 95).**

| **Trial no. (acronym)** | **P2938-0721 QUANTUM (re-treatment)** | **11-1-0258 SPARE** | **P7977-0724 ATOMIC** | **P7977-0523 ELECTRON** |
|---|---|---|---|---|
| Was randomisation carried out appropriately? | Yes (for Groups C and G) | Yes | Yes | Yes |
| Was the concealment of treatment allocation adequate? | NA | NA | NA | NA |
| Were the groups similar at the outset of the study in terms of prognostic factors? | Yes | Yes | Yes | Yes |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | NA | NA | NA | NA |
| Were there any unexpected imbalances in drop-outs between groups? | No | No | No | No |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | No | No | No | No |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Yes | Yes | Yes | Yes |

NA- not applicable as an open label study

A3. **Priority Question: Please clarify what is meant by the full analysis population (FAS) in the NEUTRINO (manufacturer's submission p. 84), POSITRON (manufacturer's submission p. 88) and VALENCE trials (manufacturer's submission p. 90).**

| Study | Full analysis set |
|---|---|
| GS-US-334-0110<br>NEUTRINO | Full analysis set includes subjects with genotype 1, 4, 5, or 6 HCV infection who were enrolled and received at least 1 dose of study drug. |
| GS-US-334-0107<br>POSITRON | Full analysis set includes (subjects with chronic genotype 2 or 3 HCV infection who were randomized and received at least 1 dose of study drug). |
| GS-US-334-0133<br>VALENCE | Full analysis set includes subjects with genotype 2 or 3 HCV infection who were randomized and received at least 1 dose of sofosbuvir. |

A4. **Priority Question: According to the Lalezari abstract (ref 47) the QUANTUM trial included a placebo arm. Please clarify why a description of the placebo arm and the results for this patient population have not been included in the manufacturer's submission (p. 127-128).**

The QUANTUM trial was initially a randomised, 8-arm trial assessing the safety and efficacy of regimens containing the HCV NS5B nucleotide inhibitor, GS-0938, as well as sofosbuvir + ribavirin (SOF + RBV) for 12 and 24 weeks. One of these 8 arms was a placebo arm. Due to liver enzyme (ALT and AST) elevations in patients receiving GS-0938, dosing of all GS-0938 arms was halted in December 2011 with patients having received ≤9 weeks of treatment. These patients were followed off treatment for 12 weeks (safety follow-up period) and if eligible (based on ALT and HCV RNA levels and consenting), patients were retreated with SOF + RBV for 24 weeks and then followed off treatment for 24 weeks.

Most ALT elevations resolved during the 12-week safety follow-up period and these 132 patients (initially randomized to GS-0938 (n=40), GS-0938 + SOF (n=35), GS-0938 + SOF + RBV (n=36), or placebo (n=21) and who did not achieve SVR) were re-treated with SOF + RBV for 24 weeks and then followed off treatment for 24 weeks.

Development of GS-0938 has been discontinued. Results of all SOF + RBV treatment arms are included in the full submission document.

A5. **Priority Question: Please explain why no results are presented for the placebo arm from the VALENCE trial (manufacturer's submission p. 119-121). According to the flow chart in the manufacturer's submission (p. 93) and the abstract by Zeuzem et al. (ref 40), 93% (79/85) of the placebo group discontinued the study due to termination by the sponsor (patients receiving placebo were offered treatment in an alternative protocol).**

**Please clarify at what time in the trial this discontinuation occurred and whether it influenced the purpose of the placebo arm.**

Patients were intially randomised 4:1 to receive 12 weeks of SOF +RBV or placebo. During the conduct of the study, emerging data from the other SOF Phase 3 trials suggested GT 3 patients would benefit from extending treatment duration beyond 12 weeks. The VALENCE trial was subsequently amended so that GT3 patients would receive 24 weeks of SOF + RBV therapy and GT 2 patients would continue to receive 12 weeks of SOF + RBV. In order to quickly implement this amendment prior to a large number of GT3 patients completing 12 weeks of therapy, the study was unblinded. Hence, patients initially assigned to placebo were discontinued from the study (and offered treatment in an alternative protocol). The median treatment duration for placebo recipients at the time of discontinuation was 8 weeks. The purpose of the placebo arm was to provide information on the background incidence of adverse events in chronic HCV patients not on active treatment. The primary endpoint of SVR12 was not influenced by the discontinuation of the placebo arm as no patients, as expected, in this group achieved SVR12.

A6. **Priority Question: In the VALENCE trial (manufacturer's submission p. 89-90) data imputation is mentioned for some outcomes but not others. Please clarify for all the reported outcomes whether data were imputed and which method(s) were employed**

Values for missing data were not imputed for any endpoint with the exception of HCV RNA data.

Details from the statistical analysis plan are as follows:

*For analyses of* categorical *HCV RNA data, if a data point is missing and is preceded and followed in time by values that are* (academic in confidence)

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*Except for the imputation rules described above for HCV RNA and cirrhotic status, values for other missing data (including all safety data and health related quality of life data) will not be imputed.*

LLOQ TND = lower limit of quantitation target not detected

A7. **The flow chart for clinical effectiveness search results (Figure 3, manufacturer's submission p. 54) indicates that 30 eligible citations were included in the systematic review, and these reported on 21 studies (as shown in the table on manufacturer's submission p. 55). However, there are 35 unique citations given in the table. Please account for all of the listed citations in the table (manufacturer's submission p. 55) to ensure that the number cited in the table is in agreement with the number reported in the flow chart (Figure 3, manufacturer's submission p. 54).**

The cited value for eligible citations identified via the systematic review is correct at 30, however in order to fully inform Table 8 and subsequent tables additional information for Gilead sponsored trials were sourced from six clinical study reports / protocols (refs 19,42,43,45,16 and 54). Whilst we make reference to the fact that CSRs and protocols were used in the footnote to the table in section 6.2.3 we appreciate that a similar footnote should have been added to Figure 3 to explain that the systematic review identified 30 unique citations and that for Gilead sponsored studies the additional citations were utilised to inform subsequent tables.

