NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ombitasvir-paritaprevir-ritonavir with or without dasabuvir for treating chronic hepatitis C

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
AbbVie	**EXECUTIVE SUMMARY** AbbVie welcomes the opportunity to comment on the Appraisal Consultation Document (ACD). We are pleased with the preliminary decision to recommend ombitasvir/ paritaprevir/ ritonavir (Viekirax®) given in combination with dasabuvir (Exviera®) for all chronic hepatitis C genotype 1b (HCV GT1b) patients and chronic hepatitis C genotype 1a (HCV GT1a) patients without cirrhosis. We are also pleased with the preliminary decision to recommend ombitasvir/ paritaprevir/ ritonavir for previously treated chronic hepatitis C genotype 4 (HCV GT4) patients without cirrhosis. However, we are disappointed with the preliminary decision not to recommend ombitasvir/ paritaprevir/ ritonavir given in combination with dasabuvir for HCV GT1a patients with compensated cirrhosis and ombitasvir/ paritaprevir/ ritonavir for previously untreated HCV GT4 patients without cirrhosis and all HCV GT4 patients with compensated cirrhosis. For the rest of this document the HCV GT1 regimen composed of ombitasvir/ paritaprevir/ ritonavir given in combination with dasabuvir will be denoted as 3D as it contains three direct acting antiviral therapies and the HCV GT4 regimen, composed of ombitasvir/ paritaprevir/ ritonavir, is referred to as 2D as it contains two direct	Comments noted. The Committee recommended ombitasvir–paritaprevir–ritonavir with or without dasabuvir within its marketing authorisation (see FAD section 1.1)

Consultee	Comment [sic]	Response
	acting antiviral therapies. The 3D regimen for HCV GT1 patients and the 2D regimen for GT4 patients represent a step change in the management of HCV compared to current standard of care. In clinical trials they resulted in consistently high SVR rates across a broad population of patients and they were associated with very few side effects. Given the regimens are interferon-free and all oral, they have the additional clinical benefit over existing treatments of a dramatically improved tolerability profile as well as removing the need for patients to self-inject on a weekly basis. AbbVie believes that all HCV GT1 and GT4 patients should be able to benefit from access to the 3D and 2D regimens respectively in order to ensure equity of access. In relation to the indications for which NICE did not make a positive recommendation, AbbVie's position is that some of NICE's summaries of cost effectiveness are not reasonable interpretations of the evidence provided. Therefore, we do not think the provisional "no" recommendations are sound and we believe that the 3D regimen should also be recommended for previously treated HCV GT1a patients with compensated cirrhosis and the 2D regimen should also be recommended for treatment naïve GT4 patients without cirrhosis and treatment experienced GT4 patients with compensated cirrhosis. In particular we would like to discuss the following points: A. We believe that the utility scenario that the Committee has chosen underestimates the health related quality of life benefit of achieving an SVR and so overestimates the ICERs of the 3D and 2D regimens. This scenario	

Consultee	Comment [sic]	Response
	is inconsistent with the approach used in other appraisals for medicines treating chronic hepatitis C. B. We support the discussion in the ACD about the innovation of 3D and 2D and would agree with the authors that the health related quality of life of the regimens has been underestimated and, therefore, the ICERs upon which the recommendations have been based are likely to be overestimated. C. We believe that the ICERs for some of the 3D and 2D regimens that have not been recommended are in fact within a range that would generally be considered acceptable and would usually lead to positive recommendations by NICE Committees particularly as the regimens offer a high chance to achieve viral cure. D. We understand the NICE position that the 2014 - 2018 Pharmaceutical Price Regulation Scheme (PPRS) should not be regarded as a relevant consideration in the assessment of the cost-effectiveness of individual branded medicines but we believe it should be a consideration if budget impact is a factor in the assessment as is inferred by the ACD. This would allow a proper consideration of the likely rebate payments that are made under the PPRS. All medicines produced by manufacturers who are a member of the voluntary scheme including new medicines launched during the lifetime of the scheme, are covered. AbbVie has joined this voluntary scheme and believes it is especially relevant considering that the Department of Health and industry agree that the PPRS aims to improve access to, and appropriate use of, clinically and cost-effective medicines	

Consultee	Comment [sic]	Response
	These points are discussed within Sections A, B, C and D of our response. Appendix 1 contains confidential details of the pricing arrangement agreed by AbbVie with the Commercial Medicines Unit following a tender process. Appendix 2 contains further points related to factual inaccuracies. This draft decision does not give access to the 3D and 2D regimens to some of the sickest patients with hepatitis C who NHS England would like to treat within their recently published interim commissioning policy for the treatment of chronic hepatitis C in patients with cirrhosis. We sincerely encourage the Committee to reconsider its draft guidance in light of our comments and in particular to extend the recommendation of the 3D and 2D regimens to the HCV patients outlined above.	
AbbVie	**Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?** **A. We believe that the utility scenario that the Committee has chosen underestimates the health related quality of life benefit of achieving an SVR and so overestimates the ICERs of the 3D and 2D regimens** AbbVie is surprised and disappointed that the Committee has decided that utility "Scenario 1" is the most plausible scenario and so it should be used to inform their decision. "Scenario 1" estimates the utility gain for having an SVR from the difference between the pooled EQ-5D values collected at baseline and at 12 weeks after treatment in people who had an SVR in the clinical trials. These EQ-5D values were collected before the patients were aware of their SVR status and therefore, as the Committee accepts, they do not capture the psychological and emotional benefits of being cured. They are clearly an underestimate of the health related	Comments noted. The Committee agreed that because the final EQ-5D values were collected before people were aware of their SVR status, the psychological and emotional benefits of being cured were less likely to be captured and concluded that the most appropriate estimate would likely lie between the trial estimate and the estimate of 0.05 used in the base case (see section 4.13 of the FAD).

Consultee	Comment [sic]	Response
	quality of life (HRQoL) benefit of an HCV patient achieving SVR. The utility gain for having an SVR in "Scenario 1" is considerably less than the gain assumed in the "Revised Base Case". The gain in the "Revised Base Case" is consistent with the approach used in other appraisals for medicines treating chronic hepatitis C including other interferon-free regimens that are currently being assessed by NICE[1,2] and so we do not see why our submission would be treated differently. For example, as stated in section 4.13 of the ACD, the Committee is already aware that the utility benefits from Wright et al.[3] (0.05) and Vera-Llonch et al.[4] (0.041) have been used in technology appraisal guidance for both sofosbuvir[5] and simeprevir[6] for treating chronic hepatitis C. This approach is consistent with the NICE appraisals of boceprevir[7] and telaprevir[8] and AbbVie understands that NICE is also using similar values to these in the two ongoing appraisals for medicines for chronic hepatitis C (ledipasvir/sofosbuvir and daclatasvir)[1,2]: • In the ongoing appraisal of ledipasvir-sofosbuvir[1], the submitting company used the utility benefit of 0.04 from Vera-Llonch.[4] In this appraisal the ERG commented that the value from Wright et al[3] of 0.05 would be more appropriate as it reflects the preferences of the general public in England because it used the UK EQ-5D tariff and while the Committee did express some reservations with the approach used by the Company in this submission, it concluded that it was prepared to accept the utility benefit of 0.04 of Vera-Llonch[4]. • In the submitting company's model in the ongoing appraisal of daclatasvir[2] for treating chronic hepatitis C, the utility gain by a patient achieving an SVR varied by initial fibrosis stage between a range from 0.05 to 0.17. The ERG	

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	preferred to assume that SVR results in equal utility increments across the different fibrosis stages from which people may start treatment and the Committee concluded that the effect of SVR on HRQoL in the model should be assumed to be the same whether or not the person has cirrhosis. The amended basecase run by the ERG assumed equal utility increments of 0.05 for having an SVR in all fibrosis stages. There is evidence in Vera-Llonch[4] that it takes time for the utility of a patient to stop increasing post-treatment once they have attained SVR. In fact, the ADVANCE trial found that patients' utility was still increasing 48 weeks after treatment had stopped for patients who received 24 weeks of treatment. In conclusion, the utility scenario that the Committee has chosen to inform their decision underestimates the HRQoL benefit of a patient achieving SVR and is inconsistent with the approach used in both recent and current appraisals of medicines for chronic hepatitis C. Therefore, "Scenario 1" overestimates the ICERs of 3D and 2D.	
AbbVie	**B. We support the discussion about the innovation of 3D and 2D and would agree that the health related quality of life of the regimens has been underestimated and, therefore, the ICERs upon which the recommendations have been based are likely to be overestimates** AbbVie agree with the Committee that 3D and 2D offer oral, shortened, and interferon-free treatments, which are particularly important to patients, and a major development in the clinical management of chronic hepatitis C. We welcome the acknowledgement in Section 4.19 of the ACD that 3D and 2D are valuable new therapies for treating chronic hepatitis C compared with peginterferon alfa and	Comments noted. The FAD has been updated to state that Committee had taken these potential benefits into account when considering the cost effectiveness of 3D and 2D (see section 4.19 of the FAD).

Consultee	Comment [sic]	Response
	ribavirin. Further, that they are associated with other benefits for people with chronic hepatitis C that if taken into account, are likely to decrease the ICERs such as: • possible regression of fibrosis • reduced transmission of HCV • improved earning capacity of patients with chronic hepatitis C	
AbbVie	**C. We believe that the ICERs for some of the 3D and 2D regimens that have not been recommended are in fact within a range that would generally be considered acceptable and would usually lead to positive recommendations by NICE Committees particularly as the regimens offer a high chance to achieve viral cure** Both the 3D and 2D regimens offer the chance to achieve a viral cure. Given the evidence discussed in Sections A and B of our response above, AbbVie strongly believes that the ICERs for 3D and 2D are lower than those that the Committee have used to inform their decisions. In particular we believe that the ICERs for the 3D regimen for previously treated HCV GT1a patients with compensated cirrhosis and the 2D regimen for treatment naïve GT4 patients without cirrhosis and treatment experienced GT4 patients with compensated cirrhosis are highly likely to be within the normal range of acceptability for the Committee. Under the "Revised Base Case" these ICERs are currently £26,516, £20,351 and £22,331 respectively. These ICERs result from including the utility gain for achieving an SVR that is consistent with other recent and ongoing appraisals for treatments for chronic hepatitis C as described in Section A. Also, these ICERs are likely to be overestimates given the factors described in Section B. For treatment naïve GT4 patients without cirrhosis, 2D is likely to represent the only available interferon-free regimen. Section 6.3 of the NICE methods guide[9] describes the factors that will be taken into account "above a most plausible ICER of £20,000 per QALY gained". These factors will be used to judge the acceptability of the technology as an effective use of NHS resources. One such factor is "the innovative nature of the technology, specifically if	Comments noted. The Committee has recommended ombitasvir–paritaprevir–ritonavir with or without dasabuvir within its marketing authorisation (see section 1.1 of the FAD)

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	the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure." Clearly this factor should be taken into account for 3D and 2D given the Committee's view of the treatments described in 4.19 of the ACD and as the 3D and 2D offer the chance to achieve a viral cure. AbbVie notes from paragraph 4.22 of the ACD document that NICE believe the acceptable ICERs are impacted by any perceived increase in budget impact. However, if budget impact is to be taken into account in this way AbbVie believe additional considerations must be taken into account also (please see point D for further detail).	
AbbVie	**D. We understand the NICE position that the 2014 PPRS payment mechanism should not be regarded as a relevant consideration in the assessment of the cost-effectiveness of branded medicines but we believe it should be a consideration if budget impact is a factor in the assessment as seems to be inferred by the ACD** The ACD described the concerns that NHS England have about the increase in investment and capacity needed for the implementation of 3D and 2D and for the other treatments for hepatitis C currently being appraised by NICE. The Committee recognised in paragraph 4.22 that the Guide to Methods of Technology Appraisal[9] indicates that there needs to be increasing certainty of the cost effectiveness of a technology as the NHS budget impact of its adoption increases. This implies that budget impact is having an impact on the decision the Committee is making for 3D and 2D. This implication is supported by the inclusion of paragraph 1.2 in the recommendations section of the ACD. AbbVie's position is that budget impact should not determine the Appraisal	Comments noted. The Committee acknowledged that there would be significant impact on the total budget for specialised services associated with making these drugs available in the NHS. The Committee recognised that the NICE guide to the methods of technology appraisal indicates the need to be increasingly certain of the cost effectiveness of a technology as the NHS budget impact of its adoption increases. However, the Committee noted that the ICERs were generally below £20,000 per QALY gained for ombitasvir–paritaprevir–ritonavir with or without dasabuvir for the populations specified in the marketing authorisation. (see sections 4.21 -4.22 of the FAD) The Committee understood that NHS England is exploring other ways of managing the financial impact of use of these new drugs, such as tendering, and it could be argued that the rebate provided by companies as part of the 2014 Pharmaceutical Price Regulation Scheme (PPRS) payment mechanism could be considered as a way of managing the budgetary impact of access to these treatments. The Committee understood, in

Consultee	Comment [sic]	Response
	Committee's decision. We are concerned about the comments made by NHS England on these points and the influence that it seems to have had on the Committee (as evidenced in particular by paragraph 1.2). In this regard, the Pharmaceutical Price Regulation Scheme (PPRS)[10] is highly relevant. For the NHS, the total medicines budget is pre-determined and agreed between the ABPI and the Department of Health for medicines supplied by members of the voluntary scheme, which includes AbbVie. The current 2014 PPRS[10] agreement provides a cap on expenditure on branded medicines of voluntary scheme members and any overspend above this cap is effectively underwritten by industry in the form of rebate payments. This ensures that the NHS has predictability of the branded medicines bill for voluntary scheme members and should certainly be taken into account in an appraisal of a voluntary scheme member's medicines, should budget impact be taken into account by NICE's recommendations. As NICE makes clear in its position statement on the PPRS, the medicines bill cap encompasses new products, which are "included in the calculation of the growth rate of sales for all medicines, that is, they are taken into account in determining whether the agreed growth level has been exceeded and a PPRS payment will be required, and determining the size of the percentage". Therefore the introduction and usage of the 3D and 2D regimens in the treatment of Hepatitis C cannot have an incremental effect on the total drugs bill for the NHS, but any additional cost will effectively be rebated by the industry accordingly. One of the aims of the PPRS is to improve patient access to clinically- and cost-effective medicines. If NICE is taking into account budget impact then we request that NICE issues a formal position statement (specific to the facts in this appraisal)	this context, that one of the key objectives of the PPRS is to 'improve access to innovative medicines commensurate with the outcomes they offer patients by ensuring that medicines approved by NICE are available widely in the NHS' (see section 4.21 of the FAD). However, the Committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal of ombitasvir–paritaprevir–ritonavir with or without dasabuvir. It therefore concluded that the PPRS payment mechanism was irrelevant for the consideration of the cost effectiveness of ombitasvir–paritaprevir–ritonavir with or without dasabuvir. (see section 4.25 of the FAD). For clarity, section 1.2 of the FAD has been amended to state "It is recommended that the decision to treat and the prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, in order to prioritise treatments for patients with the highest unmet clinical need".

Consultee	Comment [sic]	Response
	on PPRS and budget impact. Given the budget cap provided by PPRS, AbbVie believes that the potential budget impact of 3D and 2D should not be influencing influence the Committee's decision and, therefore, the Committee should not require increasing certainty of the cost-effectiveness of 3D and 2D and these medicines should be judged to be cost-effective in the patient groups described in Section C above. It should be noted that no rebate is paid for any spend above the medicines bill cap on products that are produced by manufacturers of the statutory scheme.	
AbbVie	**HAS ALL OF THE RELEVANT EVIDENCE BEEN TAKEN INTO ACCOUNT?** The ACD does not take into account the confidential pricing arrangement that has been agreed with the Commercial Medicines Unit following a tender process. Please see Appendix 1 which illustrates the impact of this pricing arrangement on the cost-effectiveness of the 3D and 2D regimens.	Comments noted. The Committee noted that the company presented additional analyses using confidential contract prices and that these contract prices were the relevant prices the NHS pays for 3D and 2D.The Committee concluded that the contract prices were the appropriate prices on which to base its decision. (see section 4.14 of the FAD section).
AbbVie	**ARE THE PROVISIONAL RECOMMENDATIONS SOUND AND A SUITABLE BASIS FOR GUIDANCE TO THE NHS?** Section 1.2 of the ACD states: *1.2 It is recommended that access to the drugs used to treat hepatitis C is managed through the specialised commissioning programme put in place by NHS England with prescribing decisions made by multidisciplinary teams/centres to ensure that treatment is prioritised for patients with the highest unmet clinical need.*	Comment noted. For clarity, Section 1.2 of the FAD has been updated to state "It is recommended that the decision to treat and the prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, in order to prioritise treatments for people with the highest unmet clinical need".

