

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

The following documents are made available to the consultees and commentators:

- 1. Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**
- 2. Consultee and commentator comments on the Appraisal Consultation Document from:**
 - Gilead Sciences
 - Hepatitis C Trust
 - British HIV Association (BHIVA)
 - British Society of Gastroenterology, endorsed by the RC Physicians
 - British Viral Hepatitis Group (BVHG) and British Association for the Study of the Liver (BASL) (joint response)
 - AbbVie

The Department of Health submitted a 'no comments' response. There were no individual comments received from the clinical or patient experts and no comments were received through the NICE website

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Sofosbuvir-velpatasvir 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
British HIV Association	<p>We would like to congratulate the Appraisal Committee for their timely and thorough review of this recently licensed DAA regimen and are in complete agreement with the draft recommendations.</p> <p>We sincerely hope that NHS England will adopt this technology as soon as feasible, as it will add to the currently available therapies, and with the recently approved Grazoprevir-Elbasvir will increase competition in the market with reducing prices. We hope that this will enable more patients than the current cap of 10,000 patients per year to clear HCV.</p> <p>We particularly welcome the option of Sofosbuvir-Velpatasvir as the only interferon-free option for the treatment of chronic genotype 3 HCV in patients with milder forms of liver disease, and for patients with genotype 5 and 6 infections.</p> <p>We have no further comments on this ACD at this stage.</p>	<p>Thank you for your comments. Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.</p>
British Society of Gastroenterology, endorsed by the Royal College of Physicians	<p>I have reviewed the NICE appraisal and find the comments fair and balanced. The major issue of the data concerning cost effectiveness is the rate of reinfection in HCV patients, which as stated in the report is at best debatable and probably too high at 2.4% for the UK population based on clinical experience.</p> <p>In answer to specific questions:</p> <p>Has all of the relevant evidence been taken into account? YES</p> <ul style="list-style-type: none"> · Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? YES · Are the recommendations sound and a suitable basis for guidance to the NHS? :YES · 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?: No 	<p>Thank you for your comments.</p>

Consultee	Comment [sic]	Response
British Viral Hepatitis Group (BVHG) / British Association for the Study of the Liver (BASL)	<p>BVHG and BASL would like to congratulate the committee on their robust, extensive and comprehensive review of Sofosbuvir/Velpatasvir, and support all the main conclusions reached and the recommendations proposed.</p> <p>We have some minor comments only on the September 2016 Appraisal Consultation Document.</p> <ul style="list-style-type: none"> In section 4.8 we would like to congratulate the committee on considering the potential impacts upon onward transmission to others. It is important that such appraisals analyse either the impacts of both re-infections and transmission, or analyse neither (as in this case). Including the impact of one, but not the other, would result in an unbalanced assessment. In section 4.9 there is the comment that 'the company should have included other study types such as uncontrolled and non-randomised studies'. We are not aware that any such extra data exists for the company to provide. 	Thank you for your comments.
Gilead	Gilead welcomes the draft recommendation from NICE that Eplclusa is a clinically- and cost-effective option for the treatment of the majority of HCV patient populations in England and Wales.	Thank you for your comments.
Hepatitis C Trust	<p>We will confine our comments to a single point.</p> <p>We do not believe that the provisional recommendations are sound on a reasonable basis for guidance to the NHS, for a critical reason: they are unclear.</p> <p>Specifically, clause 1.2 states:</p> <p>'It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.'</p> <p>This same sentence formed part of TAs 363, 364 and 365. At a meeting on May 18, 2016 between The Hepatitis C Trust and NICE, in the presence of solicitors, NICE said that this clause was inserted only in response to the concern of clinicians that they might be overwhelmed by demand and was to give them comfort that they could prioritise patients according to clinical need in that circumstance and that circumstance only. NICE was clear that the clause was only concerned with system capacity and that it was wholly unconnected to the cost or the affordability of the drugs.</p> <p>NHS England, however, chose to interpret the clause to mean it could cap the number of people being treated at an arbitrary 10,011 on the grounds that it wished only to spend a certain amount of money on the drugs. Furthermore in the High Court on September 21, 2016 Mr Justice Blake said in a judgement, referring to this clause: 'the plain words of the policy are inconsistent with a treatment as of right approach.'</p> <p>It is, therefore, clear that this clause is being used to mean something other than NICE, by its own admission, intended. We feel that, now that NICE is aware of this issue, it is absolutely essential that NICE clarifies the meaning of clause 1.2.</p> <p>If NICE wishes to limit access of Sofosbuvir-Velpatasvir to however many NHS England decides it will treat, then it should be clear. Equally, if NICE wishes this drug to be available to everyone for whom it is clinically</p>	Comments noted. Given that there is not yet a steady state of implementation of the hepatitis C guidance, it was considered necessary to include recommendations relating to treatment and prescribing decisions in the guidance for sofosbuvir-velpatasvir (that is, paragraph 1.2). Paragraph 1.2 is consistent with the recommendations included in previous NICE guidance for the oral hepatitis C treatments, and it was considered that the wording of paragraph 1.2 accurately reflects the intended meaning. Please refer to paragraph 4.24 of the FAD for a summary of the