1. Gilead Sciences Inc. Interim clinical study report: GS-US-334-0133. A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of GS-7977 + Ribavirin for 12 Weeks in Treatment Naïve and Treatment Experienced Subjects with Chronic Genotype 2 or 3 HCV Infection. *Data on file* 2013.
2. Gilead Sciences Inc. Second interim synoptic clinical study report: GS-US-334-0123. A Phase 3, Open-label Study to Investigate the Efficacy and Safety of GS-7977 plus Ribavirin in Chronic Genotype 1, 2 and 3 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Subjects. *Data on file* 2013.
3. Gilead Sciences Inc. Second interim synoptic clinical study report: GS-US-334-0123. A Phase 3, Open-label Study to Investigate the Efficacy and Safety of GS-7977 plus Ribavirin in Chronic Genotype 1, 2 and 3 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) Co-infected Subjects. *Data on file* 2013.
4. Gilead Sciences Inc. Clinical study protocol: A Phase 2, Open-Label study of Sofosbuvir in Combination with PEG and Ribavirin for 12 Weeks in Treatment Experienced Subjects with Chronic HCV Infection Genotype 2 or 3. *Data on file* 2013.

5. Gilead Sciences Inc. Interim clinical study report: P20938-0721. QUANTUM An International, Multi-center, Blinded, Randomized Study to Investigate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Administration of Regimens Containing PSI-352938, PSI-7977, and Ribavirin in Patients with Chronic HCV Infection. *Data on file* 2013.
6. Gilead Sciences Inc. Abbreviated final clinical study report: QUANTUM: An International, Multi-center, Blinded, Randomized Study to Investigate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Administration of Regimens Containing PSI-352938, PSI-7977, and Ribavirin in Patients with Chronic HCV Infection. *Data on file* 2013.

A8. **Please provide participant flow charts for the following phase 2 trials (LONESTAR-2, QUANTUM, ELECTRON, PHOTON-1 and P7977-0221), indicating the number of participants starting and completing the trial and the number of patients who were included in the statistical analyses, as per section 6.3.8 of the manufacturer's submission.**

<u>Patient disposition – LONESTAR-2 (Lawitz *et al.* 2013 – ref 44*) – Academic in confidence</u>

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Please note that for the GT2 group which one subject discontinued treatment due to non-compliance all 23 subjects completed the study (e.g. the appropriate follow up). For the GT3 group 22 subjects completed the study.

*A copy of the presentation slides for reference 44 is included alongside this response for information

Patient disposition QUANTUM ( CSR – ref 46) (Confidential)

*All study subjects*

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*a.Withdrawn consent or enrolment closed.*

*DC= discontinued, WK=week*

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*Further details on re-treatment group* (Academic in confidence)

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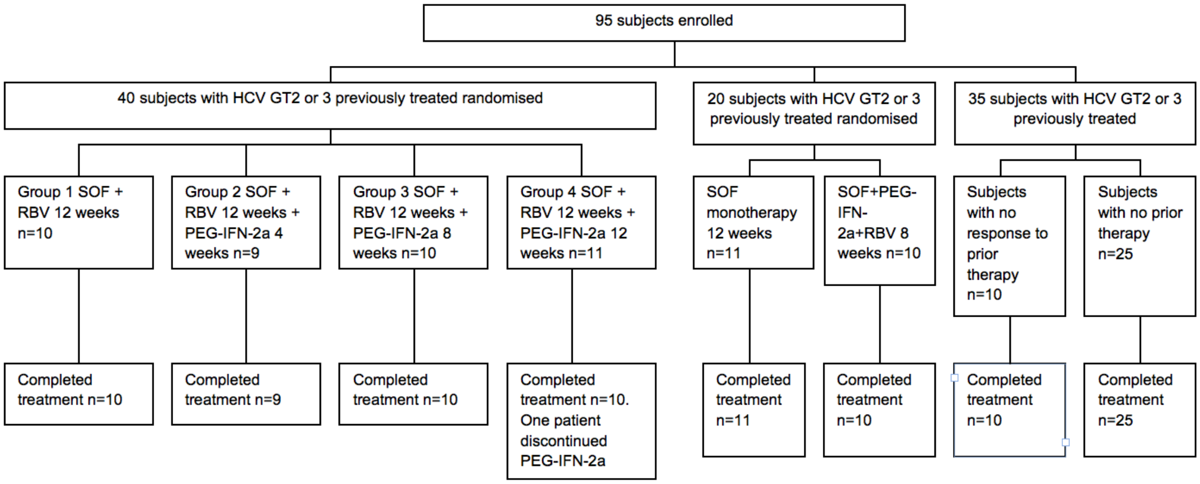
Patient disposition – ELECTRON (Gane *et al.* 2013- ref 57)




Patient disposition – PHOTON-1 (Sulkowski *et al.* 2013 – ref 41, Interim CSR – ref 42) (Academic in confidence)