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	AbbVie notes this point in the ACD and seeks clarity on its intended meaning and effect. It would be useful for NICE to expand upon this point and its rationale for inclusion in future public communication relating to this appraisal so that there is not ambiguity over its meaning or effect. AbbVie would also request that this section is moved from the recommendations section to section 4 of the ACD. AbbVie assumes that this point is not intended to run contrary to the recommendations in paragraph 1.1 and also the NHS Constitution[12] which states "You have the right to drugs and treatments that have been recommended by NICE for use in the NHS, if your doctor says they are clinically appropriate for you." AbbVie seeks reassurance that section 1.2 of the ACD does not conflict with this right and further assumes that it may be relating more specifically to any prioritisation based upon clinical capacity. Please confirm. In addition, whilst we understand that NICE is required to make decisions on the basis of the cost-effectiveness of new technologies, this draft decision does not give access to the 3D and 2D regimens to the sickest patients with hepatitis C who NHS England would like to treat within their recently published interim commissioning policy[13] for the treatment of chronic hepatitis C in patients with cirrhosis.	
AbbVie	**ARE THERE ANY ASPECTS OF THE RECOMMENDATIONS THAT NEED PARTICULAR CONSIDERATION TO ENSURE NICE AVOID UNLAWFUL DISCRIMINATION AGAINST ANY GROUP OF PEOPLE ON THE GROUNDS OF RACE, GENDER, DISABILITY, RELIGION OR BELIEF, SEXUAL ORIENTATION, AGE, GENDER REASSIGNMENT, PREGNANCY AND MATERNITY?** No aspects of the recommendations need particular consideration under these	Comments noted.

Consultee	Comment [sic]	Response
	grounds.	
British Association for the Study of the Liver	Many thanks for allowing BASL (British Association for the Study of the Liver) and BVHG (British Viral Hepatitis Group – a Special Interest Group within BASL) to respond to the ACD for Ombitasvir/Paritaprevir/Ritonavir +/- Dasabuvir. The first and primary response we would like to make is to fully support the decision by NICE to progress with this assessment despite the requests put forward by NHSE. We fully agree that the current and future technology assessment processes for hepatitis C agents should continue unaffected and welcome this decision and outcome. We are however unclear on the wording in section 1.2. NHSE does not have specific 'specialised commissioning programmes' – it prepares, commissions and delivers policies, and commissions operational delivery networks, and the term 'programme' is not one which is clear when used in reference to NHSE. Clarity on what NICE are suggesting would be useful. In reference to the more specific detail related to the Ombitasvir/Paritaprevir/Ritonavir +/- Dasabuvir ACD we generally support the conclusions reached by NICE. Our only comments are to point out that 12 weeks of therapy in G1a and G4 cirrhotic patients would be acceptable to clinicians and there is increasing data becoming available supporting this regimen length. We appreciate that NICE assesses such technologies against the current licensed posology regimens and list prices, and that the current license in these patient groups is 24 and not 12 weeks and that reimbursement programmes cannot be considered. We would however urge NICE to potentially reconsider a 12 week regimen if Abbvie apply for and gain such a	Comments noted. The Committee has recommended ombitasvir–paritaprevir–ritonavir with or without dasabuvir within its marketing authorisation (see FAD section 1.1) For clarity, section 1.2 of the FAD has been updated to state "It is recommended that the decision to treat and the prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, in order to prioritise treatments for people with the highest unmet clinical need".

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	license in the future. Many thanks for allowing us to comment on this ACD and we would like to congratulate NICE on balanced and thorough processes and conclusions.	
British HIV Association (BHIVA) and British Association of Sexual Health and HIV (BASHH)	Many thanks for asking us to comment on the ACD for the STA for ombitasvir/paritaprevir/ritonavir (with or without dasabuvir) for treating chronic HCV (ID731). We would like to congratulate the Appraisal Committee for performing a thorough appraisal and coming up with fair recommendations for the use of this combination for patients with HCV infection. We would also like to express our gratitude to the Committee for recognising the needs of HIV/HCV co-infected patients and ensuring inclusion of co-infected in these recommendations. We have no further comments on this ACD at this stage.	Comment noted, thank you. No action required
British Society of Gastroenterology	In relation to the above consultation exercise we agree with the recommendations in table 1.1 but we feel paragraph 1.2 is incorrect and would recommend the following paragraph be inserted in its place "It is recommended that in England the decision to treat and the prescribing decisions are made by the multidisciplinary teams in the operational delivery networks now established by NHS England and this should be in partnership with and supported by NHS England"	Comments noted. Section 1.2 of the FAD has been updated to state “It is recommended that the decision to treat and the prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, in order to prioritise treatments for people with the highest unmet clinical need”.
Haemophilia Society	The Appraisal Committee is interested in receiving comments on the following: • Has all of the relevant evidence been taken into account? • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • Are the provisional recommendations sound and a suitable basis for guidance to the NHS?	Comments noted. Section 1.2 of the FAD has been updated to state “It is recommended that the decision to treat and the prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, in order to prioritise treatments for people with the highest unmet clinical need”. The Committee also noted the consultation comment that any delay in access to treatment

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	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Section 1.2 recommends that access to drugs is managed by NHS England. The Haemophilia Society are extremely concerned that this could lead to discrimination of some patient groups. For example patients that are hard to reach or for the community affected by contaminated blood. The Haemophilia Society believes any delay in access to treatment would have a significant adverse impact on the haemophilia and other bleeding disorder patient population who have a diagnosis of hepatitis C. Every patient from this community who has hepatitis C was infected via their NHS treatment between 1970 and 1991 and so have had chronic hepatitis for a minimum of 23 years. The World Health Organisation states 'A significant number of those who are chronically infected will develop liver cirrhosis or liver cancer. Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15–30% within 20 years'. In light of this there is a strong possibility that that more people with haemophilia and other bleeding disorders will progress from chronic hepatitis to cirrhosis or liver cancer than those who were infected more recently. If treatment were prescribed with no delay they may be prevented from progressing to the advanced stage of hepatitis C. Additionally people with a bleeding disorder have a much greater risk of severe bleeding from the consequences of Hepatitis C and the cost of their Factor replacement treatment would significantly outweigh the cost of Hepatitis C treatment if bleeding were to occur due to delayed treatment. The Haemophilia Society seek reassurance that patients who have had chronic infection for many years would be treated as a priority to prevent further progression	would have a significant adverse impact on people with haemophilia and other bleeding disorders. However, having decided that 3D and 2D treatments should be recommended for all the groups specified in the marketing authorisation, the Committee concluded that no further consideration of these potential equality issues was necessary to meet NICE's obligation to promote equality of access to treatment (see section 4.26 of the FAD).

Consultee	Comment [sic]	Response
	of the disease, and patients would not have to rely on a local policy to identify them as a priority patient group to treat immediately.	
Hepatitis C Trust	The Hepatitis C Trust very much welcomes the fact that NICE is proposing to treat this as a technology appraisal in the usual way, without allowing NHS England's budget difficulties to disadvantage people with hepatitis C who are in need of curative treatment. Access to this interferon-free regimen is a huge step forward that will enormously benefit patients and especially those who may only be in touch with services for short time, such as prisoners and people who inject drugs. We do however have some concerns around clause 1.2, which states: "It is recommended that access to the drugs used to treat hepatitis C is managed through the specialised commissioning programme put in place by NHS England with prescribing decisions made by multidisciplinary teams/centres to ensure that treatment is prioritised for patients with the highest unmet clinical need." After requesting clarification, we have received assurances from NICE that 'prioritisation' as referred to in this context should only be necessary when there are constraints caused by capacity, and should not be dictated by NHS England's Specialised Commissioning drug budget. We would therefore like it to be made abundantly clear in the text that this clause cannot be used to justify some of the schemes proposed by NHS England in their submission to the first ACD, such as 'watchful waiting' or sequential treatment, whereby patients are forced to try a much less tolerable and ineffective regimen first, in other words to ration access to these cost-effective drugs. We are also concerned about the term 'clinical need' being referred to as the only basis for prioritisation. This is generally taken to mean fibrosis stage. Because hepatitis C is a systemic disease that is also stigmatised, people living with the disease may have other pressing needs for treatment, such as:	Comments noted. Section 1.2 of the FAD has been updated to state "It is recommended that the decision to treat and the prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, in order to prioritise treatments for people with the highest unmet clinical need". For clarity on the term 'clinical need', please see section 4.20 of the FAD, which states "The Committee heard from the patient expert that people with chronic hepatitis C appreciated the capacity constraints placed on the NHS in delivering treatment for every eligible person. The Committee recalled that treatment decisions are influenced by clinical characteristics including HCV genotype, level of liver damage, comorbidities and treatment history (see section 4.2 of the FAD). With these factors in mind, people with chronic hepatitis C may accept treatment being prioritised for those with the highest unmet clinical need (including some people without cirrhosis), potentially determined by multidisciplinary teams".

Consultee	Comment [sic]	Response
	- The desire not to infect others (e.g. through maternal transmission) - Significant symptoms that may impact on work, relationships, emotional well-being, indeed all aspects of life - Experience of discrimination, such as losing a job as a result of disclosing hepatitis C infection We would ideally like need to be defined as in the draft Scottish Sexual Health and Blood-borne Virus Framework 2015-2020: • patients with F3/F4 hepatic fibrosis; • and/or patients with severe extra-hepatic manifestations of hepatitis C; • and/or patients with significant psychosocial morbidity as a consequence of hepatitis C	
Royal College of Physicians	Please take this email as confirmation that the RCP would like to endorse the consultation response submitted by the British Society of Gastroenterology. We would also like to note that we have liaised with the JSC for Genitourinary Medicine who felt that the Appraisal Committee had performed a thorough appraisal and come up with fair recommendations for the use of this combination for patients with HCV infection. Furthermore, they have expressed their gratitude to the committee for recognising and including the needs of HIV/HCV co-infected patients.	Comment noted, thank you. No action required.
United Kingdom Clinical Pharmacy Association	As a committee member of the United Kingdom Clinical Pharmacy Association (UKCPA) Gastroenterology and Hepatology Group I would like to thank NICE for requesting us to respond to the NICE led ACD consultation on the above anti-virals for hepatitis C. Due to the confidential nature of the NHSE comments the committee response is based on my overall senior opinion and discussion themes which we as a group	Comments noted. Section 1.2 of the FAD has been updated to state “It is recommended that the decision to treat and the prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, in order to prioritise treatments for patients with the

Consultee	Comment [sic]	Response
	have had since the previous documents were received. The ACD consultation document for all of the above mentioned anti-virals is robust and we feel that overall our previous comments with regards the STA have been outlined fairly. Our feedback is brief and includes the following; • In section 1.2 of each ACD we feel the terminology lacks some clarity. Could the Committee please consider the wording 'specialised commissioning programme'. From a pharmacy standpoint this could take on a number of definitions and could include the current NHSE Cirrhotic Policy which is in place. There are members of the group including I which would see this loosely defined as a specialist commissioned programme. • The NHS England section in each ACD for example section 4.31 of ID742 and section 4.21 of ID731 outline the comments made by UKCPA in our previous submission with reference to the estimated treatment numbers. We as a group would again reinforce that a far more realistic option is as outlined by the clinical experts which is 7000 to 10000. However if one is basing this on financial year 15/16 the number is likely to be on the lower end of this due to the delays seen in implementation of ODNs and the treatment pathway itself. We thank you again for inviting us to comment on the ACDs for Harvoni®, Daklinza®, Viekirax® and Exviera® and we welcome all future involvement with NICE.	highest unmet clinical need".
Royal College of Pathologists	No comments	Response noted

Consultee	Comment [sic]	Response
Department of Health	No comments	Response noted
NHS England	**Background** NHS England is supportive of expanded new treatment options for people with Hepatitis C, and has already begun funding their care. However, we also want to ensure that unresolved questions about the best treatment strategies are answered and that phased investment in Hepatitis C services based on clinical need prevents damaging cuts elsewhere. The National Institute for Health and Care Excellence (NICE) Appraisal Committee is in the process of considering three products for the treatment of hepatitis C; sofosbuvir plus ledipasvir (Harvoni®) [ID742], daclatasvir (Daklinza®) [ID766], and paritaprevir/ritonavir/ombitasvir (Viekirax®) +/- dasabuvir (Exviera®) [ID731]. In the context of consultation on the preliminary recommendations for sofosbuvir/ledipasvir NHS England submitted a comment that relates to NICE's general duties to 'have regard to the broad balance between benefits and costs of the provision of health services or of social care in England and the degree of need of persons for health services or social care in England'. As NHS England confirmed during the first consultation, the introduction of the oral treatments for hepatitis C is a major change in the management of this disease and NHS England is supporting the implementation of these treatments in a stepwise fashion with: a) the early access scheme for patients with decompensated cirrhosis; b) the expansion of access for all patients with cirrhosis; and c) the formation of the work programme to establish access to oral drugs for patients with F3 liver fibrosis in conjunction with an effective program of surveillance for other patients and a focus on the specific needs of the complex patient groups with hepatitis C. However, we also raised concerns regarding the optimal use of these drugs in particular patient groups and the relative value to the NHS of treating such groups. In particular, NHS England questioned whether resource should be utilised to treat people without cirrhosis who have never received treatment. Emerging data in such groups suggest shorter courses of treatment will be as effective as the longer courses recommended by the medicines Marketing Authorisation. NHS England understands NICE cannot make recommendations outside the MA. However, NHS England would wish such evidence to be taken into consideration. It has come to NHS England's attention that a planned study, supported by the	Comments noted. The Committee was aware that STOP-HCV-1 had not started and that the final protocol had not been agreed. It considered that the clinical-effectiveness evidence available for 3D for this population was more robust than the evidence available for other populations considered in this technology appraisal, and that the ICER was below £20,000 per QALY gained. The Committee further agreed that its recommendation would not stop people from taking part in the proposed STOP-HCV-1 trial because the treatment of chronic hepatitis C will be managed through established operational delivery networks in the NHS. The Committee concluded that an 'only in research' recommendation was not appropriate for ombitasvir–paritaprevir–ritonavir and dasabuvir in people with untreated genotype 1 HCV without cirrhosis (see section 4.24 of the FAD).

Consultee	Comment [sic]	Response
	MRC, is due to open which will examine the optimal treatment course length in patients with Genotype 1 Hepatitis C without cirrhosis who have never received previous treatment. Given the likely benefits both to patients able to receive shorter courses of treatment and to the NHS in reducing the overall cost of treatment, NHS England would ask NICE to consider an 'only in research' recommendation for naïve Genotype 1 patients without cirrhosis. This will ensure a rapid uptake of patients within the proposed trial. **The STOP-HCV-1 trial and implementation of NICE guidance for interferon-free hepatitis C treatment** The STOP-HCV-1 trial has received endorsement by the MRC and will be funded by the NIHR and is due to commence in 2016. The MRC in reviewing the trial recognised the potential importance to the NHS of the proposed trial. In particular, the primary end-point to assess cure rates of targeted treatments utilising shorter course lengths. **Rationale for the trial design** • Several new, interferon-free, treatments for hepatitis C look set to be recommended as cost-effective by NICE. • Two new combinations (Abbvie 3D, Harvoni®) treat Genotype 1 infection, the most prevalent in England (and Wales) • The efficacy of these treatments is very high (>90% cure) • The cost of a standard 12 week treatment is very high (currently> £30k) • 12 weeks of treatment is more than most patients with mild disease need to be cured • 12 weeks treatment, although a major improvement on current treatment options, is still a long course • Many patients can be cured with treatments as short as 4 weeks but there is a lack of sufficient evidence to know which patients these are before treatment is started • There is strong evidence that both human and viral genetics play a role in the response to treatment • An evidence-based approach to tailored short course treatment has the potential to save over 1/3 of overall treatment costs in those with mild disease • If NICE recommendations are implemented as they stand the opportunity to	

Consultee	Comment [sic]	Response
	collect the data required to use the treatments more rationally will be lost **An approach through stratified medicine** • The MRC funded STOP HCV (Stratified Treatment Optimisation) consortium (goo.gl/DW0n16) has prioritised short course treatment as an area of study for stratified (precision/personalised) medicine. • The first proposed national trial (STOP-HCV-1) has been funded by the NIHR EME board (£1.8m) and is due to start in 2016 targeting short course treatment in patients with mild genotype 1 disease • This study as it currently stands will enrol 408 patients with mild (non-fibrotic) genotype 1 infection • Patients will received one of two shortened courses of Abbvie 3D drugs +/- ribavirin with those failing treatment retreated with the sofosbuvir/ledipasvir combination as part of the current study design • An additional parallel component could be added to the study investigating treatment with short course sofosbuvir/ledipasvir followed by retreatment with Abbvie 3D, in comparison with standard sofosbuvir/ledipasvir treatment. • Patients in the study will become part of a major effort to sequence viral genomes and human genomes to inform the delivery of care and could be included in the 100,000 genomes project **Potential benefits in supporting the study** • The data gathered will provide vital information for clinicians managing hepatitis C with limited resources allowing more precise selection of treatments for patients • This, in turn, should allow many more patients to be treated within fixed budgets • The overall costs of running the study (including trial costs and drug costs), will lead to lower overall costs for the NHS in comparison to implementing the current NICE recommendations for Genotype 1 • The UK is uniquely well placed in the world to deliver this work which will serve as a template for other countries and other disease areas in the UK • Delivering trials before implementation of NICE guidance will demonstrate the potential value of an evaluation process before it is required that technologies approved by NICE must be commissioned **Summary**	

Consultee	Comment [sic]	Response
	NHS England is fully committed to supporting the treatment of people diagnosed with Hepatitis C. However, as highlighted in our previous consultation responses, the affordability of treating all potential patients who meet the recommendations in the current appraisal consultation documents remains uncertain. The proposed STOP-HCV-1 study provides an opportunity to the NHS to determine the optimal course length for Genotype 1 patients without cirrhosis (one of the largest groups eligible for treatment). NHS England would like to maximise the benefit of the study and as such would ask NICE to consider an 'only in research' recommendation for patients eligible for the study. A full recommendation will reduce the ability of the study group to recruit eligible patients and has the potential to increase unnecessarily the overall costs of these treatments to the NHS with no extra benefit to patients being accrued.	