Consultee	Comment [sic]	Response
	<p>appropriate – since it is cost-effective – then this should be stated in language that is unambiguous and not open to misinterpretation.</p> <p>This is extremely important because the way that NHS England has chosen to interpret Clause 1.2 broadly speaking means that people with advanced liver disease get treatment, while those with mild disease have to wait for an indeterminate amount of time. In terms of preventing mortality this assumes that people made to wait will be available next year or the year after or whenever treatment becomes available. Unfortunately, many of the most disadvantaged people with hepatitis C are only infrequently in touch with services, for example those with mental health or substance use issues. If we fail to treat and cure them now when we have them in front of us, we risk that they will not be in services again until they have conditions such liver cancer for which anti-viral treatment is too late. Furthermore the system of CQUINs NHS England has put in place to support its ‘run rate’ approach removes money from Operational Delivery Networks if they are not able to follow up patients 48-60 weeks after the end of treatment, further disincentivising the treatment of those less likely to remain in contact with services.</p> <p>We are completely aware of NHS England’s need to balance its books. We simply do not want people with hepatitis C, an already disadvantaged group, to be singled out for what amounts to rationing, while people with other conditions get full access to NICE-approved drugs. The current position is that NICE-approved drugs have to be fully funded by the NHS. That may well change in the future under the proposals put forward today by NICE and NHSE. However, this TA must be considered under the existing arrangement.</p> <p>The question we would ask the committee to consider is whether NICE would recommend rationing of cost-effective drugs or by being vague in its recommendation permit NHS England to ration cost-effective drugs if the drugs were to cure young women with breast cancer, or indeed whether NHS England would seize on an apparently unclear clause to undertake such rationing. Surely fairness and equity must underlie all that NICE does.</p> <p>We consider the principle here to be so important that we ask NICE in the strongest possible terms to publish this response in full.</p>	<p>committee’s discussion of this issue</p>