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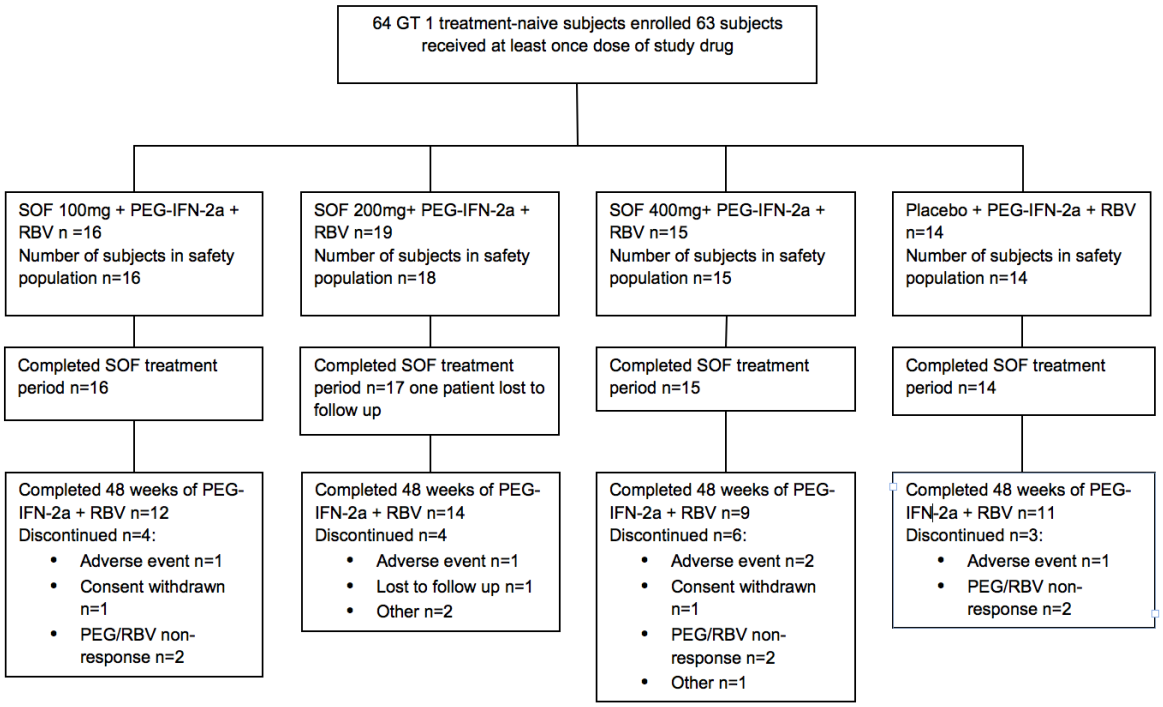
The status of PHOTON as per the interim CSR is as follows:

| | SOF+RBV 12 weeks GT2/3 TN | SOF+RBV 24 weeks GT2/3 TE | SOF+RBV 24 weeks GT1 TN |
|---|---|---|---|
| Study status | | | |
| Ongoing (n) | 0 | 26 | 80 |
| Completed study (n) | 47 | 13 | 7 |
| Discontinued study (n) | 21 | 2 | 27 |
| Reason for discontinuation | | | |
| Efficacy failure (n) | X | X | X |
| Lost to follow-up (n) | X | X | X |
| Subject withdrew consent (n) | X | X | X |
| Death (n) | X | X | X |

<u>Patient disposition - P7977-0221 (Rodriguez Torres *et al.* 2013 – ref 58)</u>




48 weeks PEG-IFN-2a = SOF or placebo plus PEG-IFN-2a + RBV for 28 days followed by PEG-IFN-2a + RBV for 44 weeks

A9. **Please provide critical appraisal of the four included non-randomised phase 2 trials (PROTON (cohort B), PHOTON-1, LONESTAR-2 and P7977-2025) as described in section 6.8.1 of the manufacturer's submission.**

| **Trial no. (acronym)** | **P7077-0422 PROTON (Cohort B only)** | **GS-US-334-0123 PHOTON-1** | **GS-US-334-0151 LONESTAR-2** | **P7977-2025 (Pre- liver transplantation)** |
|---|---|---|---|---|
| Was randomisation carried out appropriately? | Yes | NA | NA | NA |
| Was the concealment of treatment allocation adequate? | NA - Cohort B was open-label | NA | NA | NA |
| Were the groups similar at the outset of the study in terms of prognostic factors? | Yes | Yes | Yes | Yes |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | NA | NA | NA | NA |
| Were there any unexpected imbalances in drop-outs between groups? | No | No | No | No |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | No | No | No | No |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Yes | Yes | Yes | Yes |

NA-not applicable open label

A10. **In the FUSION, POSITRON and VALENCE trials please explain what is meant by a "matching placebo", that is, do the placebo elements substitute sofosbuvir alone or both sofosbuvir plus ribavirin?**

The placebo elements substituted both sofosbuvir and ribavirin in the FUSION, POSITRON and VALENCE trials:

- Placebo tablets to match ribavirin tablets were identical in physical appearance to the 200 mg strength ribavirin tablets
- Placebo tablets to match sofosbuvir tablets were identical in appearance to the 400 mg strength sofosbuvir tablets.

The sofosbuvir, ribavirin and placebo tablets all met the applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2003) and/or other local regulations as applicable.