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Bristol Myers Squibb	This consultee is pleased to note the NICE recommendations for these regimens with the implication that treatment to prevent the onset of cirrhosis can commence shortly. The clinical community will be delighted that their concerns have been heard. The NICE statement and NHS England's acceptance ushers in a new era of treatment. This reviewer accepts that finite resources are available for the care of hepatitis C, but is pleased that NICE and NHS England have accepted that targeting treatment exclusively to patients with advanced fibrosis and cirrhosis is not ideal, or a good value proposition. The outcomes of shorter duration of treatment for certain patients with 1a will require monitoring and consideration of value based pricing to extend treatment in selected patients if pre-existing NS5A resistant associated variants, viral kinetics, or other pre-treatment and on treatment parameters suggest a benefit of extending treatment. We will need to monitor data in real time to ensure a learning curve that benefits patients and avoids detriment. I note clause 1.2 which is taken to mean that NHS England will engage with treatment centres (Operational Delivery Networks, ODN) to advance	Comments noted. Section 1.2 of the FAD has been updated to state "It is recommended that the decision to treat and the prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, in order to prioritise treatments for people with the highest unmet clinical need". The Committee understood from NHS England that the STOP-HCV-1 trial is assessing SVR rates for people with untreated genotype 1 HCV without cirrhosis who are treated with directly acting anti-viral drugs, including 3D, for shorter durations than stipulated in the marketing authorisation. (see section 4.24 of the FAD)

Nominating organisation	Comment [sic]	Response
	treatment in a manageable and equitable manner. As a result, NHS policy will be ostensibly to support ODNs to implement the NICE guidelines. NHS England's position is now transformative, and remarkable in scope and will provide an important example. The change in policy is positive and provides a new dynamic. ODNs, however will be expected to implement treatment and will indeed be charged with the responsibility of widening the care and management of hepatitis C in their jurisdictions. Clause 1.2 suggests that the advice of ODN leaders will be sought, for example, regarding the pros and cons of creating a national registry and ticketed queue for treatment. The advice of HCV Research UK and STOP HCV and an independent oversight committee could be sought to monitor capacity, operational effectiveness and efficiency, and delivery and to provide research opportunities to gauge the most effective, efficient and cost effective means of treatment within tertiary referral centres and community centres. Treatment failure and NS5A resistance and possible transmissibility will require monitoring. These imperatives require that the NHS England set their objectives and put in place strategic plans for people with injecting drug use, drug services, community treaters, prisons and to engage with civil society. The lowered thresholds recently proposed by Claxton et al are important health economic considerations. However as is evident from table 2 below, (16) (and Claxton K personal communication), the burden of primary liver cancer should provide a particular weighting toward value for treating genotype 3 infection with the most appropriate (and the most effective) regimens.	

Comments received from commentators

Commentator	Comment [sic]	Response
Merck Sharp Dohlm	No comments	Response noted
Roche	No comments	Response noted.

Comments received from members of the public

No comments received from members of the public

abbvie

National Institute for Health and Care Excellence

Single Technology Appraisal

Ombitasvir-paritaprevir-ritonavir with or without dasabuvir for treating chronic hepatitis C

AbbVie's Response to the Appraisal Consultation Document

August 2015

AbbVie Ltd
AbbVie House
Vanwall Business Park
Vanwall Road
Maidenhead
Berkshire SL6 4UB

OFFICE +44 (0)1628 561090
FAX +44 (0)1628 461153
www.abbvie.co.uk

Registered Number: 08004972
Registered Office: AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire SL6 4UB

abbvie

EXECUTIVE SUMMARY

AbbVie welcomes the opportunity to comment on the Appraisal Consultation Document (ACD).

We are pleased with the preliminary decision to recommend ombitasvir/ paritaprevir/ ritonavir (Viekirax®) given in combination with dasabuvir (Exviera®) for all chronic hepatitis C genotype 1b (HCV GT1b) patients and chronic hepatitis C genotype 1a (HCV GT1a) patients without cirrhosis. We are also pleased with the preliminary decision to recommend ombitasvir/ paritaprevir/ ritonavir for previously treated chronic hepatitis C genotype 4 (HCV GT4) patients without cirrhosis. However, we are disappointed with the preliminary decision not to recommend ombitasvir/ paritaprevir/ ritonavir given in combination with dasabuvir for HCV GT1a patients with compensated cirrhosis and ombitasvir/ paritaprevir/ ritonavir for previously untreated HCV GT4 patients without cirrhosis and all HCV GT4 patients with compensated cirrhosis.

For the rest of this document the HCV GT1 regimen composed of ombitasvir/ paritaprevir/ ritonavir given in combination with dasabuvir will be denoted as 3D as it contains three direct acting antiviral therapies and the HCV GT4 regimen, composed of ombitasvir/ paritaprevir/ ritonavir, is referred to as 2D as it contains two direct acting antiviral therapies.

The 3D regimen for HCV GT1 patients and the 2D regimen for GT4 patients represent a step change in the management of HCV compared to current standard of care. In clinical trials they resulted in consistently high SVR rates across a broad population of patients and they were associated with very few side effects. Given the regimens are interferon-free and all oral, they have the additional clinical benefit over existing treatments of a dramatically improved tolerability profile as well as removing the need for patients to self-inject on a weekly basis.

AbbVie believes that all HCV GT1 and GT4 patients should be able to benefit from access to the 3D and 2D regimens respectively in order to ensure equity of access. In relation to the indications for which NICE did not make a positive recommendation, AbbVie's position is that some of NICE's summaries of cost effectiveness are not reasonable interpretations of the evidence provided. Therefore, we do not think the provisional "no" recommendations are sound and we believe that the 3D regimen should also be recommended for previously treated HCV GT1a patients with compensated cirrhosis and the 2D regimen should also be recommended for treatment naïve GT4 patients without cirrhosis and treatment experienced GT4 patients with compensated cirrhosis. In particular we would like to discuss the following points:

A. We believe that the utility scenario that the Committee has chosen underestimates the health related quality of life benefit of achieving an SVR and so overestimates the ICERs of the 3D and 2D regimens. This scenario is inconsistent with the approach used in other appraisals for medicines treating chronic hepatitis C.

B. We support the discussion in the ACD about the innovation of 3D and 2D and would agree with the authors that the health related quality of life of the regimens has been underestimated and, therefore, the ICERs upon which the recommendations have been based are likely to be overestimated.

C. We believe that the ICERs for some of the 3D and 2D regimens that have not been recommended are in fact within a range that would generally be considered acceptable and would usually lead to positive recommendations by NICE Committees particularly as the regimens offer a high chance to achieve viral cure.

D. We understand the NICE position that the 2014 - 2018 Pharmaceutical Price Regulation Scheme (PPRS) should not be regarded as a relevant consideration in the assessment of the cost-effectiveness of individual branded medicines but we believe it should be a consideration if budget impact is a factor in the assessment as is inferred by the ACD. This would allow a proper consideration of the likely rebate payments that are made under the PPRS. All medicines produced by manufacturers who are a member of the voluntary scheme including new medicines launched during the lifetime of the scheme, are covered. AbbVie has joined this voluntary scheme and believes it is especially relevant considering that the Department of Health and industry agree that the PPRS aims to improve access to, and appropriate use of, clinically and cost-effective medicines

These points are discussed within Sections A, B, C and D of our response. Appendix 1 contains confidential details of the pricing arrangement agreed by AbbVie with the Commercial Medicines Unit following a tender process. Appendix 2 contains further points related to factual inaccuracies.

This draft decision does not give access to the 3D and 2D regimens to some of the sickest patients with hepatitis C who NHS England would like to treat within their recently published interim commissioning policy for the treatment of chronic hepatitis C in patients with cirrhosis. We sincerely encourage the Committee to reconsider its draft guidance in light of our comments and in particular to extend the recommendation of the 3D and 2D regimens to the HCV patients outlined above.

abbvie

ARE THE SUMMARIES OF CLINICAL AND COST-EFFECTIVENESS REASONABLE INTERPRETATIONS OF THE EVIDENCE?

A. We believe that the utility scenario that the Committee has chosen underestimates the health related quality of life benefit of achieving an SVR and so overestimates the ICERs of the 3D and 2D regimens

AbbVie is surprised and disappointed that the Committee has decided that utility "Scenario 1" is the most plausible scenario and so it should be used to inform their decision. "Scenario 1" estimates the utility gain for having an SVR from the difference between the pooled EQ-5D values collected at baseline and at 12 weeks after treatment in people who had an SVR in the clinical trials. These EQ-5D values were collected before the patients were aware of their SVR status and therefore, as the Committee accepts, they do not capture the psychological and emotional benefits of being cured. They are clearly an underestimate of the health related quality of life (HRQoL) benefit of an HCV patient achieving SVR.

The utility gain for having an SVR in "Scenario 1" is considerably less than the gain assumed in the "Revised Base Case". The gain in the "Revised Base Case" is consistent with the approach used in other appraisals for medicines treating chronic hepatitis C including other interferon-free regimens that are currently being assessed by NICE[1,2] and so we do not see why our submission would be treated differently. For example, as stated in section 4.13 of the ACD, the Committee is already aware that the utility benefits from Wright et al.[3] (0.05) and Vera-Llonch et al.[4] (0.041) have been used in technology appraisal guidance for both sofosbuvir[5] and simeprevir[6] for treating chronic hepatitis C. This approach is consistent with the NICE appraisals of boceprevir[7] and telaprevir[8] and AbbVie understands that NICE is also using similar values to these in the two ongoing appraisals for medicines for chronic hepatitis C (ledipasvir/sofosbuvir and daclatasvir)[1,2]:

- In the ongoing appraisal of ledipasvir-sofosbuvir[1], the submitting company used the utility benefit of 0.04 from Vera-Llonch.[4] In this appraisal the ERG commented that the value from Wright et al[3] of 0.05 would be more appropriate as it reflects the preferences of the general public in England because it used the UK EQ-5D tariff and while the Committee did express some reservations with the approach used by the Company in this submission, it concluded that it was prepared to accept the utility benefit of 0.04 of Vera-Llonch[4].

- In the submitting company's model in the ongoing appraisal of daclatasvir[2] for treating chronic hepatitis C, the utility gain by a patient achieving an SVR varied by initial fibrosis stage between a range from 0.05 to 0.17. The ERG preferred to assume that SVR results in equal utility increments across the

different fibrosis stages from which people may start treatment and the Committee concluded that the effect of SVR on HRQoL in the model should be assumed to be the same whether or not the person has cirrhosis. The amended basecase run by the ERG assumed equal utility increments of 0.05 for having an SVR in all fibrosis stages.

There is evidence in Vera-Llonch[4] that it takes time for the utility of a patient to stop increasing post-treatment once they have attained SVR. In fact, the ADVANCE trial found that patients' utility was still increasing 48 weeks after treatment had stopped for patients who received 24 weeks of treatment.

In conclusion, the utility scenario that the Committee has chosen to inform their decision underestimates the HRQoL benefit of a patient achieving SVR and is inconsistent with the approach used in both recent and current appraisals of medicines for chronic hepatitis C. Therefore, "Scenario 1" overestimates the ICERs of 3D and 2D.

B. We support the discussion about the innovation of 3D and 2D and would agree that the health related quality of life of the regimens has been underestimated and, therefore, the ICERs upon which the recommendations have been based are likely to be overestimates

AbbVie agree with the Committee that 3D and 2D offer oral, shortened, and interferon-free treatments, which are particularly important to patients, and a major development in the clinical management of chronic hepatitis C. We welcome the acknowledgement in Section 4.19 of the ACD that 3D and 2D are valuable new therapies for treating chronic hepatitis C compared with peginterferon alfa and ribavirin. Further, that they are associated with other benefits for people with chronic hepatitis C that if taken into account, are likely to decrease the ICERs such as:

- possible regression of fibrosis
- reduced transmission of HCV
- improved earning capacity of patients with chronic hepatitis C

C. We believe that the ICERs for some of the 3D and 2D regimens that have not been recommended are in fact within a range that would generally be considered acceptable and would usually lead to positive recommendations by NICE Committees particularly as the regimens offer a high chance to achieve viral cure

Both the 3D and 2D regimens offer the chance to achieve a viral cure. Given the evidence discussed in Sections A and B of our response above, AbbVie strongly believes that the ICERs for 3D and 2D are lower than those that the Committee have used to inform their decisions. In particular we believe that the ICERs for the 3D regimen for previously treated HCV GT1a patients with compensated cirrhosis and the 2D regimen for treatment naïve GT4 patients without cirrhosis and treatment experienced GT4 patients with compensated cirrhosis are highly likely to be within the normal range of acceptability for the Committee. Under the "Revised Base Case" these ICERs are currently £26,516, £20,351 and £22,331 respectively. These ICERs result from including the utility gain for achieving an SVR that is consistent with other recent and ongoing appraisals for treatments for chronic hepatitis C as described in Section A. Also, these ICERs are likely to be overestimates given the factors described in Section B. For treatment naïve GT4 patients without cirrhosis, 2D is likely to represent the only available interferon-free regimen.

Section 6.3 of the NICE methods guide[9] describes the factors that will be taken into account "above a most plausible ICER of £20,000 per QALY gained". These factors will be used to judge the acceptability of the technology as an effective use of NHS resources. One such factor is "the innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure." Clearly this factor should be taken into account for 3D and 2D given the Committee's view of the treatments described in 4.19 of the ACD and as the 3D and 2D offer the chance to achieve a viral cure.

AbbVie notes from paragraph 4.22 of the ACD document that NICE believe the acceptable ICERs are impacted by any perceived increase in budget impact. However, if budget impact is to be taken into account in this way AbbVie believe additional considerations must be taken into account also (please see point D for further detail).

D. We understand the NICE position that the 2014 PPRS payment mechanism should not be regarded as a relevant consideration in the assessment of the cost-effectiveness of branded medicines but we believe it should be a consideration if budget impact is a factor in the assessment as seems to be inferred by the ACD

The ACD described the concerns that NHS England have about the increase in investment and capacity needed for the implementation of 3D and 2D and for the other treatments for hepatitis C currently being appraised by NICE. The Committee recognised in paragraph 4.22 that the Guide to Methods of Technology Appraisal[9] indicates that there needs to be increasing certainty of the cost effectiveness of a technology as the NHS budget impact of its adoption increases. This implies that budget impact is having an impact on the decision the Committee is making for 3D and 2D. This implication is supported by the inclusion of paragraph 1.2 in the recommendations section of the ACD.

AbbVie's position is that budget impact should not determine the Appraisal Committee's decision. We are concerned about the comments made by NHS England on these points and the influence that it seems to have had on the Committee (as evidenced in particular by paragraph 1.2).

In this regard, the Pharmaceutical Price Regulation Scheme (PPRS)[10] is highly relevant. For the NHS, the total medicines budget is pre-determined and agreed between the ABPI and the Department of Health for medicines supplied by members of the voluntary scheme, which includes AbbVie.

The current 2014 PPRS[10] agreement provides a cap on expenditure on branded medicines of voluntary scheme members and any overspend above this cap is effectively underwritten by industry in the form of rebate payments. This ensures that the NHS has predictability of the branded medicines bill for voluntary scheme members and should certainly be taken into account in an appraisal of a voluntary scheme member's medicines, should budget impact be taken into account by NICE's recommendations.

As NICE makes clear in its position statement on the PPRS, the medicines bill cap encompasses new products, which are "included in the calculation of the growth rate of sales for all medicines, that is, they are taken into account in determining whether the agreed growth level has been exceeded and a PPRS payment will be required, and determining the size of the percentage". Therefore the introduction and usage of the 3D and 2D regimens in the treatment of Hepatitis C cannot have an incremental effect on the total drugs bill for the NHS, but any additional cost will effectively be rebated by the industry accordingly.

One of the aims of the PPRS is to improve patient access to clinically- and cost-effective medicines. If NICE is taking into account budget impact then we request that NICE issues a formal position statement (specific to the facts in this appraisal) on PPRS and budget impact.

Given the budget cap provided by PPRS, AbbVie believes that the potential budget impact of 3D and 2D should not be influencing influence the Committee's decision and, therefore, the Committee should not require increasing certainty of the cost-effectiveness of 3D and 2D and these medicines should be judged to be cost-effective in the patient groups described in Section C above. It should be noted that no rebate is paid for any spend above the medicines bill cap on products that are produced by manufacturers of the statutory scheme.

HAS ALL OF THE RELEVANT EVIDENCE BEEN TAKEN INTO ACCOUNT?

The ACD does not take into account the confidential pricing arrangement that has been agreed with the Commercial Medicines Unit following a tender process. Please see Appendix 1 which illustrates the impact of this pricing arrangement on the cost-effectiveness of the 3D and 2D regimens.

ARE THE PROVISIONAL RECOMMENDATIONS SOUND AND A SUITABLE BASIS FOR GUIDANCE TO THE NHS?

Section 1.2 of the ACD states:

1.2 It is recommended that access to the drugs used to treat hepatitis C is managed through the specialised commissioning programme put in place by NHS England with prescribing decisions made by multidisciplinary teams/centres to ensure that treatment is prioritised for patients with the highest unmet clinical need.

AbbVie notes this point in the ACD and seeks clarity on its intended meaning and effect. It would be useful for NICE to expand upon this point and its rationale for inclusion in future public communication relating to this appraisal so that there is not ambiguity over its meaning or effect. AbbVie would also request that this section is moved from the recommendations section to section 4 of the ACD.

AbbVie assumes that this point is not intended to run contrary to the recommendations in paragraph 1.1 and also the NHS Constitution[12] which states "You have the right to drugs and treatments that have been recommended by NICE for use in the NHS, if your doctor says they are clinically appropriate for you." AbbVie seeks reassurance that section 1.2 of the ACD does not conflict with this

right and further assumes that it may be relating more specifically to any prioritisation based upon clinical capacity. Please confirm.

In addition, whilst we understand that NICE is required to make decisions on the basis of the cost-effectiveness of new technologies, this draft decision does not give access to the 3D and 2D regimens to the sickest patients with hepatitis C who NHS England would like to treat within their recently published interim commissioning policy[13] for the treatment of chronic hepatitis C in patients with cirrhosis.

ARE THERE ANY ASPECTS OF THE RECOMMENDATIONS THAT NEED PARTICULAR CONSIDERATION TO ENSURE NICE AVOID UNLAWFUL DISCRIMINATION AGAINST ANY GROUP OF PEOPLE ON THE GROUNDS OF RACE, GENDER, DISABILITY, RELIGION OR BELIEF, SEXUAL ORIENTATION, AGE, GENDER REASSIGNMENT, PREGNANCY AND MATERNITY?

No aspects of the recommendations need particular consideration under these grounds.

abbvie

APPENDIX 2

Factual inaccuracies

<table>
<tr><th>Section of ACD</th><th>Description of Inaccuracy</th><th>Suggested amendment</th></tr>
<tr><td>Page 4

Section 2.1</td><td>Lack of parallelism in the final sentence</td><td>The recommended dose is 2 tablets once daily. It is taken orally for 12 or 24 weeks with or without dasabuvir, with or without ribavirin.</td></tr>
<tr><td>Page 8

Section 3.2

Ongoing trials

CORAL I</td><td>Description of CORAL I is incorrect</td><td>CORAL I: 3D with ribavirin for genotype 1 HCV in …</td></tr>
<tr><td>Page 9

Table 3

The end two columns – numerous entries</td><td>The last column requires a correction to one n number and we suggest clarification of the nature of the denominators. Some clarifications also suggested in the “comparison” column</td><td>
<table>
<tr><th>Trial</th><th>HCV genotype</th><th>Comparison</th><th>Trial arm or subgroup</th></tr>
<tr><td>PEARL II</td><td>1b</td><td>3D + RBV versus 3D</td><td>3D treatment arm

(n=95)</td></tr>
<tr><td>PEARL III</td><td>1b</td><td>3D + RBV versus 3D</td><td>3D treatment arm

(n=209)</td></tr>
<tr><td>TURQUOISE II</td><td>1a and 1b</td><td>3D + RBV:

12 weeks versus

24 weeks</td><td>GT1b

12 week treatment arm

(n=68 of 208 in 12 week arm)</td></tr>
<tr><td>SAPPHIRE I</td><td>1a and 1b</td><td>3D + RBV versus 3D + placebo</td><td>GT1a

(n=322 of 473 in 3D + RBV arm)</td></tr>
<tr><td>SAPPHIRE II</td><td>1a and 1b</td><td>3D + RBV versus 3D + placebo</td><td>GT1a

(n=173 of 297 in 3D + RBV arm)</td></tr>
</table>
</td></tr>
</table>

		PEARL IV	1a	3D + RBV versus 3D	3D plus ribavirin treatment arm (n=100)
		TURQUOISE II	1a and 1b	3D + RBV: 12 weeks versus 24 weeks	GT1a 24 week treatment arm (n=121 of 172 in 24 week arm)
		PEARL I	4	2D + RBV (TN) versus 2D (TN) and 2D + RBV (TE)	Treatment arms with 2D plus ribavirin TN (n=42) TE (n=49)
Page 11	Historical control for telaprevir, is available for TURQUOISE II study	The historical control for telaprevir, with 95% CI is provided in the manuscript for the TURQUOISE II study and is **47% (95% CI 41-54)**			
Page 11	Historical control for telaprevir is not applicable for GT4	The historical control for telaprevir for genotype 4 HCV, without cirrhosis, is **not applicable** rather than not available, as indicated in Table 4 on page 11. Telaprevir does not have a marketing authorisation for the treatment of patients with GT4 chronic hepatitis C.			
Page 13 **Section 3.11**	Missing parenthesis	The proportion of people who had at least 1 adverse reaction ranged from 67% (for 3D in genotype 1b HCV in PEARL III) to 92% (for 3D plus ribavirin in genotype 1a in PEARL I).			
Page 42 **Section 4.20**	Missing text	• The implementation of 3 oral treatments for hepatitis C in the NHS (ledipasvir-sofosbuvir, daclatasvir, and ombitasvir-paritaprevir-ritonavir with or without dasabuvir).			

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The Haemophilia Society response to NICE consultation on Hepatitis C (chronic) - ombitasvir/paritaprevir/ritonavir (with or without dasabuvir))

The Appraisal Committee is interested in receiving comments on the following:

• Has all of the relevant evidence been taken into account?

• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

• Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Section 1.2 recommends that access to drugs is managed by NHS England. The Haemophilia Society are extremely concerned that this could lead to discrimination of some patient groups. For example patients that are hard to reach or for the community affected by contaminated blood.

The Haemophilia Society believes any delay in access to treatment would have a significant adverse impact on the haemophilia and other bleeding disorder patient population who have a diagnosis of hepatitis C. Every patient from this community who has hepatitis C was infected via their NHS treatment between 1970 and 1991 and so have had chronic hepatitis for a minimum of 23 years. The World Health Organisation states **'**A significant number of those who are chronically infected will develop liver cirrhosis or liver cancer. Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15–30% within 20 years'. **In light of this there is a strong possibility that that more people with haemophilia and other bleeding disorders will progress from chronic hepatitis to cirrhosis or liver cancer than those who were infected more recently. If treatment were prescribed with no delay they may be prevented from progressing to the advanced stage of hepatitis C. Additionally people with a bleeding disorder have a much greater risk of severe bleeding from the consequences of Hepatitis C and the cost of their Factor replacement treatment would significantly outweigh the cost of Hepatitis C treatment if bleeding were to occur due to delayed treatment.**

The Haemophilia Society seek reassurance that patients who have had chronic infection for many years would be treated as a priority to prevent further progression of the disease, and patients would not have to rely on a local policy to identify them as a priority patient group to treat immediately.

The Hepatitis C Trust response to the NICE appraisal consultation document on Ombitasvir-Paritaprevir-Ritonavir with or without Dasabuvir for treating chronic hepatitis C

The Hepatitis C Trust very much welcomes the fact that NICE is proposing to treat this as a technology appraisal in the usual way, without allowing NHS England's budget difficulties to disadvantage people with hepatitis C who are in need of curative treatment. Access to this interferon-free regimen is a huge step forward that will enormously benefit patients and especially those who may only be in touch with services for short time, such as prisoners and people who inject drugs.

We do however have some concerns around clause 1.2, which states:

"It is recommended that access to the drugs used to treat hepatitis C is managed through the specialised commissioning programme put in place by NHS England with prescribing decisions made by multidisciplinary teams/centres to ensure that treatment is prioritised for patients with the highest unmet clinical need."

After requesting clarification, we have received assurances from NICE that 'prioritisation' as referred to in this context should only be necessary when there are constraints caused by capacity, and should not be dictated by NHS England's Specialised Commissioning drug budget. We would therefore like it to be made abundantly clear in the text that this clause cannot be used to justify some of the schemes proposed by NHS England in their submission to the first ACD, such as 'watchful waiting' or sequential treatment, whereby patients are forced to try a much less tolerable and ineffective regimen first, in other words to ration access to these cost-effective drugs.

We are also concerned about the term 'clinical need' being referred to as the only basis for prioritisation. This is generally taken to mean fibrosis stage. Because hepatitis C is a systemic disease that is also stigmatised, people living with the disease may have other pressing needs for treatment, such as:

- The desire not to infect others (e.g. through maternal transmission)
- Significant symptoms that may impact on work, relationships, emotional well-being, indeed all aspects of life
- Experience of discrimination, such as losing a job as a result of disclosing hepatitis C infection

We would ideally like need to be defined as in the draft Scottish Sexual Health and Blood-borne Virus Framework 2015-2020:

- patients with F3/F4 hepatic fibrosis;
- and/or patients with severe extra-hepatic manifestations of hepatitis C;
- and/or patients with significant psychosocial morbidity as a consequence of hepatitis C

17 August 2015

Meindert Boysen
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT

Dear Mr Boysen

Single Technology Appraisal (STA): Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C [ID731]: Appraisal consultation document

Many thanks for asking us to comment on the ACD for the STA for ombitasvir/paritaprevir/ritonavir (with or without dasabuvir) for treating chronic HCV (ID731).

We would like to congratulate the Appraisal Committee for performing a thorough appraisal and coming up with fair recommendations for the use of this combination for patients with HCV infection. We would also like to express our gratitude to the Committee for recognising the needs of HIV/HCV co-infected patients and ensuring inclusion of co-infected in these recommendations.

We have no further comments on this ACD at this stage.

Please contact the BHIVA Secretariat if you have any queries regarding these comments.

Yours sincerely

[redacted] *BHIVA Hepatitis Society Subcommittee*

[redacted] *BASHH General Secretary*

BASL/BVHG response to NICE ACD for **Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C [ID731]**

Many thanks for allowing BASL (British Association for the Study of the Liver) and BVHG (British Viral Hepatitis Group – a Special Interest Group within BASL) to respond to the ACD for Ombitasvir/Paritaprevir/Ritonavir +/- Dasabuvir.

The first and primary response we would like to make is to fully support the decision by NICE to progress with this assessment despite the requests put forward by NHSE. We fully agree that the current and future technology assessment processes for hepatitis C agents should continue unaffected and welcome this decision and outcome.

We are however unclear on the wording in section 1.2. NHSE does not have specific 'specialised commissioning programmes' – it prepares, commissions and delivers policies, and commissions operational delivery networks, and the term 'programme' is not one which is clear when used in reference to NHSE. Clarity on what NICE are suggesting would be useful.

In reference to the more specific detail related to the Ombitasvir/Paritaprevir/Ritonavir +/- Dasabuvir ACD we generally support the conclusions reached by NICE.

Our only comments are to point out that 12 weeks of therapy in G1a and G4 cirrhotic patients would be acceptable to clinicians and there is increasing data becoming available supporting this regimen length. We appreciate that NICE assesses such technologies against the current licensed posology regimens and list prices, and that the current license in these patient groups is 24 and not 12 weeks and that reimbursement programmes cannot be considered. We would however urge NICE to potentially reconsider a 12 week regimen if Abbvie apply for and gain such a license in the future.

Many thanks for allowing us to comment on this ACD and we would like to congratulate NICE on balanced and thorough processes and conclusions.

Comments collated by [redacted], BVHG [redacted] and BASL Committee Member.

Final Response to Apprasial Consultation Document 'Hepatitis C (chronic) - ombitasvir/paritaprevir/ritonavir (with or without dasabuvir)'

On behalf of the British Society of Gastroenterology,

In relation to the above consultation exercise we agree with the recommendations in table 1.1 but we feel paragraph 1.2 is incorrect and would recommend the following paragraph be inserted in its place "It is recommended that in England the decision to treat and the prescribing decisions are made by the multidisciplinary teams in the operational delivery networks now established by NHS England and this should be in partnership with and supported by NHS England"

ACD - Consultees & Commentators: (Hepatitis C (chronic) - ombitasvir/paritaprevir/ritonavir (with or without dasabuvir)) [731]

Dear Meindert,

Please take this email as confirmation that the RCP would like to endorse the consultation response submitted by the British Society of Gastroenterology.

We would also like to note that we have liaised with the JSC for Genitourinary Medicine who felt that the Appraisal Committee had performed a thorough appraisal and come up with fair recommendations for the use of this combination for patients with HCV infection. Furthermore, they have expressed their gratitude to the committee for recognising and including the needs of HIV/HCV co-infected patients.

Best wishes,

[redacted]
Royal College of Physicians
11 St Andrews Place | Regent's Park | London NW1 4LE

Direct line [redacted]

13th August 2015

Dear NICE Team,

Re: NHS England response consultation: (Hepatitis C (chronic)

- Ledipasvir-sofosbuvir for treating chronic hepatitis C [ID742] ACD
- Daclatasvir for treating chronic hepatitis C [ID766] ACD
- Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C [ID731] ACD

As a [redacted] member of the United Kingdom Clinical Pharmacy Association (UKCPA) Gastroenterology and Hepatology Group I would like to thank NICE for requesting us to respond to the NICE led ACD consultation on the above anti-virals for hepatitis C.

Due to the confidential nature of the NHSE comments the committee response is based on my overall senior opinion and discussion themes which we as a group have had since the previous documents were received.

The ACD consultation document for all of the above mentioned anti-virals is robust and we feel that overall our previous comments with regards the STA have been outlined fairly.

Our feedback is brief and includes the following;

- In section 1.2 of each ACD we feel the terminology lacks some clarity. Could the Committee please consider the wording 'specialised commissioning programme'. From a pharmacy standpoint this could take on a number of definitions and could include the current NHSE Cirrhotic Policy which is in place. There are members of the group including I which would see this loosely defined as a specialist commissioned programme.

- The NHS England section in each ACD for example section 4.31 of ID742 and section 4.21 of ID731 outline the comments made by UKCPA in our previous submission with reference to the estimated treatment numbers. We as a group would again reinforce that a far more realistic option is as outlined by the clinical experts which is 7000 to 10000. However if one is basing this on financial year 15/16 the number is likely to be on the lower end of this due to the delays seen in implementation of ODNs and the treatment pathway itself.

We thank you again for inviting us to comment on the ACDs for Harvoni®, Daklinza®, Viekirax® and Exviera® and we welcome all future involvement with NICE.

Yours Sincerely,

[redacted]

On behalf of the Gastroenterology and Hepatology UKCPA Group

CONFIDENTIAL UNTIL PUBLISHED

NHS ENGLAND RESPONSE TO CONSULTATION 2 - HEPATITIS C DRUG APPRAISALS [ID731, ID742 and ID766]

Background

NHS England is supportive of expanded new treatment options for people with Hepatitis C, and has already begun funding their care. However, we also want to ensure that unresolved questions about the best treatment strategies are answered and that phased investment in Hepatitis C services based on clinical need prevents damaging cuts elsewhere.

The National Institute for Health and Care Excellence (NICE) Appraisal Committee is in the process of considering three products for the treatment of hepatitis C; sofosbuvir plus ledipasvir (Harvoni®) [ID742], daclatasvir (Daklinza®) [ID766], and paritaprevir/ritonavir/ombitasvir (Viekirax®) +/- dasabuvir (Exviera®) [ID731]. In the context of consultation on the preliminary recommendations for sofosbuvir/ledipasvir NHS England submitted a comment that relates to NICE's general duties to 'have regard to the broad balance between benefits and costs of the provision of health services or of social care in England and the degree of need of persons for health services or social care in England'.

As NHS England confirmed during the first consultation, the introduction of the oral treatments for hepatitis C is a major change in the management of this disease and NHS England is supporting the implementation of these treatments in a stepwise fashion with:

a) the early access scheme for patients with decompensated cirrhosis;

b) the expansion of access for all patients with cirrhosis; and

c) the formation of the work programme to establish access to oral drugs for patients with F3 liver fibrosis in conjunction with an effective program of surveillance for other patients and a focus on the specific needs of the complex patient groups with hepatitis C.

However, we also raised concerns regarding the optimal use of these drugs in particular patient groups and the relative value to the NHS of treating such groups. In particular, NHS England questioned whether resource should be utilised to treat people without cirrhosis who have never received treatment. Emerging data in such groups suggest shorter courses of treatment will be as effective as the longer

courses recommended by the medicines Marketing Authorisation. NHS England understands NICE cannot make recommendations outside the MA. However, NHS England would wish such evidence to be taken into consideration.