A11. **In the VALENCE trial please clarify how many patients were included in the statistical analysis, and please specify if the patient numbers differ by outcome (manufacturer's submission p. 89-90 and p. 93).**

In VALENCE the following patient numbers were included in the Full Analysis Set and the Safety Analysis Set (Source: interim CSR). The numbers do not differ by outcome.

| | **GT2/3 Placebo N=85** | **GT 2 SOF + RBV 12 weeks n=73** | **GT3 SOF+RBV 12 weeks n=11** | **GT3 SOF+RBV 24 weeks (n=250)** | **Total n=419** |
|---|---|---|---|---|---|
| Subjects in Safety Analysis Set | 85 | 73 | 11 | 250 | 419 |
| Subjects in Full Analysis Set | 0 | 73 | 11 | 250 | 334 |

A12. **In the manufacturer's submission, Table 10 (p. 68) indicates that the effect of treatment on health related quality of life was measured in the VALENCE trial, but the results for this outcome are not provided (manufacturer's submission p. 119-121). Please provide the results or clarify why they have not been included.**

While the quality of life results for VALENCE were not available at the time of submission preliminary data is now available and is provided (as academic in confidence) alongside this response. This data will be presented at EASL 2014 on April 9th.

A13. **In the NEUTRINO trial (manufacturer's submission p. 100), FISSION trial (manufacturer's submission p. 106), FUSION trial (manufacturer's submission p. 111), POSITRON trial (manufacturer's submission p. 118) and VALENCE trial (manufacturer's submission p. 119-121) the analyses of health related quality of life are classed as 'exploratory'. Please clarify what this means. Please explain how the quality of life outcomes were analysed statistically and the numbers of patients in these trials who were included in the statistical analyses of quality of life**.

The analysis of health related quality of life data are classified as "exploratory" because the analysis focuses on the summary statistics with graphical presentations. P-values are provided for the between- and within- treatment comparisons using Nonparametric methods, but no hypotheses were pre-specified and the p values should be interpreted with caution as multiple endpoints are being tested, and the study has not been powered to test these exploratory endpoints.

Multiple composite scores for each visit and change from baseline for each post-baseline visit were calculated and analysed.

All continuous quality of life scores were summarized with descriptive statistics (n, mean, SD, median, Q1, Q3, min and max) by treatment group and analysis visit. Change from baseline to each post-baseline visit and change from end of treatment to follow ups at weeks 4 and 12 was

also summarized. A Wilcoxon signed rank test was used to explore the statistical significance of the change from baseline to each post-baseline visit and change from end of treatment to each follow-up visit within a treatment group.

For the quality of life analysis, the full analysis set were used and all the subjects having at least one quality of life measure were included in the analysis but the number of subjects varies over time. Full details on patient numbers can be found in the clinical study reports provided.

Please note that since submission a paper detailing the quality of life data has been published (Younossi ZM et al. Minimal impact of sofosbuvir and ribavirin on health related quality of life in Chronic Hepatitis (CH-C). Journal of Hepatology. 2013. http://dx.doi.org/10.1016/j.jhep2013.12.006) and a copy is provided alongside this response.

## Section B: Clarification on cost-effectiveness data

B1. **Priority Question: Table 56 (manufacturer's submission p. 212-213) shows that the utility decrements owing to adverse events differed for sofosbuvir by each sub-category of genotype, treatment experience and interferon eligibility as based on the individual trials for each category. The decrements therefore ranged considerably for the different sofosbuvir arms in each trial. Please re-run the economic model using a pooled estimate of the utility decrement due to adverse events from all relevant trials and provide the results.**

A pooled utility decrement of -8% was estimated for sofosbuvir, based on the quality of life data collected in FUSION, FISSION, NEUTRINO and POSITRON. The calculation was conducted using patient-level data. First, the difference between the baseline utility and the utility at the end of the treatment was calculated for each patient for all of the above-mentioned trials. Then the average across all patients was computed. The model was re-run with the new utility decrement for all sofosbuvir arms. As shown in the table below the ICERs/QALY did not change substantially compared to those originally submitted.

| | | Submitted | New |
|---|---|---|---|
| GT2 TN IE | SOF vs. PR (24 wks) | 46,324 £/QALY | 47,079 £/QALY |
| GT2 TN UI | SOF vs. No treatment | 8,154 £/QALY | 8,156 £/QALY |
| GT2 TE IE | SOF vs. No treatment | 9,274 £/QALY | 9,282 £/QALY |
| | SOF vs. PR (48 wks) | 12,519 £/QALY | 12,536 £/QALY |
| GT2 TE UI | SOF vs. No treatment | 8,591 £/QALY | 8,594 £/QALY |
| GT3 TN IE | SOF vs. PR (24 wks) | 20,613 £/QALY | 20,422 £/QALY |
| GT3 TN UI | SOF vs. No treatment | 21,478 £/QALY | 21,489 £/QALY |
| GT3 TE IE | SOF vs. No treatment | 8,557 £/QALY | 8,515 £/QALY |
| | SOF vs. PR (48 wks) | 12,246 £/QALY | 12,146 £/QALY |
| GT3 TE UI | SOF vs. No treatment | 28,569 £/QALY | 28,589 £/QALY |
| GT1 TN IE | SOF vs. Telaprevir | 11,836 £/QALY | 11,540 £/QALY |

| | | | |
|---|---|---|---|
| | SOF vs. Boceprevir | 7,292 £/QALY | 7,170 £/QALY |
| | SOF vs. PR (48 wks) | 14,930 £/QALY | 14,798 £/QALY |
| GT1 TN UI | SOF vs. No treatment | 49,249 £/QALY | 48,397 £/QALY |
| GT4/5/6 | SOF vs. PR (48 wks) | 26,797 £/QALY | 26,459 £/QALY |

GT: Genotype; SOF: Sofosbuvir; PR: PEGINF2a + RBV; QALY: Quality Adjusted Life Year; TE: Treatment-experienced; TN: Treatment-naïve; UI: Unsuitable for interferon; Wks: Weeks

B2**. Priority Question: The manufacturer's submission (p. 168) states that an economic analysis was not conducted for HCV treatment-experienced patients with genotype 1 infection. The reason given is that the SVR for these patients is extrapolated based on an FDA model (as no trial data were available). Please provide a reference for the FDA model. Please provide an estimate of cost-effectiveness based on the FDA model for genotype 1 treatment experienced patients, explaining, if necessary, the limitations of the approach.**

During the FDA's Advisory Committee meeting on the 25th October 2013, the FDA asked whether the high SVR rate of 89%* in the GT1 treatment-naïve population provided enough evidence to support use of SOF + PEG-IFN + RBV for treatment of CHC in GT1 patients who had previously failed to respond to a course of PEG-IFN and RBV.