It has come to NHS England's attention that a planned study, supported by the MRC, is due to open which will examine the optimal treatment course length in patients with Genotype 1 Hepatitis C without cirrhosis who have never received previous treatment.

Given the likely benefits both to patients able to receive shorter courses of treatment and to the NHS in reducing the overall cost of treatment, NHS England would ask NICE to consider an 'only in research' recommendation for naïve Genotype 1 patients without cirrhosis. This will ensure a rapid uptake of patients within the proposed trial.

The STOP-HCV-1 trial and implementation of NICE guidance for interferon-free hepatitis C treatment

The STOP-HCV-1 trial has received endorsement by the MRC and will be funded by the NIHR and is due to commence in 2016. The MRC in reviewing the trial recognised the potential importance to the NHS of the proposed trial. In particular, the primary end-point to assess cure rates of targeted treatments utilising shorter course lengths.

Rationale for the trial design

- Several new, interferon-free, treatments for hepatitis C look set to be recommended as cost-effective by NICE.
- Two new combinations (Abbvie 3D, Harvoni®) treat Genotype 1 infection, the most prevalent in England (and Wales)
- The efficacy of these treatments is very high (>90% cure)
- The cost of a standard 12 week treatment is very high (currently> £30k)
- 12 weeks of treatment is more than most patients with mild disease need to be cured
- 12 weeks treatment, although a major improvement on current treatment options, is still a long course
- Many patients can be cured with treatments as short as 4 weeks but there is a lack of sufficient evidence to know which patients these are before treatment is started
- There is strong evidence that both human and viral genetics play a role in the response to treatment
- An evidence-based approach to tailored short course treatment has the potential to save over 1/3 of overall treatment costs in those with mild disease
- If NICE recommendations are implemented as they stand the opportunity to collect the data required to use the treatments more rationally will be lost

An approach through stratified medicine

- The MRC funded STOP HCV (Stratified Treatment Optimisation) consortium (goo.gl/DW0n16) has prioritised short course treatment as an area of study for stratified (precision/personalised) medicine.
- The first proposed national trial (STOP-HCV-1) has been funded by the NIHR EME board (£1.8m) and is due to start in 2016 targeting short course treatment in patients with mild genotype 1 disease
- This study as it currently stands will enrol 408 patients with mild (non-fibrotic) genotype 1 infection
- Patients will received one of two shortened courses of Abbvie 3D drugs +/- ribavirin with those failing treatment retreated with the sofosbuvir/ledipasvir combination as part of the current study design
- An additional parallel component could be added to the study investigating treatment with short course sofosbuvir/ledipasvir followed by retreatment with Abbvie 3D, in comparison with standard sofosbuvir/ledipasvir treatment.
- Patients in the study will become part of a major effort to sequence viral genomes and human genomes to inform the delivery of care and could be included in the 100,000 genomes project

Potential benefits in supporting the study

- The data gathered will provide vital information for clinicians managing hepatitis C with limited resources allowing more precise selection of treatments for patients
- This, in turn, should allow many more patients to be treated within fixed budgets
- The overall costs of running the study (including trial costs and drug costs), will lead to lower overall costs for the NHS in comparison to implementing the current NICE recommendations for Genotype 1
- The UK is uniquely well placed in the world to deliver this work which will serve as a template for other countries and other disease areas in the UK
- Delivering trials before implementation of NICE guidance will demonstrate the potential value of an evaluation process before it is required that technologies approved by NICE must be commissioned

Summary

NHS England is fully committed to supporting the treatment of people diagnosed with Hepatitis C. However, as highlighted in our previous consultation responses, the affordability of treating all potential patients who meet the recommendations in the current appraisal consultation documents remains uncertain.

The proposed STOP-HCV-1 study provides an opportunity to the NHS to determine the optimal course length for Genotype 1 patients without cirrhosis (one of the largest groups eligible for treatment).

NHS England would like to maximise the benefit of the study and as such would ask NICE to consider an ‘only in research’ recommendation for patients eligible for the study.

A full recommendation will reduce the ability of the study group to recruit eligible patients and has the potential to increase unnecessarily the overall costs of these treatments to the NHS with no extra benefit to patients being accrued.

G M Dusheiko

Clinical Expert

Declaration of interests

I have acted as an advisor to Gilead Sciences, Bristol Myers Squibb and AbbVie

Sofosbuvir and ledispavir, and ombitasvir and paritaprevir and dasabuvir

This consultee is pleased to note the NICE recommendations for these regimens with the implication that treatment to prevent the onset of cirrhosis can commence shortly. The clinical community will be delighted that their concerns have been heard. The NICE statement and NHS England's acceptance ushers in a new era of treatment. This reviewer accepts that finite resources are available for the care of hepatitis C, but is pleased that NICE and NHS England have accepted that targeting treatment exclusively to patients with advanced fibrosis and cirrhosis is not ideal, or a good value proposition.

The outcomes of shorter duration of treatment for certain patients with 1a will require monitoring and consideration of value based pricing to extend treatment in selected patients if pre-existing NS5A resistant associated variants, viral kinetics, or other pre-treatment and on treatment parameters suggest a benefit of extending treatment. We will need to monitor data in real time to ensure a learning curve that benefits patients and avoids detriment.

I note clause 1.2 which is taken to mean that NHS England will engage with treatment centres (Operational Delivery Networks, ODN) to advance treatment in a manageable and equitable manner. As a result, NHS policy will be ostensibly to support ODNs to implement the NICE guidelines. NHS England's position is now transformative, and remarkable in scope and will provide an important example. The change in policy is positive and provides a new dynamic. ODNs, however will be expected to implement treatment and will indeed be charged with the responsibility of widening the care and management of hepatitis C in their jurisdictions.

Clause 1.2 suggests that the advice of ODN leaders will be sought, for example, regarding the pros and cons of creating a national registry and ticketed queue for treatment. The advice of HCV Research UK and STOP HCV and an independent oversight committee could be sought to monitor capacity, operational effectiveness and efficiency, and delivery and to provide research opportunities to gauge the most effective, efficient and cost effective means of treatment within tertiary referral centres and community centres. Treatment failure and NS5A resistance and possible transmissibility will require monitoring. These imperatives require that the NHS England set their objectives and put in place strategic plans for people with injecting drug use, drug services, community treaters, prisons and to engage with civil society.

Genotype 3 and daclatasvir

There is a great concern at the lack of a positive recommendation for daclatasvir and sofosubuvir ± ribavirin for patients with or without cirrhosis for persons with genotype 3. The negative recommendation will fail to both address and correct a potentially remediable unmet need for this group.

Clinical importance of genotype 3

Although there are regional differences in prevalence, genotype 3 affects more than one third of the hepatitis C infected population in the United Kingdom. It is important for NICE to consider the altered biology of genotype 3 HCV and more rapid rates of progression in patients with genotype 3. Genotype 3 is a cause of significant morbidity and mortality. A comprehensive body of evidence has suggested that patients with genotype 3 have higher rates of steatosis, faster fibrosis progression and higher risk of end stage liver disease, HCC and death. It has long been known that genotype 3 HCV has a lower sensitivity to interferon than genotype 2 and therapy with interferon is less successful in this group. With the advent of DAA therapies, it is now recognised genotype 3 patients with cirrhosis have become the difficult to treat genotype –but can be successfully treated before the onset of cirrhosis - a point that will be made repeatedly in this submission. Genotype 3 infection is over-represented in the young, in people with injecting drug use, and in persons originating from the Indian subcontinent and Southeast Asia.

Biology of genotype 3

Genotype 3 is a unique "strain" of HCV; The substantial nucleotide sequence diversity places this genotype at a considerable phylogenetic distance from genotypes 1 and 4 – explaining the geographic and probably the biological differences in disease caused by genotype 3 (1-4). The HCV genotype 3 core protein results in a greater level of cellular triglyceride accumulation compared with other genotypes and profound interactions with the cholesterol synthesis pathway; an interference that resolves after achievement of an SVR. Also the intrahepatic accumulation of steatosis leads to increased necro - inflammatory activity via oxidative stress, an effect that is specific to genotype 3 (5). This is considered a specific cytopathic effect of hepatitis C genotype 3. Several authors have confirmed the steatogenic effect and the disproportionate prevalence of steatosis in genotype 3 infection (6). This effect is independent of body mass index. Histologic steatosis is associated with progression of fibrosis (7). Steatosis is also known to be an important harbinger of progression and underlies the accelerated fibrosis observed in this group.

Interference with hepatocyte lipid metabolism has an impact upon treatment success. Leandro et al (8) found that steatosis was independently was associated with fibrosis and that consequently hepatitis C genotype 3 was the most powerful driver of steatosis. Treatment fortunately reverses this effect as an SVR significantly reduces hepatic steatosis.

Natural history

As a result of the unique cytopathology of genotype 3, chronic HCV infection has a worse natural history. Several thorough evaluations to support this contention have been concluded: For example, the Swiss hepatitis C cohort study, which evaluated the outcome in 3412 treatment naive patients found that in this group the most significant effects in a multivariate model were histological activity and hepatitis C genotype 3 infection. For any given stage of fibrosis HCV 3 infected persons were far more likely to advance at least one fibrosis stage compared with non-HCV 3 patients (9).

Chronic hepatitis C genotype 3 has also been associated with a disproportionately increased risk of hepatocellular carcinoma (HCC). Nkontchou et al determined that HCV genotype 3 infection was the strongest predictor of HCC with a hazard ratio of 3.54 (10). The rate of HCC occurrence after 5 years was 34% in those with genotype 3: twice the rate observed in non-genotype 3 infection. These data have not been restricted to French patients: significantly greater rates of cirrhosis and HCC compared with European patients have been found in patients from South East Asian countries (10). Thus the presence of genotype 3 has been added to weighted models of disease progression (11, 12).

Interferon and DAA treatment of genotype 3

It has long realised that although genotype 3 can be treated with interferon, poor therapeutic response have been observed, particularly in those with cirrhosis. Relapse rates are problematical (1).

Host factors are important. A favourable IL28b haplotypes predict a rapid virus response (RVR) which in turn predicts an SVR. A consistent trend has been observed with DAA therapy, in particular sofosbuvir.

Lower response rates have been observed in genotype 3 versus genotype 2 and in patients with genotype 3 and cirrhosis. However as detailed below, excellent response rates can be achieved with the combination of daclatasvir and sofosbuvir in non-cirrhotic patients treated for 12 weeks. (13-15). These data have been summarised in international guidelines.

The first generation protease inhibitors have limited activity against genotype 3. New NS5A inhibitors show activity, particularly daclatasvir, which has greater in vitro potency than ledipasvir. Thus the combination of daclatasvir therefore with the NS5B polymerase inhibitor has proven to be an important treatment for patients with genotype 3, particularly if patients are treated before the onset of cirrhosis. There is an important unmet need in this group which has been met by the combination of sofosbuvir and daclatasvir plus or minus ribavirin, and which fundamentally alters treatment prospects for this group if applied appropriately.

A detailed tabulation of the results of recent trials with sofosbuvir and daclatasvir, sofosbuvir and ribavirin and PEG IFN sofosbuvir and ribavirin in the FISSION, FUSION, POSITRON, ALLY-3, BOSON, the UK EXPANDED ACCESS AND FRENCH EXPANDED ACCESS PROGRAMS is provided in separate tables below.

It is apparent that efficacy becomes curtailed with more advanced disease. It is important to note that the cost effective parameter and important comparator used by NICE and the ERG, i.e. 92% SVR in 12/13 patients observed in the VALENCE trial with 24 weeks of sofosbuvir and ribavirin in treatment naïve cirrhotics is almost certainly an outlier result, and has not been matched with other studies of sofosbuvir and ribavirin in genotype 3. Thus the high ICERS found as a result need to be judged against the efficacy observed with sofosbuvir and daclatasvir for 12 weeks versus the more realistic use of sofosbuvir and ribavirin for 12 weeks. It is unlikely that sofosbuvir and ribavirin for 24 weeks will be used in patients for genotype 3 if a 12 week option is available. The tables supplied have some limitations: comparisons are made across trials, and in these trials, the presence of cirrhosis was established by varying combinations of liver biopsy Fibrotest, and transient elastography. However the degradation of response with advancing fibrosis is a consistent observation. It is difficult to achieve complete eradication of genotype 3 with sofosbuvir and ribavirin for 12 weeks and the alternative therefore is to add an NS5A inhibitor, active against genotype 3 to sofosbuvir to replace ribavirin and improve SVR rates. Treatment response rates with sofosbuvir and daclatasvir for 12 weeks are extremely high in non –cirrhotic patients (table 2)

International guidelines and posology

The EASL guidelines recommend, as a priority, that all adults with chronic hepatitis C and evidence of compensated or decompensated cirrhosis should be treated. Also, treatment is justified for adults with chronic hepatitis C who do not have evidence of cirrhosis but have evidence of ongoing HCV replication and necroinflammatory change. Sofosbuvir and daclatasvir for 12 weeks is recommended for genotype 3 patients

without cirrhosis, without ribavirin, based on the ALLY-3 data. (The EASL guidelines do not recommend the combination of sofosbuvir plus ledipasvir for genotype 3 infection)

FDA approval has been given to sofosbuvir and daclatasvir (12 weeks without ribavirin for genotype 3)
Critically, the most recent daclatasvir SmPC includes the ALLY-3 type II variation changes adopted by the CHMP on 23 July 2015 which again, recommend the combination of sofosbuvir plus daclatasvir without ribavirin for 12 weeks in genotype 3 patients who do not have cirrhosis. Given these guidelines, therefore and the change in posology, is very doubtful that treatment sequencing with interferon and ribavirin will be considered an acceptable regimen in 2016 and few patients are likely to participate in such a policy. Treatment sequencing may have detrimental effects: for example the response rates in treatment naïve patients with genotype 3 and cirrhosis in the VALENCE study were inferior to those naïve patients. The reasons for this is unknown but may be the results of a perturbation of the quasipecies or even the development of ribavirin resistance. (Table 4)

The results achieved with a short duration of sofosbuvir and daclatasvir without ribavirin provide a very favourable alternative to sofosbuvir plus PEG IFN and ribavirin for 12 weeks in genotype 3 patients. Considerable real world experience has been obtained through the United Kingdom expanded access program with sofosbuvir and Daclatasvir, and it would seem very unlikely that NHS England would not wish to commission daclatasvir as a highly favourable, effective as well as safe alternative in patients with less advanced disease as well as those with cirrhosis given the experience in the UK. The majority of patients will be treated for 12 weeks, providing a favourable option for the National Health Service, with low levels of monitoring given the absence of PEG interferon and ribavirin from the regimen.

It will be important to strive for high cure rates because relapse observed after treatment with and NS5A inhibitor is frequently associated with the selection of high-level NS5A resistant mutations threatening future treatments for patients, their ultimate outcome and a change in evolutionary patterns in the extent disease. Although BOSON did not include a comparator arm comparing sofosbuvir plus daclatasvir to sofosbuvir plus peginterferon and ribavirin, it is clear that the interferon free option of sofosbuvir and daclatasvir is likely to result in very similar responses in patients with less advanced disease.

Duration remains an important factor as indicated by the posology. The majority of non-cirrhotic patients will respond to a 12 week regimen and the place of lengthening treatment to 24 weeks with sofosbuvir plus daclatasvir plus or minus ribavirin is an unanswered question that can only be answered by further clinical experience and careful monitoring of patients for pre-treatment and on treatment responses, that could predict a higher likelihood of response with 24 versus 12 weeks of treatment. At this point of time the number of patients who require 24 weeks of sofosbuvir plus daclatasvir is not established, but it is hoped that with careful discussion, value-based pricing can be introduced to optimise response rates for selected patients with genotype 3 infection and advanced disease, as was the case in the UK expanded access program.

The inherent problem of a suboptimal cure of disease again forces the question of whether patients with chronic hepatitis C should be treated earlier in the disease to pprevent the irreversible fibrosis, architectural and structural damage, vascular shunting and systemic complications that are characteristic of cirrhosis and to ensure response rates of higher than 90% rather than < 70%.

The ALLY 3 studies provide powerful evidence for the efficacy of sofosbuvir and daclatasvir for 12 weeks in patients without cirrhosis, and for lower responses rates in patients with cirrhosis. These data, together with the natural history of genotype 3 infection, point to a particular need to treat genotype 3 disease earlier, before the onset of cirrhosis and to treat to forestall progression to cirrhosis in this cohort.

The concept of “holding the line” by sequential treatment with interferon ignores the fact that interferon treatment has not sufficiently increased the number of treated patients to reduce the burden of liver disease.

There are unique advantages to offering an interferon free DAA treatment (sofosbuvir plus daclatasvir) to non-cirrhotic genotype 3 persons with injecting drug use whose acceptance of interferon has been limited to date. Interferon use is possible in this group but would be more complicated, and to date has had very little low impact and effectiveness on the prevalence of hepatitis C in those with injecting drug use. PEG IFN and RBV together with sofosbuvir can no longer considered a first line preferential treatment.