Historically, approximately 50% of treatment-naïve GT1 patients have responded to PEG-IFN + RBV treatment with 50% failing to respond. In NEUTRINO, 89%* of treatment-naïve GT1 patients responded to the combination of SOF + PEG-IFN-2a + RBV. The higher rate of overall SVR observed in NEUTRINO is likely driven by successful treatment of a proportion of patients who would likely be PEG-IFN + RBV failures (with the assumption that all patients that would have achieved SVR with PEG-IFN+RBV achieved an SVR with SOF+ PEG-IFN+RBV). The increase in SVR (from 50% to 89%*) is representative of the efficacy of SOF + PEG-IFN + RBV in the 50% non-responders that historically would be expected to be in the study. The FDA therefore concluded that given the high SVR rates in NEUTRINO, 39/50 (78%) of PEG-IFN + RBV non-responders are likely to respond to SOF + PEG-IFN + RBV treatment, yielding the approximate SVR rate of 78% in the GT1 PEG+RBV treatment naive population

PEG-IFN +RBV treatment failures have historically been classified as relapsers, partial responders, null responders and patients who discontinue treatment. These patients historically have differential responses (due to variable 'interferon-responsiveness') to re-treatment with a PEG-IFN +RBV based regimen. The FDA bridging analysis does not take this into consideration and views the GT1 TE patient group as a single homogenous entity, which could be seen as a weakness of this modeling. However, given the high unmet medical need of this population, its inclusion within the SPC and the excellent safety profile of the SOF + PEG + RBV 12-week regimen, we have included this analysis for consideration within the submission given the high unmet need and lack of suitable treatment options available. Based on the FDA modeling we believe that this would represent both a clinically and cost effective option.

***** Please note that the Lawitz *et al* 2013 manuscript reported a rate of 89% (261/292). The revised value added one additional GT1 patient who was <LLOQ at SVR4 and was "lost to follow-up = failure" at SVR12, but was subsequently "found" and achieved SVR24

The GT1 treatment-naïve interferon eligible indication currently programmed in the model was re-run to provide ICERs/QALY for SOF + PEG-IFN + RBV (12 weeks) in GT1 treatment-experienced patients against telaprevir, boceprevir and PEG-IFN-2a + RBV. The following changes were made:

- SVR rates for telaprevir and PEG-IFN-2a + RBV were obtained from REALIZE, as reported in the telaprevir NICE STA. SVR rates for boceprevir were obtained from RESPOND-2, as reported in the corresponding NICE STA.

| **SVR rates** | **Non-cirrhotic** | **Cirrhotic** |
|---|---|---|
| SOF + PR (12 weeks) | 78% | 78% |
| Telaprevir | 70.6% | 47.2% |
| Boceprevir | 64.4% | 35.3% |
| PEG_IFN-2a + RBV | 17.6% | 13.3% |

- Grade 3 and 4 anaemia, thrombocytopenia and neutropenia for telaprevir and PEG-IFN-2a + RBV were obtained from REALIZE as reported by Kaufman (2011).[1] For boceprevir grade 3 and 4 anaemia was obtained from RESPOND-2, as reported by Bacon (2011).[2]

- Average treatment duration for telaprevir (39.0 weeks) and PEG-IFN-2a + RBV (29.7 weeks) was calibrated from REALIZE, as reported in the telaprevir NICE STA. For boceprevir (36.7 weeks) it was calibrated from RESPOND-2, as reported by Bacon (2011).

- The costs associated with the initial evaluation of a new patient with confirmed HCV was removed from the monitoring costs.

- No change was made to the proportion of cirrhotic patients within the combined cohort (that is, 19% of patients started the model in the cirrhotic state).

Results show that SOF + PEG-IFN-2a + RBV is cost-effective in GT1 treatment-experienced patients against telaprevir (£8,203/QALY), boceprevir (£683/QALY) and PEG-IFN-2a + RBV (£12,641/QALY).

[1] Kauffman, RS, Muir, AJ, Nelson, DR, Andreone, P, Everson, GT, Dusheiko, GM, Pol, S, Adda, N, Wright, CI, Bengtsson, L, Martin, M, Sankoh, AJ, George, S, Jacobson, IM, Sherman, KE, and Zeuzem, S. Review Activity/Safety: Telaprevir in combination with Peginterferon Alfa-2a and Ribavirin Increased Sustained Virologic Response in Genotype 1 Chronic HCV. HepDART 2011. 4-12-2011. 4-12-2011

[2] Bacon BR, Gordon SC, Lawitz E., *et al.* Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011; 364: 1207–17

In addition to this analysis, we have just learnt that an abstract of a phase-2 study that is relevant for this population i.e treating patients who have failed PEG-IFN + RBV + a third directly acting antiviral (DAA) with SOF + PEG-IFN + RBV will be presented at the European EASL Liver meeting in London next month (attached). This study is an ad-hoc rollover study containing patients from various Gilead studies and was not in our formal Phase 3 development programme. This publication was not expected by the UK project team to be presented and published until next year. As such, we would like to apologise for omitting it from the original submission but include it here in order to help answer the ERG's question around this particular patient population.

B3. **Priority Question: The economic model is based on previous economic models for chronic hepatitis C developed by SHTAC. The most recent SHTAC model (Hartwell et al 2011) includes a possible transition from the SVR state to the HCC state. Please clarify why this transition was not included in the sofosbuvir economic model. If possible, please provide an amended model and results to include the transition from the cirrhotic state with SVR to the HCC state (including the transition probabilities used).**

Data is scarce to support the transition from SVR state to HCC state. In Hartwell et al. and in the telaprevir submission this probability was assumed the same as the probability of moving from compensated cirrhosis to HCC for patients who did not reach SVR, that is 0.014.[3] This assumption seems unrealistic since clinical expert opinion and recent long-term follow-up studies indicate a markedly reduced rate of HCC in those patients with cirrhosis who achieve SVR.[4] Recent evidence would in fact suggest that the incidence of HCC (once SVR is achieved) is almost 5 times lower than that of non-SVR to HCC.[5] In the boceprevir submission this transition probability was assumed to be 0.001 but no source for this value was provided.

Nevertheless, the model included in the DSA the possibility of recurrence for patients who reach SVR (that is, patients who reached SVR can go back to the compensated cirrhosis state). This means that these patients can then progress to the HCC state. The probability of recurrence was set to 0.01 based on consultation with a clinical expert.

Despite this, as requested by NICE the model was re-run assuming that the transition probability from cirrhotic with SVR to HCC is 0.005.[6] This was considered a reasonable value since it not only falls within the range of the two extreme values used in previous submissions (0.001 and 0.014) but this is also a recent study based on about 300 patients who did or did not reach SVR and were followed for up to 4 years (median estimates). The model was also re-run

[3] Fattovich G, Giustina G, Degos F et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112:463-472

[4] Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferonalpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology 2007;45:579-87.
Zhang CH, Xu GL, Jia WD, et al. Effects of interferon treatment on development and progression of hepatocellular carcinoma in patients with chronic virus infection: a metaanalysis of randomized controlled trials. Int J Cancer 2011;129:1254-64

[5] Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol 2010;52:652–7.

[6] Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol 2010;52:652–7.

with the lower and upper bounds provided for this transition probability, that is, 0.002 and 0.013, respectively. As shown in the table below the ICERs/QALY did not change substantially compared to those originally submitted.

| | | Submitted | BC: 0.005 | LB: 0.002 | UB: 0.013 |
|---|---|---|---|---|---|
| GT2 TN IE | SOF vs. PR (24 wks) | 46,324 £/QALY | 49,617 £/QALY | 47,636 £/QALY | 54,957 £/QALY |
| GT2 TN UI | SOF vs. No treatment | 8,154 £/QALY | 8,694 £/QALY | 8,371 £/QALY | 9,544 £/QALY |
| GT2 TE IE | SOF vs. No treatment | 9,274 £/QALY | 9,825 £/QALY | 9,496 £/QALY | 10,684 £/QALY |
| | SOF vs. PR (48 wks) | 12,519 £/QALY | 13,189 £/QALY | 12,788 £/QALY | 14,227 £/QALY |
| GT2 TE UI | SOF vs. No treatment | 8,591 £/QALY | 9,149 £/QALY | 8,815 £/QALY | 10,027 £/QALY |
| GT3 TN IE | SOF vs. PR (24 wks) | 20,613 £/QALY | 22,850 £/QALY | 21,489 £/QALY | 26,771 £/QALY |
| GT3 TN UI | SOF vs. No treatment | 21,478 £/QALY | 23,032 £/QALY | 22,096 £/QALY | 25,574 £/QALY |
| GT3 TE IE | SOF vs. No treatment | 8,557 £/QALY | 9,273 £/QALY | 8,842 £/QALY | 10,442 £/QALY |
| | SOF vs. PR (48 wks) | 12,246 £/QALY | 13,214 £/QALY | 12,631 £/QALY | 14,796 £/QALY |
| GT3 TE UI | SOF vs. No treatment | 28,569 £/QALY | 30,190 £/QALY | 29,219 £/QALY | 32,758 £/QALY |
| GT1 TN IE | SOF vs. Telaprevir | 11,836 £/QALY | 12,743 £/QALY | 12,197 £/QALY | 14,216 £/QALY |
| | SOF vs. Boceprevir | 7,292 £/QALY | 7,829 £/QALY | 7,507 £/QALY | 8,684 £/QALY |
| | SOF vs. PR (48 wks) | 14,930 £/QALY | 16,070 £/QALY | 15,384 £/QALY | 17,934 £/QALY |
| GT1 TN UI | SOF vs. No treatment | 49,249 £/QALY | 51,294 £/QALY | 50,074 £/QALY | 54,434 £/QALY |
| GT4/5/6 | SOF vs. PR (48 wks) | 26,797 £/QALY | 27,468 £/QALY | 27,071 £/QALY | 28,451 £/QALY |

BC: Base case; GT: Genotype; LB: Lower bound; PR: PEGINF2a + RBV; QALY: Quality Adjusted Life Year; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; UB: Upper bound; UI: Unsuitable for interferon; Wks: Weeks

B4. **Priority Question: Table 44 (manufacturer's submission p. 184) states that all-cause mortality is calculated as the average of male and female age-specific mortality rates (from 2011). Please clarify if a weighted average of male and female age-specific mortality was used, rather than a simple average.**