The lowered thresholds recently proposed by Claxton et al are important health economic considerations. However as is evident from table 2 below, (16) (and Claxton K personal communication), the burden of primary liver cancer should provide a particular weighting toward value for treating genotype 3 infection with the most appropriate (and the most effective) regimens.

Table II. Measures of Burden (Appendix A) and wider social benefits (Appendix B) associated with the average of displaced quality-adjusted life year effects (Claxton *et al.*, 2013)

Proportionate shortfall (% QALY loss)			Absolute shortfall (QALY loss)			Wider social benefits (net production)		
C22	Liver cancer	73%	C22	Liver cancer	10.7	M05	Rheumatoid arthritis	£30 034
C25	Pancreatic cancer	73%	C25	Pancreatic cancer	9.97	E11	Diabetes	£27 421
C34	Lung cancer	71%	C34	Lung cancer	9.68	M45	Ankylosing spondylitis	£26 190
C92	Myeloid leukaemia	38%	F20	Schizophrenia	7.62	F30	Depression	£23 489
G20	Parkinson's disease	31%	G35	Multiple sclerosis	6.18	F20	Schizophrenia	£22 697
C90	Myeloma	31%	C92	Myeloid leukaemia	6.15	J45	Asthma	£20 100
C64	Kidney cancer	22%	G20	Parkinson's disease	4.6	M81	Osteoporosis	£17 910
G35	Multiple sclerosis	18%	C90	Myeloma	4.45	G35	Multiple sclerosis	£15 482
J43	Emphysema and COPD	17%	J43	Emphysema and COPD	3.8	J43	Emphysema and COPD	£14 525
G30	Alzheimer's disease	14%	C64	Kidney cancer	3.75	G40	Epilepsy	£14 245
F03	Dementia	14%	F30	Depression	3.63	L40	Psoriasis	£11 890
F20	Schizophrenia	12%	M05	Rheumatoid arthritis	2.83	**Displaced**	**Average of displaced QALYs**	**£11 611**
M05	Rheumatoid arthritis	11%	E11	Diabetes	2.68	E66	Obesity	£8138
C61	Prostate cancer	11%	**Displaced**	**Average of displaced QALYs**	**2.07**	C53	Cervical cancer	£6912
I26	Embolisms, fibrillation, thrombosis	11%	J45	Asthma	1.86	K50	Irritable Bowel Syndrome	£6284
E11	Diabetes	11%	G30	Alzheimer's disease	1.68	J30	Allergic rhinitis	£5234
C18	Colon cancer	10%	F03	Dementia	1.68	G20	Parkinson's disease	£3102
I21	Acute myocardial infarction	9%	G40	Epilepsy	1.32	C50	Breast cancer	£2888
I64	Stroke	8%	C18	Colon cancer	1.28	G30	Alzheimer's disease	£351
Displaced	**Average of displaced QALYs**	**8%**	I26	Embolisms, fibrillation, thrombosis	1.16	A40	Streptococcal septicaemia	−£513
F30	Depression	6%	C61	Prostate cancer	1.06	F03	Dementia	−£2430
G40	Epilepsy	4%	I21	Acute myocardial infarction	1	I64	Stroke	−£6949
J45	Asthma	4%	I64	Stroke	0.83	C18	Colon cancer	−£8061
C50	Breast cancer	3%	C53	Cervical cancer	0.6	C61	Prostate cancer	−£10 602
C53	Cervical cancer	3%	C50	Breast cancer	0.55	C64	Kidney cancer	−£13 211
L40	Psoriasis	2%	A40	Streptococcal septicaemia	0.38	I21	Acute myocardial infarction	−£14 395
J10	Influenza	2%	J30	Allergic rhinitis	0.3	I26	Embolisms, fibrillation, thrombosis	−£16 752
M81	Osteoporosis	2%	M81	Osteoporosis	0.28	J10	Influenza	−£21 568
J30	Allergic rhinitis	2%	K50	Irritable Bowel Syndrome	0.26	C90	Myeloma	−£23 382
A40	Streptococcal septicaemia	2%	J10	Influenza	0.19	C92	Myeloid leukaemia	−£24 813
K50	Irritable Bowel Syndrome	1%	L40	Psoriasis	0.19	C22	Liver cancer	−£32 709
E66	Obesity	0%	E66	Obesity	0.18	C34	Lung cancer	−£36 067
M45	Ankylosing spondylitis	0%	M45	Ankylosing spondylitis	0.11	C25	Pancreatic cancer	−£53 860

QALY, quality-adjusted life year.

Conclusions

In summary, genotype 3 infection poses an important healthcare problem because of the potentially more aggressive disease. However, it is possible to achieve the same 90% plus SVR rates achieved with other genotypes. Close to 100% of genotype 3 patients without cirrhosis respond to 12 weeks of sofosbuvir and daclatasvir without ribavirin; those with established cirrhosis or more advanced fibrosis respond less well, pointing to the necessity and advisability of treating genotype 3 with an interferon free regimen prior to cirrhosis. It will be possible to arrest disease before the onset of cirrhosis and to use the combination of sofosbuvir and daclatasvir more effectively if patients can be treated relatively early, and since interferon is frequently not desired or optimal in many population groups, without interferon and ribavirin.

The likelihood of progression would be curtailed. Higher response rates will greatly reduce the risk of an evolutionary drift to a higher prevalence of NS5A resistant variants, which given their fitness and persistence, are highly likely to be transmissible. Treatment of patients with NS5A resistant variants is likely to remain challenging even with the advent of true 2nd generation NS5A inhibitors in genotype 3 infection. There is a suggestion that all-cause mortality in patients with hepatitis C is reduced by cure (17). Cures in patients with injecting drug use will lead to a reduction in incident chronic disease.

Tables: comparisons of SVR by regimen and duration, treatment and disease stage.

Table 1. SVR in treatment naïve, or classed as naïve and experienced, non cirrhotic showing similar efficacy of sofosbuvir and daclatasvir without ribavirin and sofosbuvir PEG IFN and RBV (96%, 12 weeks).

Study	Protocol	Duration (weeks)	Percent SVR	Numbers	Disease status	Treatment status	Reference
ALLY-3	SOF DCV	12	96	73/76	Non Cirrhotic	Naïve	Nelson
BOSON	SOF PEG RBV	12	96	68/71	Non Cirrhotic	Naïve	Foster
VALENCE	SOF RBV	24	95	87/92	Non Cirrhotic	Naïve	Zeuzem
French ATU	SOF DCV ± RBV	12	92	11/12	Non Cirrhotic	Naïve or experienced	Hezode
BOSON	SOF RBV	24	90	65/72	Non Cirrhotic	Naïve	Foster
BOSON	SOF RBV	16	83	58/70	Non Cirrhotic	Naïve	Foster
LONESTAR 2	SOF PEG RBV	12	83	10/12	Non Cirrhotic	Naïve	Lawitz
French ATU	SOF DCV ± RBV	24	83	5/6	Non Cirrhotic	Naïve or experienced	Hezode
FISSION	SOF RBV	12	61	44/51	Non Cirrhotic	Naïve	Lawitz

Table 2. SVR in treatment naïve, non cirrhotic genotype 3 showing similar efficacy of sofosbuvir and daclatasvir 12 weeks without ribavirin and sofosbuvir PEG IFN and RBV (96%, 12 weeks). Greater than 90% efficay was observed with sofosbuvir plus ribavirin in VALENCE and in BOSON but with 24 weeks treatment.

Study	Protocol	Duration (weeks)	Percent SVR	Numbers	Disease status	Treatment status	Reference
ALLY-3	SOF DCV	12	96	73/76	Non Cirrhotic	Naïve	Nelson
BOSON	SOF PEG RBV	12	96	68/71	Non Cirrhotic	Naïve	Foster
VALENCE	SOF RBV	24	95	87/92	Non Cirrhotic	Naïve	Zeuzem
BOSON	SOF RBV	24	90	65/72	Non Cirrhotic	Naïve	Foster
BOSON	SOF RBV	16	83	58/70	Non Cirrhotic	Naïve	Foster
LONESTAR 2	SOF PEG RBV	12	83	10/12	Non Cirrhotic	Naïve	Lawitz
FISSION	SOF RBV	12	61	44/51	Non Cirrhotic	Naïve	Lawitz

Table 3. SVR in treatment naïve cirrhotic G3. The SVR rates of 92% (in 12/13 patients) in VALENCE achieved with 24 weeks sofosbuvir and ribavirin were not confirmed in BOSON and appear to be an overestimate of the SVR in patients with cirrhosis.

Study	Protocol	Duration (weeks)	Percent SVR	Numbers	Disease status	Treatment status	Reference
VALENCE	SOF RBV	24	92	12/13	Cirrhotic	Naïve	Zeuzem
BOSON	SOF PEG RBV	12	91	21/23	Cirrhotic	Naïve	Foster
LONESTAR 2	SOF PEG RBV	12	83	10/12	Cirrhotic	Naïve	Lawitz
BOSON	SOF RBV	24	82	18/22	Cirrhotic	Naïve	Foster
ALLY-3	SOF DCV	12	73	18/22	Cirrhotic	Naïve	Nelson
ALLY-3	SOF DCV	12	73	18/22	Cirrhotic	Naïve	Nelson
BOSON	SOF RBV	16	57	12/21	Cirrhotic	Naïve	Foster
FISSION	SOF RBV	12	34	13/38	Cirrhotic	Naïve	Lawitz

(18, 19)

Table 4. SVR rates in patients categorised as cirrhotic. SVR rates are generally lower than 90% even in those treated wth sofosbuvir PEG IFN and RBV, particularly in treatment experienced patients. The percent SVR in 12/13 patients achieved with 24 weeks sofosbuvir and ribavirin in VALENCE appear to be an outlier figure for a DAA regimen

Study	Protocol	Duration (weeks)	Percent SVR	Numbers	Disease status	Treatment status	Reference
VALENCE	SOF RBV	24	92	12/13	Cirrhotic	Naïve	Zeuzem
BOSON	SOF PEG RBV	12	91	21/23	Cirrhotic	Naïve	Foster
BOSON	SOF PEG RBV	12	88	51/58	Cirrhotic	Overall	Foster
Estaban	SOF PEG RBV	12	88	7/9	Cirrhotic	Experienced DAA	Estaban
French ATU	SOF DCV ± RBV	24	88	52/59	Cirrhotic	Naïve or experienced	Hezode
BOSON	SOF PEG RBV	12	86	30/35	Cirrhotic	Experienced	Foster
LONESTAR 2	SOF PEG RBV	12	83	10/12	Cirrhotic	Naïve	Lawitz
BOSON	SOF RBV	24	82	18/22	Cirrhotic	Naïve	Foster
BOSON	SOF RBV	24	79	44/56	Cirrhotic	Overall	Foster
BOSON	SOF RBV	24	76	26/34	Cirrhotic	Experienced	Foster
French ATU	SOF DCV ± RBV	12	76	22/29	Cirrhotic	Naïve or experienced	Hezode
ALLY-3	SOF DCV	12	73	18/22	Cirrhotic	Naïve	Nelson
ALLY-3	SOF DCV	12	73	18/22	Cirrhotic	Naïve	Nelson
UK Exp Access	SOF DCV	12	71	79/114	Cirrhotic	Unknown	UK
ALLY-3	SOF DCV	12	70	21/30	Cirrhotic	Overall	Nelson
UK Exp Access	SOF DCV RBV	12	70	79/115	Cirrhotic	Naïve or experienced	UK
VALENCE	SOF RBV	24	68	41/60	Cirrhotic	Overall	Zeuzem
ALLY-3	SOF DCV	12	63	20/32	Cirrhotic	Overall	Nelson
ALLY-3	SOF DCV	12	63	5/8	Cirrhotic	Experienced	Nelson
VALENCE	SOF RBV	24	62	29/47	Cirrhotic	Experienced	Zeuzem
FUSION	SOF RBV	16	61	14/23	Cirrhotic	Experienced	Jacobson
BOSON	SOF RBV	16	57	12/21	Cirrhotic	Naïve	Foster
BOSON	SOF RBV	16	51	29/57	Cirrhotic	Overall	Foster
BOSON	SOF RBV	16	47	17/36	Cirrhotic	Experienced	Foster
FISSION	SOF RBV	12	34	13/38	Cirrhotic	Naïve	Lawitz
POSITRON	SOF RBV	12	21	3/14	Cirrhotic	Intolerant	Jacobson
FUSION	SOF RBV	12	19	5/26	Cirrhotic	Experienced	Jacobson

Table 5. SVR in genotype 3 cirrhotic treatment experienced patients. SVR rates of < 90% in all studies.

Study	Protocol	Duration (weeks)	Percent SVR	Numbers	Disease status	Treatment status	Reference
BOSON	SOF PEG RBV	12	86	30/35	Cirrhotic	Experienced	Foster
BOSON	SOF RBV	24	76	26/34	Cirrhotic	Experienced	Foster
ALLY-3	SOF DCV	12	63	5/8	Cirrhotic	Experienced	Nelson
VALENCE	SOF RBV	24	62	29/47	Cirrhotic	Experienced	Zeuzem
FUSION	SOF RBV	16	61	14/23	Cirrhotic	Experienced	Jacobson
BOSON	SOF RBV	16	47	17/36	Cirrhotic	Experienced	Foster
FUSION	SOF RBV	12	19	5/26	Cirrhotic	Experienced	Jacobson

Table 6 SVR in genotype 3 non cirrhotic treatment patients, naïve or experienced. High > 95% response rates were observed with sofosbuvir + daclatasvir without ribavirin for 12 weeks and sofobuvir + PEG IFN RBV for 12 weeks

Study	Protocol	Duration (weeks)	Percent SVR	Numbers	Disease status	Treatment status	Reference
ALLY-3	SOF DCV	12	97	73/75	Non Cirrhotic	Overall	Nelson
ALLY-3	SOF DCV	12	96	73/76	Non Cirrhotic	Naïve	Nelson
BOSON	SOF PEG RBV	12	96	68/71	Non Cirrhotic	Naïve	Foster
BOSON	SOF PEG RBV	12	95	117/123	Non Cirrhotic	Overall	Foster
VALENCE	SOF RBV	24	95	87/92	Non Cirrhotic	Naïve	Zeuzem
ALLY-3	SOF DCV	12	94	112/119	Non Cirrhotic	Overall	Nelson
BOSON	SOF PEG RBV	12	94	49/52	Non Cirrhotic	Experienced	Foster
Estaban	SOF PEG RBV	12	93	13/14	Non Cirrhotic	Experienced DAA	Estaban
French ATU	SOF DCV ± RBV	12	92	11/12	Non Cirrhotic	Naïve or experienced	Hezode
VALENCE	SOF RBV	24	91	172/190	Non Cirrhotic	Overall	Zeuzem
ALLY-3	SOF DCV	12	90	39/43	Non Cirrhotic	Experienced	Nelson
BOSON	SOF RBV	24	90	65/72	Non Cirrhotic	Naïve	Foster
BOSON	SOF RBV	24	87	109/126	Non Cirrhotic	Overall	Foster
VALENCE	SOF RBV	24	87	85/98	Non Cirrhotic	Experienced	Zeuzem
BOSON	SOF RBV	16	83	58/70	Non Cirrhotic	Naïve	Foster
LONESTAR 2	SOF PEG RBV	12	83	10/12	Non Cirrhotic	Naïve	Lawitz
French ATU	SOF DCV ± RBV	24	83	5/6	Non Cirrhotic	Naïve or experienced	Hezode
BOSON	SOF RBV	24	81	44/54	Non Cirrhotic	Experienced	Foster
BOSON	SOF RBV	16	80	99/124	Non Cirrhotic	Overall	Foster
TARGET	SOF RBV	24	80	48/60	Non Cirrhotic	Overall	Alqahtani
TARGET	SOF RBV	24	78	18/23	Non Cirrhotic	Experienced	Alqahtani
BOSON	SOF RBV	16	76	41/54	Non Cirrhotic	Experienced	Foster
POSITRON	SOF RBV	12	68	57/84	Non Cirrhotic	Intolerant	Jacobson
FUSION	SOF RBV	16	63	25/40	Non Cirrhotic	Experienced	Jacobson
FISSION	SOF RBV	12	61	44/51	Non Cirrhotic	Naïve	Lawitz
FUSION	SOF RBV	12	37	14/38	Non Cirrhotic	Experienced	Jacobson

- 112/119 = F0-F3 by fibrotest

Table 7. SVR rates in 12 week regimens. High > 90% SVR rates achieved by sofosbuvir plus daclatasvir without or with ribavirin, SOF PEG IFN and RBV only. Attrition in response rates with advancing disease.

Study	Protocol	Duration (weeks)	Percent SVR	Numbers	Disease status	Treatment status	Reference
ALLY-3	SOF DCV	12	100	45/45	F0	Overall	Nelson
ALLY-3	SOF DCV	12	100	14/14	F2	Overall	Nelson
ALLY-3	SOF DCV	12	97	73/75	Non Cirrhotic	Overall	Nelson
ALLY-3	SOF DCV	12	96	73/76	Non Cirrhotic	Naïve	Nelson
BOSON	SOF PEG RBV	12	96	68/71	Non Cirrhotic	Naïve	Foster
BOSON	SOF PEG RBV	12	95	117/123	Non Cirrhotic	Overall	Foster
BOSON	SOF PEG RBV	12	95	89/94	Overall	Naïve	Foster
ALLY-3	SOF DCV	12	94	112/119	F0-F3	Overall	Nelson
ALLY-3	SOF DCV	12	94	31/33	F1	Overall	Nelson
ALLY-3	SOF DCV	12	94	112/119	Non Cirrhotic	Overall	Nelson
BOSON	SOF PEG RBV	12	94	49/52	Non Cirrhotic	Experienced	Foster
BOSON	SOF PEG RBV	12	93	168/181	Overall	Overall	Foster
Estaban	SOF PEG RBV	12	93	13/14	Non Cirrhotic	Experienced DAA	Estaban
French ATU	SOF DCV ± RBV	12	92	11/12	Non Cirrhotic	Naïve or experienced	Hezode
ALLY-3	SOF DCV	12	91	129/142	Age < 65 years	Overall	Nelson
ALLY-3	SOF DCV	12	91	92/101	Overall	Naïve	Nelson
ALLY-3	SOF DCV	12	91	92/101	Overall	Naïve	Nelson
BOSON	SOF PEG RBV	12	91	21/23	Cirrhotic	Naïve	Foster
BOSON	SOF PEG RBV	12	91	79/87	Overall	Experienced	Foster
ALLY-3	SOF DCV	12	90	39/43	Non Cirrhotic	Experienced	Nelson
ALLY-3	SOF DCV	12	89	135/152	Overall	Overall	Nelson
ALLY-3	SOF DCV	12	89	135/152	Overall	Overall	Nelson
BOSON	SOF PEG RBV	12	88	51/58	Cirrhotic	Overall	Foster
Estaban	SOF PEG RBV	12	88	7/9	Cirrhotic	Experienced DAA	Estaban
ALLY-3	SOF DCV	12	86	44/51	Overall	Experienced	Nelson
BOSON	SOF PEG RBV	12	86	30/35	Cirrhotic	Experienced	Foster
LONESTAR 2	SOF PEG RBV	12	83	10/12	Cirrhotic	Naïve	Lawitz
LONESTAR 2	SOF PEG RBV	12	83	10/12	Non Cirrhotic	Naïve	Lawitz
ALLY-3	SOF DCV	12	82	22/27	F3	Overall	Nelson
French ATU	SOF DCV ± RBV	12	76	22/29	Cirrhotic	Naïve or experienced	Hezode
ALLY-3	SOF DCV	12	73	18/22	Cirrhotic	Naïve	Nelson
ALLY-3	SOF DCV	12	73	18/22	Cirrhotic	Naïve	Nelson
UK Exp Access	SOF DCV	12	71	79/114	Cirrhotic	Unknown	UK
ALLY-3	SOF DCV	12	70	21/30	F4	Overall	Nelson
ALLY-3	SOF DCV	12	70	21/30	F4	Overall	Nelson
ALLY-3	SOF DCV	12	70	7/10	Age > 65 years	Overall	Nelson
ALLY-3	SOF DCV	12	70	21/30	Cirrhotic	Overall	Nelson
UK Exp Access	SOF DCV RBV	12	70	79/115	Cirrhotic	Naïve or experienced	UK
POSITRON	SOF RBV	12	68	57/84	Non Cirrhotic	Intolerant	Jacobson
ALLY-3	SOF DCV	12	63	20/32	Cirrhotic	Overall	Nelson
ALLY-3	SOF DCV	12	63	5/8	Cirrhotic	Experienced	Nelson
FISSION	SOF RBV	12	61	44/51	Non Cirrhotic	Naïve	Lawitz
FISSION	SOF RBV	12	56	102/183	Overall	Naïve	Lawitz
FISSON	SOF RBV	12	56	102/183	Overall	Naïve	Lawitz
FUSION	SOF RBV	12	37	14/38	Non Cirrhotic	Experienced	Jacobson
FISSION	SOF RBV	12	34	13/38	Cirrhotic	Naïve	Lawitz
POSITRON	SOF RBV	12	21	3/14	Cirrhotic	Intolerant	Jacobson
FUSION	SOF RBV	12	19	5/26	Cirrhotic	Experienced	Jacobson

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[redacted]

APPENDIX 1

Note: The information in this Appendix 1 is solely for the purpose of this NICE appraisal and constitutes commercial in confidence information. The information highlighted should be redacted

The ACD does not take into account the contracted pricing arrangements that have been agreed between AbbVie Ltd and the Commercial Medicines Unit (**CMU)**. This process culminated in the implementation of a national framework agreement (**Framework Agreement**) for Viekirax® and Exviera® with effect from 1 August 2015.

This Framework Agreement covers supply of Viekirax® and Exviera® to all regions and therefore all NHS hospitals in England who are participants. The term of the Framework differs between the regions:

Midlands and East/North of England – term is from 1 August 2015 to 29 February 2016; and
Pan London and South of England – term is from 1 August 2015 to 31 August 2016.

The CMU has informed AbbVie and other suppliers that they will tender for new Framework Agreements to cover all regions and hospitals in England, to commence as the current Framework Agreement expires.

In addition to the Framework Agreement, the supply of AbbVie's products is also governed by the NHS terms and conditions of contract for the purchase of goods (supplementary) May 2015 and the NHS supplementary conditions of contract for the purchase of pharmaceuticals (October 2012). Under these standard NHS conditions, AbbVie agrees to supply Viekirax® and Exviera® subject to these terms at the agreed prices during the term of the Framework Agreement.

AbbVie Ltd
AbbVie House
Vanwall Business Park
Vanwall Road
Maidenhead
Berkshire SL6 4UB

OFFICE +44 (0)1628 561090
FAX +44 (0)1628 461153
www.abbvie.co.uk

Registered Number: 08004972
Registered Office: AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire SL6 4UB

The Framework Agreement itself is not confidential but the annexed contract award schedule which contains our confidential price information discussed below is. AbbVie is happy to supply a copy of the Framework Agreement on request without the contract award schedule.

Any information provided to NICE on AbbVie's current prices for Viekirax and Exviera is highly competitively sensitive. If this pricing data were disclosed by NICE (intentionally or inadvertently) to an actual or potential competitor of AbbVie, this could involve AbbVie (and NICE in effecting the disclosure) in a breach of EU and English competition law. We emphasise the importance of the confidentiality conditions that are attached to the information that we have labelled as commercial in confidence

Under the Framework Agreement described above, AbbVie Ltd has agreed to make the 3D regimen available to the NHS at a total price of [redacted] exclusive of VAT per patient [redacted] and the 2D regimen available to the NHS at a total price [redacted] exclusive of VAT per patient [redacted]

[redacted]

In accordance with section 5.5.2 of the NICE Guide to the Methods of Technology Appraisal 2013, the national Framework Agreement, [redacted] meet all of the specific requirements concerning nationally available prices which are transparent and consistent for the NHS but are commercial in confidence.

[redacted]

In AbbVie's opinion these prices should be considered by the ACD as the most relevant prices to the NHS in the calculation of the reference case

Table 1 below shows the revised fully incremental analyses based on the contracted pricing arrangements for treatments recommended in the summary of product

characteristics for different groups stratified by treatment history as requested by the Committee. This is consistent with Table 6 of the ACD. .

Table 1 ICERs according to treatments in the summary of product characteristics – with contract price

Treatment	Total Costs, £	Total QALYs	Incremental costs*	Incremental QALYs*	ICER (£/QALY gained)
Genotype 1a HCV without cirrhosis; previously untreated					
PR	£20,888	14.26	NA	NA	NA
Boceprevir + PR	£30,114	14.77	£9,226	0.51	Extended Dominance
Telaprevir + PR	£34,208	15.07	£13,320	0.81	Extended Dominance
Simeprevir + PR	£35,395	15.11	£14,507	0.85	Extended Dominance
3D + R (for 12 weeks)	[redacted]	**15.73**	[redacted]	**1.47**	**£11,098**
Sofosbuvir + PR	£42,144	15.64	£21,256	1.38	Dominated
Genotype 1a HCV without cirrhosis; previously treated					
PR	£21,907	12.91	NA	NA	NA
Telaprevir + PR	£36,138	13.77	£14,231	0.86	Extended Dominance
3D + R (for 12 weeks)	[redacted]	**14.74**	[redacted]	**1.84**	**£8,117**
Simeprevir + PR	£39,911	13.76	£18,005	0.86	Dominated
Sofosbuvir +	£44,336	14.22	£22,429	1.31	Dominated

PR					
Genotype 1a HCV with cirrhosis; previously untreated					
PR	£45,057	8.08	NA	NA	NA
3D + R (for 24 weeks)	[redacted]	**10.19**	[redacted]	**2.11**	**£4,884**
Telaprevir + PR	£55,907	9.00	£10,850	0.92	Dominated
Simeprevir + PR	£57,832	8.94	£12,775	0.85	Dominated
Boceprevir + PR	£58,024	7.97	£12,967	-0.11	Dominated
Sofosbuvir + PR	£61,347	9.79	£16,290	1.70	Dominated
Genotype 1a HCV with cirrhosis; previously treated					
PR	£45,505	7.45	NA	NA	NA
3D + R (for 24 weeks)	[redacted]	**9.83**	[redacted]	**2.38**	**£3,336**
Telaprevir + PR	£59,328	8.13	£13,823	0.68	Dominated
Simeprevir + PR	£62,614	8.17	£17,109	0.72	Dominated
Sofosbuvir + PR	£64,197	8.87	£18,692	1.42	Dominated
Genotype 1b HCV without cirrhosis; previously untreated					
PR	£19,844	14.45	NA	NA	NA
hBoceprevir + PR	£29,110	14.95	£9,265	0.50	Extended Dominance
Telaprevir + PR	£33,115	15.27	£13,271	0.82	Extended

					Dominance
Simeprevir + PR	£33,972	15.37	£14,128	0.92	Extended Dominance
3D (for 12 weeks)	[redacted]	**15.84**	[redacted]	**1.39**	**£11,422**
Sofosbuvir + PR	£43,503	15.39	£23,659	0.95	Dominated
Genotype 1b HCV without cirrhosis; previously treated					
PR	£22,909	12.75	NA	NA	NA
Telaprevir + PR	£34,542	14.04	£11,633	1.29	Extended Dominance
3D (for 12 weeks)	[redacted]	**14.84**	[redacted]	**2.09**	**£5,967**
Simeprevir + PR	£37,285	14.21	£14,376	1.46	Dominated
Sofosbuvir + PR	£44,336	14.22	£21,427	1.47	Dominated
Genotype 1b HCV with cirrhosis; previously untreated					
PR	£43,298	8.32	NA	NA	NA
3D + R (for 12 weeks)	[redacted]	**10.36**	[redacted]	**2.04**	**£4,619**
Telaprevir + PR	£54,065	9.25	£10,766	0.93	Dominated
Simeprevir + PR	£55,434	9.26	£12,136	0.94	Dominated
Boceprevir + PR	£56,331	8.20	£13,033	-0.12	Dominated
Sofosbuvir +	£63,636	9.48	£20,338	1.16	Dominated

PR					
Genotype 1b HCV with cirrhosis; previously treated					
PR	£47,375	7.22	NA	NA	NA
3D + R (for 12 weeks)	[redacted]	**9.77**	[redacted]	**2.55**	**£2,042**
Telaprevir + PR	£56,534	8.47	£9,159	1.25	Dominated
Simeprevir + PR	£58,015	8.73	£10,640	1.51	Dominated
Sofosbuvir + PR	£64,197	8.87	£16,822	1.65	Dominated
Genotype 4 HCV without cirrhosis; previously untreated					
PR	£19,286	15.00	NA	NA	NA
Simeprevir + PR	£33,701	15.40	£14,415	0.41	Extended Dominance
2D + R (for 12 weeks)	[redacted]	**15.84**	[redacted]	**0.85**	**£17,539**
Sofosbuvir + PR	£41,237	15.81	£21,951	0.81	Dominated
Genotype 4 HCV without cirrhosis; previously treated					
No Treatment	£16,186	12.58	NA	NA	NA
2D + R (for 12 weeks)	[redacted]	**14.84**	[redacted]	**2.27**	**£7,760**
Simeprevir + PR	£37,421	14.30	£21,236	1.72	Dominated
Sofosbuvir + PR	£44,336	14.22	£28,150	1.64	Dominated

Genotype 4 HCV with cirrhosis; previously untreated					
PR	£45,822	8.32	NA	NA	NA
2D + R (for 24 weeks)	[redacted]	**10.33**	[redacted]	**2.01**	**£3,080**
Simeprevir + PR	£55,377	9.28	£9,555	0.96	Dominated
Sofosbuvir + PR	£61,777	9.73	£15,955	1.41	Dominated
Genotype 4 HCV with cirrhosis; previously treated					
No Treatment	£41,370	7.03	NA	NA	NA
2D + R (for 24 weeks)	[redacted]	**9.82**	[redacted]	**2.79**	**£3,503**
Simeprevir + PR	£62,249	8.30	£20,879	1.27	Dominated
Sofosbuvir + PR	£64,197	8.87	£22,827	1.84	Dominated

*Incremental cost and QALY represent increments from reference (base-line) treatment

ICER: incremental cost-effectiveness ratio, 3D: ombitasvir–paritaprevir–ritonavir with dasabuvir, 2D: ombitasvir–paritaprevir–ritonavir without dasabuvir, NA: not applicable, PR: peginterferon and ribavirin, QALY: quality-adjusted life year, R: ribavirin.

Dominated – treatment gives fewer QALYs at greater cost than cost than comparator.

Extended dominance – a combination of 2 of its comparators provides equal health at a reduced cost.

In the revised economic analysis GT1 patients are treated with 3D whereas GT4 patients are treated with 2D. [redacted]

[redacted]

Table 2 shows the revised ICERs for the contracted pricing arrangements for the scenario analyses as presented in table 7 of the ACD. This table includes the most likely ICERs for the Committee's preferred scenario (Scenario 1).

Table 2 ICERs (£/QALY gained) for 3D or 2D in the revised base-case and scenario analyses – with contract price

Population	Scenario	Previously untreated		Previously treated	
		No cirrhosis	Cirrhosis	No cirrhosis	Cirrhosis
Genotype 1a HCV	Revised base case	£11,098	-£15,013	£8,117	-£11,222
	Scenario 1	£15,284	-£18,493	£11,522	-£14,107
	Scenario 2	£14,594	-£13,087	£14,429	-£9,859
Genotype 1b HCV	Revised base case	£11,422	£4,619	£5,967	£2,042
	Scenario 1	£15,667	£5,704	£8,450	£2,555
	Scenario 2	£14,731	£3,772	£11,152	£1,639
Genotype 4 HCV	Revised base case	£17,539	-£16,405	£7,760	-£13,698
	Scenario 1	£23,633	-£19,998	£11,260	-£17,100
	Scenario 2	£16,093	-£15,948	£7,235	-£10,646

HCV; hepatitis C virus, ICER: incremental cost-effectiveness ratio, 3D: ombitasvir–paritaprevir–ritonavir with dasabuvir, 2D: ombitasvir–paritaprevir–ritonavir without dasabuvir, QALY: quality-adjusted life year,

The tables above demonstrate that under the contracted pricing arrangements the 3D and 2D regimens are cost-effective regimens for GT1 and GT4 HCV patients respectively. Specifically:

- 3D continues to be a cost-effective use of resources for treating all GT1b HCV patients under all of the scenarios

- 3D is shown to be a cost-effective use of resources for treating all GT1a HCV patients whether it is a 12 or 24 week treatment under all of the scenarios

- 2D can now be considered a cost-effective use of resources for treating all GT4 patients whether it is a 12 or 24 week treatment. Now only one patient group, previously untreated GT4 patients without cirrhosis, has an ICER above £20,000 under utility "Scenario 1". However, for the reasons discussed in sections A, B and C of this response this ICER should be considered an overestimate. The ICERs under the "Revised Base Case" and "Scenario 2" are under £20,000. If recommended, 2D is likely to represent the only available interferon-free regimen for untreated GT4 patients without cirrhosis which represents a very small percentage of chronic HCV infections in England.

[redacted]

ADDENDUM TO APPENDIX 1

Note: The information in this Appendix 1 is solely for the purpose of this NICE appraisal and constitutes commercial in confidence information. The information highlighted should be redacted

Below is a replacement for the current Table 2 in the Appendix. This table summarises the revised ICERs for the contracted pricing arrangements for the different utility scenario analyses as presented in table 7 of the ACD. This table includes the ICERs for the Revised base case, Scenario 1 and Scenario 2.