A simple average was used. Nevertheless, the model was re-run with a weighted average of male and female age-specific mortality rates. As shown in the table below the ICERs/QALY did not change substantially compared to those originally submitted.

| | | Submitted | New |
|---|---|---|---|
| GT2 TN IE | SOF vs. PR (24 wks) | 46,324 £/QALY | 46,010 £/QALY |
| GT2 TN UI | SOF vs. No treatment | 8,154 £/QALY | 8,050 £/QALY |
| GT2 TE IE | SOF vs. No treatment | 9,274 £/QALY | 9,159 £/QALY |
| | SOF vs. PR (48 wks) | 12,519 £/QALY | 12,379 £/QALY |
| GT2 TE UI | SOF vs. No treatment | 8,591 £/QALY | 8,483 £/QALY |
| GT3 TN IE | SOF vs. PR (24 wks) | 20,613 £/QALY | 20,458 £/QALY |
| GT3 TN UI | SOF vs. No treatment | 21,478 £/QALY | 21,257 £/QALY |
| GT3 TE IE | SOF vs. No treatment | 8,557 £/QALY | 8,452 £/QALY |
| | SOF vs. PR (48 wks) | 12,246 £/QALY | 12,112 £/QALY |
| GT3 TE UI | SOF vs. No treatment | 28,569 £/QALY | 28,281 £/QALY |

| | | Submitted | New |
|---|---|---|---|
| GT1 TN IE | SOF vs. Telaprevir | 11,836 £/QALY | 11,714 £/QALY |
| | SOF vs. Boceprevir | 7,292 £/QALY | 7,202 £/QALY |
| | SOF vs. PR (48 wks) | 14,930 £/QALY | 14,778 £/QALY |
| GT1 TN UI | SOF vs. No treatment | 49,249 £/QALY | 48,777 £/QALY |
| GT4/5/6 | SOF vs. PR (48 wks) | 26,797 £/QALY | 26,538 £/QALY |

B5. **Priority Question: All-cause mortality probabilities are averaged over ten year age bands (manufacturer's submission Table 44, p. 184). Please clarify reasons for not using mortality probabilities by one year age bands.**

All-cause mortality probabilities were averaged over ten-year age bands, rather than one-year age bands. Since chronic hepatitis C is a slow progressing disease the difference between the two approaches is expected to be small. To confirm this, the model was re-run using mortality probabilities by one-year bands. As shown in the table below the ICERs/QALY did not change substantially compared to those originally submitted.

| | | Submitted | New |
|---|---|---|---|
| GT2 TN IE | SOF vs. PR (24 wks) | 46,324 £/QALY | 45,778 £/QALY |
| GT2 TN UI | SOF vs. No treatment | 8,154 £/QALY | 7,952 £/QALY |
| GT2 TE IE | SOF vs. No treatment | 9,274 £/QALY | 9,052 £/QALY |
| | SOF vs. PR (48 wks) | 12,519 £/QALY | 12,213 £/QALY |
| GT2 TE UI | SOF vs. No treatment | 8,591 £/QALY | 8,381 £/QALY |
| GT3 TN IE | SOF vs. PR (24 wks) | 20,613 £/QALY | 20,326 £/QALY |
| GT3 TN UI | SOF vs. No treatment | 21,478 £/QALY | 21,080 £/QALY |
| GT3 TE IE | SOF vs. No treatment | 8,557 £/QALY | 8,350 £/QALY |
| | SOF vs. PR (48 wks) | 12,246 £/QALY | 11,946 £/QALY |
| GT3 TE UI | SOF vs. No treatment | 28,569 £/QALY | 28,060 £/QALY |
| GT1 TN IE | SOF vs. Telaprevir | 11,836 £/QALY | 11,548 £/QALY |
| | SOF vs. Boceprevir | 7,292 £/QALY | 7,097 £/QALY |
| | SOF vs. PR (48 wks) | 14,930 £/QALY | 14,578 £/QALY |
| GT1 TN UI | SOF vs. No treatment | 49,249 £/QALY | 48,427 £/QALY |
| GT4/5/6 | SOF vs. PR (48 wks) | 26,797 £/QALY | 26,158 £/QALY |

B6. **The manufacturer's submission (p. 164) shows the flow-chart for the health economic systematic review. There appear to be some errors in the flow-chart when cross referring to the numbers reported in the text of the manufacturer's submission (p. 165). For example, the final 'eligible citations' box states there were 53 eligible citations from the original review, but the numbers ('Full-text citation screening 199' - 'excluded articles after 2nd screening 163') do not correspond. Please check the numbers for this and for all other stages of the flow chart and amend them to ensure that they correspond with the text (e.g the numbers reviewed is reported at 309 in the figure but are described**