Table 2 ICERs (£/QALY gained) for 3D or 2D in the revised base-case and scenario analyses – with contract price

Population	Scenario	Previously untreated		Previously treated	
		No cirrhosis	Cirrhosis	No cirrhosis	Cirrhosis
Genotype 1a HCV	Revised base case	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 1	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 2	[redacted]	[redacted]	[redacted]	[redacted]
Genotype 1b HCV	Revised base case	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 1	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 2	[redacted]	[redacted]	[redacted]	[redacted]
Genotype 4 HCV	Revised base case	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 1	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 2	[redacted]	[redacted]	[redacted]	[redacted]

AbbVie Ltd
AbbVie House
Vanwall Business Park
Vanwall Road
Maidenhead
Berkshire SL6 4UB

OFFICE +44 (0)1628 561090
FAX +44 (0)1628 461153
www.abbvie.co.uk

Registered Number: 08004972
Registered Office: AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire SL6 4UB

HCV; hepatitis C virus, ICER: incremental cost-effectiveness ratio, 3D: ombitasvir–paritaprevir–ritonavir with dasabuvir, 2D: ombitasvir–paritaprevir–ritonavir without dasabuvir, QALY: quality-adjusted life year,

The table above demonstrate that under the contracted pricing arrangements the 3D and 2D regimens are cost-effective regimens for GT1 and GT4 HCV patients respectively. Specifically:

- 3D continues to be a cost-effective use of resources for treating all GT1b HCV patients under all of the scenarios

- 3D is shown to be a cost-effective use of resources for treating all GT1a HCV patients whether it is a 12 or 24 week treatment under all of the scenarios

- 2D can now be considered a cost-effective use of resources for treating all GT4 patients whether it is a 12 or 24 week treatment. [redacted] If recommended, 2D is likely to represent the only available interferon-free regimen for untreated GT4 patients without cirrhosis which represents a very small percentage of chronic HCV infections in England.

Tables 3 and 4 provide the fully incremental analyses for Scenarios 1 and 2 respectively.

Table 3 ICERs according to treatments in the summary of product characteristics under utility Scenario 1 – with contract price

Treatment	Total Costs, £	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
Genotype 1a HCV without cirrhosis; previously untreated					
PR	£20,888	13.95	NA	NA	NA
Boceprevir + PR	£30,114	14.32	£9,226	0.37	Extended Dominance
Telaprevir + PR	£34,208	14.53	£13,320	0.58	Extended Dominance
Simeprevir + PR	£35,395	14.56	£14,507	0.62	Extended Dominance
3D + R (for 12 weeks)	[redacted]	**15.02**	[redacted]	**1.07**	[redacted]
Sofosbuvir + PR	£42,144	14.95	£21,256	1.00	Dominated
Genotype 1a HCV without cirrhosis; previously treated					
PR	£21,907	12.77	NA	NA	NA
Telaprevir + PR	£36,138	13.36	£14,231	0.59	Extended Dominance
3D + R (for 12 weeks)	[redacted]	**14.07**	[redacted]	**1.29**	[redacted]
Simeprevir + PR	£39,911	13.36	£18,005	0.59	Dominated
Sofosbuvir + PR	£44,336	13.70	£22,429	0.93	Dominated

Genotype 1a HCV with cirrhosis; previously untreated					
PR	£45,057	7.89	NA	NA	NA
3D + R (for 24 weeks)	[redacted]	**9.60**	[redacted]	**1.70**	[redacted]
Telaprevir + PR	£55,907	8.64	£10,850	0.74	Dominated
Simeprevir + PR	£57,832	8.59	£12,775	0.70	Dominated
Boceprevir + PR	£58,024	7.81	£12,967	-0.08	Dominated
Sofosbuvir + PR	£61,347	9.27	£16,290	1.38	Dominated
Genotype 1a HCV with cirrhosis; previously treated					
PR	£45,505	7.34	NA	NA	NA
3D + R (for 24 weeks)	[redacted]	**9.24**	[redacted]	**1.90**	[redacted]
Telaprevir + PR	£59,328	7.87	£13,823	0.53	Dominated
Simeprevir + PR	£62,614	7.91	£17,109	0.57	Dominated
Sofosbuvir + PR	£64,197	8.48	£18,692	1.14	Dominated
Genotype 1b HCV without cirrhosis; previously untreated					
PR	£19,844	14.08	NA	NA	NA
Boceprevir + PR	£29,110	14.45	£9,265	0.36	Extended Dominance
Telaprevir + PR	£33,115	14.67	£13,271	0.58	Extended Dominance

Simeprevir + PR	£33,972	14.75	£14,128	0.66	Extended Dominance
3D (for 12 weeks)	[redacted]	**15.10**	[redacted]	**1.02**	[redacted]
Sofosbuvir + PR	£43,503	14.77	£23,659	0.69	Dominated
Genotype 1b HCV without cirrhosis; previously treated					
PR	£22,909	12.66	NA	NA	NA
Telaprevir + PR	£34,542	13.55	£11,633	0.89	Extended Dominance
3D (for 12 weeks)	[redacted]	**14.14**	[redacted]	**1.48**	[redacted]
Simeprevir + PR	£37,285	13.67	£14,376	1.01	Dominated
Sofosbuvir + PR	£44,336	13.70	£21,427	1.04	Dominated
Genotype 1b HCV with cirrhosis; previously untreated					
PR	£43,298	8.08	NA	NA	NA
3D + R (for 12 weeks)	[redacted]	**9.73**	[redacted]	**1.65**	[redacted]
Telaprevir + PR	£54,065	8.83	£10,766	0.75	Dominated
Simeprevir + PR	£55,434	8.85	£12,136	0.77	Dominated
Boceprevir + PR	£56,331	7.99	£13,033	-0.09	Dominated
Sofosbuvir + PR	£63,636	9.03	£20,338	0.95	Dominated
Genotype 1b HCV with cirrhosis; previously treated					

PR	£47,375	7.16	NA	NA	NA
3D + R (for 12 weeks)	[redacted]	**9.20**	[redacted]	**2.04**	[redacted]
Telaprevir + PR	£56,534	8.14	£9,159	0.99	Dominated
Simeprevir + PR	£58,015	8.36	£10,640	1.20	Dominated
Sofosbuvir + PR	£64,197	8.48	£16,822	1.32	Dominated
Genotype 4 HCV without cirrhosis; previously untreated					
PR	£19,286	14.47	NA	NA	NA
Simeprevir + PR	£33,701	14.78	£14,415	0.31	Extended Dominance
2D + R (for 12 weeks)	[redacted]	**15.10**	[redacted]	**0.63**	[redacted]
Sofosbuvir + PR	£41,237	15.06	£21,951	0.59	Dominated
Genotype 4 HCV without cirrhosis; previously treated					
No Treatment	£16,186	12.58	NA	NA	NA
2D + R (for 12 weeks)	[redacted]	**14.14**	[redacted]	**1.56**	[redacted]
Simeprevir + PR	£37,421	13.74	£21,236	1.16	Dominated
Sofosbuvir + PR	£44,336	13.70	£28,150	1.12	Dominated
Genotype 4 HCV with cirrhosis; previously untreated					
PR	£45,822	8.08	NA	NA	NA

2D + R (for 24 weeks)	[redacted]	**9.71**	[redacted]	**1.63**	[redacted]
Simeprevir + PR	£55,377	8.86	£9,555	0.78	Dominated
Sofosbuvir + PR	£61,777	9.23	£15,955	1.15	Dominated
Genotype 4 HCV with cirrhosis; previously treated					
No Treatment	£41,370	7.03	NA	NA	NA
2D + R (for 24 weeks)	[redacted]	**9.24**	[redacted]	**2.21**	[redacted]
Simeprevir + PR	£62,249	8.02	£20,879	0.98	Dominated
Sofosbuvir + PR	£64,197	8.48	£22,827	1.44	Dominated

*Incremental cost and QALY represent increments from reference (base-line) treatment

ICER: incremental cost-effectiveness ratio, 3D: ombitasvir–paritaprevir–ritonavir with dasabuvir, 2D: ombitasvir–paritaprevir–ritonavir without dasabuvir, NA: not applicable, PR: peginterferon and ribavirin, QALY: quality-adjusted life year, R: ribavirin.

Dominated – treatment gives fewer QALYs at greater cost than cost than comparator.

Extended dominance – a combination of 2 of its comparators provides equal health at a reduced cost.

Table 4 ICERs according to treatments in the summary of product characteristics under utility Scenario 2 – with contract price

Treatment	Total Costs, £	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY gained)
Genotype 1a HCV without cirrhosis; previously untreated					
PR	£20,888	16.63	NA	NA	NA
Boceprevir + PR	£30,114	17.02	£9,226	0.39	Extended Dominance
Telaprevir + PR	£34,208	17.22	£13,320	0.58	Extended Dominance
Simeprevir + PR	£35,395	17.25	£14,507	0.62	Extended Dominance
3D + R (for 12 weeks)	[redacted]	**17.75**	[redacted]	**1.12**	[redacted]
Sofosbuvir + PR	£42,144	17.68	£21,256	1.05	Dominated
Genotype 1a HCV without cirrhosis; previously treated					
PR	£21,907	14.99	NA	NA	NA
Telaprevir + PR	£36,138	15.45	£14,231	0.46	Extended Dominance
3D + R (for 12 weeks)	[redacted]	**16.02**	[redacted]	**1.03**	[redacted]
Simeprevir + PR	£39,911	15.46	£18,005	0.47	Dominated
Sofosbuvir + PR	£44,336	15.73	£22,429	0.74	Dominated
Genotype 1a HCV with cirrhosis; previously untreated					
PR	£45,057	10.80	NA	NA	NA

3D + R (for 24 weeks)	[redacted]	**13.22**	[redacted]	**2.42**	[redacted]
Telaprevir + PR	£55,907	11.86	£10,850	1.06	Dominated
Simeprevir + PR	£57,832	11.78	£12,775	0.98	Dominated
Boceprevir + PR	£58,024	10.67	£12,967	-0.13	Dominated
Sofosbuvir + PR	£61,347	12.76	£16,290	1.96	Dominated
Genotype 1a HCV with cirrhosis; previously treated					
PR	£45,505	10.04	NA	NA	NA
3D + R (for 24 weeks)	[redacted]	**12.74**	[redacted]	**2.70**	[redacted]
Telaprevir + PR	£59,328	10.82	£13,823	0.78	Dominated
Simeprevir + PR	£62,614	10.85	£17,109	0.81	Dominated
Sofosbuvir + PR	£64,197	11.65	£18,692	1.61	Dominated
Genotype 1b HCV without cirrhosis; previously untreated					
PR	£19,844	17.33	NA	NA	NA
Boceprevir + PR	£29,110	17.72	£9,265	0.39	Extended Dominance
Telaprevir + PR	£33,115	17.94	£13,271	0.61	Extended Dominance
Simeprevir + PR	£33,972	18.03	£14,128	0.69	Extended Dominance
3D (for 12	[redacted]	**18.41**	[redacted]	**1.08**	[redacted]

weeks)					
Sofosbuvir + PR	£43,503	18.07	£23,659	0.73	Dominated
Genotype 1b HCV without cirrhosis; previously treated					
PR	£22,909	15.19	NA	NA	NA
Telaprevir + PR	£34,542	15.84	£11,633	0.65	Extended Dominance
3D (for 12 weeks)	[redacted]	**16.31**	[redacted]	**1.12**	[redacted]
Simeprevir + PR	£37,285	15.94	£14,376	0.75	Dominated
Sofosbuvir + PR	£44,336	15.98	£21,427	0.79	Dominated
Genotype 1b HCV with cirrhosis; previously untreated					
PR	£43,298	11.79	NA	NA	NA
3D + R (for 12 weeks)	[redacted]	**14.29**	[redacted]	**2.50**	[redacted]
Telaprevir + PR	£54,065	12.93	£10,766	1.14	Dominated
Simeprevir + PR	£55,434	12.94	£12,136	1.15	Dominated
Boceprevir + PR	£56,331	11.64	£13,033	-0.15	Dominated
Sofosbuvir + PR	£63,636	13.21	£20,338	1.42	Dominated
Genotype 1b HCV with cirrhosis; previously treated					
PR	£47,375	10.27	NA	NA	NA
3D + R (for	[redacted]	**13.45**	[redacted]	**3.18**	[redacted]

12 weeks)					
Telaprevir + PR	£56,534	11.86	£9,159	1.58	Dominated
Simeprevir + PR	£58,015	12.17	£10,640	1.90	Dominated
Sofosbuvir + PR	£64,197	12.33	£16,822	2.05	Dominated
Genotype 4 HCV without cirrhosis; previously untreated					
PR	£19,286	17.54	NA	NA	NA
Simeprevir + PR	£33,701	17.99	£14,415	0.44	Extended Dominance
2D + R (for 12 weeks)	[redacted]	**18.47**	[redacted]	**0.92**	[redacted]
Sofosbuvir + PR	£41,237	18.43	£21,951	0.88	Dominated
Genotype 4 HCV without cirrhosis; previously treated					
No Treatment	£16,186	15.26	NA	NA	NA
2D + R (for 12 weeks)	[redacted]	**17.69**	[redacted]	**2.43**	[redacted]
Simeprevir + PR	£37,421	17.11	£21,236	1.86	Dominated
Sofosbuvir + PR	£44,336	17.02	£28,150	1.76	Dominated
Genotype 4 HCV with cirrhosis; previously untreated					
PR	£45,822	10.59	NA	NA	NA
2D + R (for 24 weeks)	[redacted]	**12.66**	[redacted]	**2.07**	[redacted]

Simeprevir + PR	£55,377	11.59	£9,555	0.99	Dominated
Sofosbuvir + PR	£61,777	12.05	£15,955	1.46	Dominated
Genotype 4 HCV with cirrhosis; previously treated					
No Treatment	£41,370	9.77	NA	NA	NA
2D + R (for 24 weeks)	[redacted]	**13.40**	[redacted]	**3.63**	[redacted]
Simeprevir + PR	£62,249	11.45	£20,879	1.67	Dominated
Sofosbuvir + PR	£64,197	12.17	£22,827	2.40	Dominated

*Incremental cost and QALY represent increments from reference (base-line) treatment

ICER: incremental cost-effectiveness ratio, 3D: ombitasvir–paritaprevir–ritonavir with dasabuvir, 2D: ombitasvir–paritaprevir–ritonavir without dasabuvir, NA: not applicable, PR: peginterferon and ribavirin, QALY: quality-adjusted life year, R: ribavirin.

Dominated – treatment gives fewer QALYs at greater cost than cost than comparator.

Extended dominance – a combination of 2 of its comparators provides equal health at a reduced cost.

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

ERG commentary on company additional analyses

Produced by	Southampton Health Technology Assessments Centre (SHTAC)	
Correspondence to	Joanne Lord Director	Jonathan Shepherd Principal Research Fellow
	Southampton Health Technology Assessments Centre (SHTAC) University of Southampton First Floor, Epsilon House Enterprise Road, Southampton Science Park Southampton SO16 7NS	

Date completed 1st September 2015

ERG assessment of company response to ACD

Following the first Appraisal Committee meeting and preliminary decision for the STA of ombitasvir/ paritaprevir/ ritonavir with or without dasabuvir for treating chronic hepatitis C, NICE provided the opportunity for the company to comment on the Appraisal Consultation Document (ACD). The company responded with a 12 page document, and separate 'Appendix 1' and 'Addendum to Appendix 1' documents. The company also submitted an updated, executable version of their model. The main document detailed four points for consideration. Appendix 1 and the Addendum presented the results of additional analyses based on confidential contracted pricing arrangements. Appendix 1 contained two tables: Table 1 which presented revised results for the base case analysis (as in Table 6 of the ACD); and Table 2 which summarised the revised ICERS for the base case and two utility scenario analyses (as in Table 7 of the ACD). The Addendum contained a corrected version of Table 2, and two additional tables that presented detailed incremental results for Scenario 1 (Table 3) and Scenario 2 (Table 4).

At the request of NICE, the ERG assessed the additional analyses for the base case and Scenario 1, comparing the results presented in Tables 1-3 of the company response with those in Tables 6 and 7 of the ACD, and the outputs of the company model under the contracted pricing arrangements. Results from the ERG assessment are reported below.

The ERG has replicated the revised analyses, confirming that the input data and assumptions in the revised model were identical to those included in the original company submission, except for the pricing which was revised to follow the contracted pricing arrangements. The total cost and total QALY results presented in Tables 1 and 3 (from Appendix 1 and the Addendum, respectively, of the company response) concur with outputs from the model with revised prices. Table 1 presents a fully incremental analysis of the revised base case results for treatments recommended in the summary of product characteristics, for the different groups stratified by treatment history as requested by the Committee, and using the same comparator treatments as presented in Table 6 of the ACD. Table 3 presents a similar incremental analysis for utility Scenario 1.

The revised version of Table 2 in the Addendum correctly collates the revised ICERs, corresponding to Table 7 of the ACD. The ERG notes that the ICERs presented in the revised Table 2 all relate to recommended 3D or 2D treatments for the 12 patient groups compared with peginterferon and ribavirin (PR), except for previously treated patients with genotype 4 HCV with or without cirrhosis, for whom the comparator was 'no treatment'. Given the included sets of comparators, which correspond with those reported in Table 6 of

the ACD, the ICERs in the revised Table 2 represent the results of a correct, fully incremental analysis.

Following the assessment of the additional material, the ERG confirms that the results are consistent with the initial submission and comparisons presented in the ACD, and differ only in terms of the pricing arrangement.