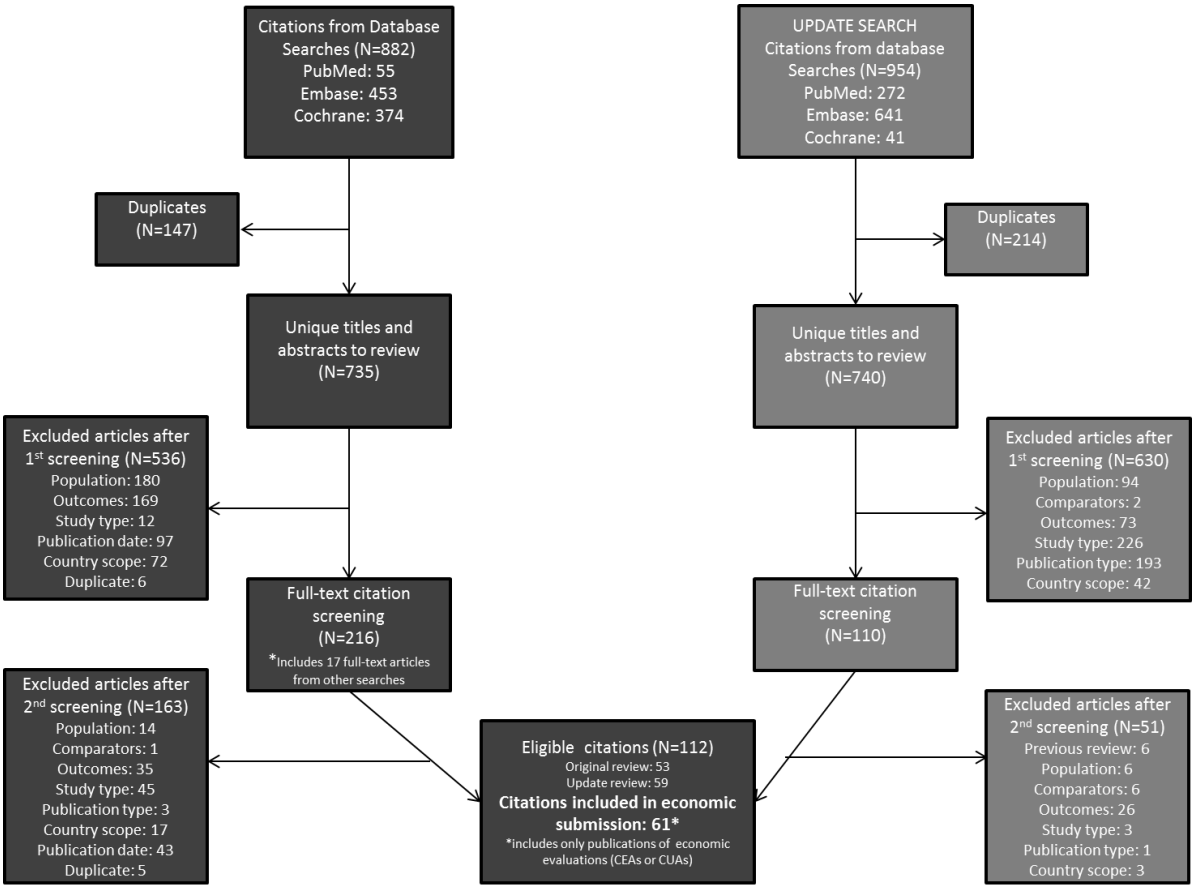
**as 316 in the text; the 'update search' numbers at the 'titles and abstracts to review stage' and the numbers for the detailed reasons for exclusion within the 'excluded studies after 2nd screening' stage of the 'original search' appear to have miscalculations)?**

There was a flow miscalculation in the flow diagram presented in the original submission. The error had been identified but the updated flow diagram was not added to the final submission document in error. This correction included the addition of 17 articles in the full-text review portion of the original search. These articles had been identified in other searches (e.g., clinical, HRQoL) and were then screened for economic data at this stage in the review. The correct diagram has now been included and the text below should be updated as follows: the search in PubMed retrieved 327 results. The search in EMBASE retrieved 1,094 results. The search in CRD retrieved 415 results. A total of 1,836 articles were retrieved by the search. After the duplicates were removed 1,475 abstracts were available to be reviewed against the criteria outlined in Table 37 and 1,166 papers were excluded. In addition, 17 articles from other searches (e.g., epidemiology, HRQoL) were added to the screening and full-text reviewed. Thus, after the abstracts were reviewed 326 (309 + 17) papers were ordered for full publication review. After the full publications were reviewed 112 papers met the inclusion criteria and data were extracted.

B7. **The manufacturer's submission states that there were 112 included studies in the systematic review of economic evaluations. Please provide a clear description of what happened to the full set of studies? In the text (manufacturer's submission p. 165), 61 of these studies are accounted for (and these are also shown in the appendices in Table 152). However, 87 studies were quality assessed in Tables 162-174, and in Tables 153-161 of the appendices there appears to be an additional 31 studies (plus numerous secondary citations within these tables) but it is unclear whether these were all identified as part of the review, because the numbers do not tally. It would be helpful if these numbers could be reconciled please.**

In total, 112 articles were included from the original literature review. However, this economic literature review was broad in nature, with the overall objective to identify all economic data with regard to HCV to provide model inputs for the cost-effectiveness model (CEAs), as well as for the budget impact models (BIMs), and assess the total economic burden of HCV. This means that we included not only cost-effectiveness and cost-utility studies, but budget impact models, cost, cost-minimisation studies, and studies looking at the overall economic burden of HCV.

For the submission to NICE, we needed to report only the economic evaluations (i.e., cost-effectiveness and cost-utility analyses). Therefore, although 112 studies were included in the initial economic literature review, only 61 economic evaluation studies were relevant for inclusion in the NICE submission. Below the flow diagram has been updated to reflect these decisions.

In addition, in the Appendix (Section 10.11) there is an appraisal table where all studies included in the literature review were quality assessed. Instead of including the 61 studies as above mentioned, this table includes 87 studies. This is because the table also included studies

which were not economic evaluations (e.g., cost studies). This occurred because, as part of the overarching literature review, all the studies included in the updated review were appraised and included in the submission not focusing on the 61 papers as it should have been. These tables have now been updated and only contain the 61 studies relevant for the submission.