Comments received from commentators

Commentator	Comment [sic]	Response																																
AbbVie	<p>1. SVR12 estimates in patients with genotype 3 with resistance-associated variants (RAVs). This population was involved in ASTRAL-3 trial and demonstrated overall SVR12 at 95%. However, when split by sub-groups, a range of different outcomes are observed (see Table 1 below).</p> <table border="1" data-bbox="584 416 1559 608"> <tbody> <tr> <td>1</td> <td>SVR₁₂ Non-cirrhotic, Treatment-naïve</td> <td>160/163</td> <td>98%</td> </tr> <tr> <td>2</td> <td>SVR₁₂ Non-cirrhotic, Treatment-experienced</td> <td>31/34</td> <td>91%</td> </tr> <tr> <td>3</td> <td>SVR₁₂ Cirrhotic, treatment-naïve</td> <td>40/43</td> <td>93%</td> </tr> <tr> <td>4</td> <td>SVR₁₂ Cirrhotic, treatment-experienced</td> <td>33/37</td> <td>89%</td> </tr> </tbody> </table> <p>Table 1: SVR12 in GT3 patients from ASTRAL-3 (1) (2) (3)</p> <p>However, when specifically considering patients with Y93H variants, the rates of SVR12 are as follows:</p> <table border="1" data-bbox="577 727 1565 919"> <tbody> <tr> <td>1</td> <td>Non-cirrhotic, no Y93H</td> <td>171/173</td> <td>98.8%</td> </tr> <tr> <td>2</td> <td>Non-cirrhotic, + Y93H</td> <td>19/21</td> <td>90.5%</td> </tr> <tr> <td>3</td> <td>Cirrhotic, no Y93H</td> <td>71/76</td> <td>93.4%</td> </tr> <tr> <td>4</td> <td>Cirrhotic, + Y93H</td> <td>2/4</td> <td>50.0%</td> </tr> </tbody> </table> <p>Table 2: SVR12 in GT3 Y93H patients (1) (2) (3)</p> <p>Considering the population enrolled into ASTRAL-3 (1) (2) (3), it was demonstrated that of the GT3 non-cirrhotics (194 patients), 11% had the Y93H variant (21/194). Also, it was demonstrated that of the GT3 cirrhotic population (80 patients), 5% had the Y93H variant (4/80). Therefore, the prevalence of Y93H in GT3 patients, as presented in the ASTRAL-3 paper, is in the region of 9.1% (25/274). In the data presented for ASTRAL-3, of those who have the Y93H variant (total 25 patients), only 21 (i.e. 19 + 2) of these patients achieve an SVR12, resulting in a pooled SVR12 rate of 84.0% (21/25). AbbVie would therefore question validity of the current cost-effectiveness recommendation for this subset of patients with GT3 + the Y93H variant - irrespective of cirrhosis status - and would like further to seek additional clarification analysis on this matter. In addition, the said population in question could be</p>	1	SVR ₁₂ Non-cirrhotic, Treatment-naïve	160/163	98%	2	SVR ₁₂ Non-cirrhotic, Treatment-experienced	31/34	91%	3	SVR ₁₂ Cirrhotic, treatment-naïve	40/43	93%	4	SVR ₁₂ Cirrhotic, treatment-experienced	33/37	89%	1	Non-cirrhotic, no Y93H	171/173	98.8%	2	Non-cirrhotic, + Y93H	19/21	90.5%	3	Cirrhotic, no Y93H	71/76	93.4%	4	Cirrhotic, + Y93H	2/4	50.0%	<p>Thank you for your comments. Please see section 4.6 of the FAD for a summary of the committee’s discussion and conclusion on this matter.</p>
1	SVR ₁₂ Non-cirrhotic, Treatment-naïve	160/163	98%																															
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4	Cirrhotic, + Y93H	2/4	50.0%																															

Commentator	Comment [sic]	Response
	presenting a failure treatment rate of ~16.0%, which may result in subsequent harder-to-treat patients with possible development of additional RAVs.	
AbbVie	<p>2. Resistance testing in ASTRAL-3 study.</p> <p>Further discussing the presentation of ASTRAL-3 study results, AbbVie would like to note that the deep sequencing for resistance-testing was conducted with a cut-off at 1%. However, a 15% cut-off better predicts treatment failure due to the selection of resistant viruses (5). Indeed, as documented in the most recent European Association for the Study of the Liver (EASL) Guidelines 2016 (4), it is clearly recommended that HCV resistance testing should be based on population sequencing, or deep sequencing with a cut-off of 15% (only RAVs that are present in more than 15% of the sequences generated should be considered).</p> <p>For example, in Table 7 of the Summary of Product Characteristics for Epclusa (3), it shows that in ASTRAL 3, it shows that there were a total of 21 GT3 patients who were non-cirrhotic with a baseline Y93H variant, and of this cohort, 2 non-cirrhotic Y93H patients relapsed, which gave an overall SVR12 of 90.5% (19/21). As further shown in Table S4 in the ASTRAL-3's supplementary appendix (2), one of these relapsed patients was detected at a 2.8% detection threshold (i.e. below the clinically relevant 15% detection threshold). However, it is unclear in Gilead's presentation of their data, as to how many of these 21 patients were detected at a <15% threshold. It is clear that in this instance, that the inclusion of subjects with clinically irrelevant resistance levels could inflate the overall SVR12 rate</p> <p>However, it is unclear in Gilead's presentation of their data, as to how many of these 21 patients were detected at a <15% threshold. It is clear that in this instance, that the inclusion of subjects with clinically irrelevant resistance levels could inflate the overall SVR12 rate</p> <p>The reason why this is important is that the SVR12 response rate at a 15% cut off could theoretically be 0% in GT3 cirrhotic patients with a baseline Y93H RAV. For example, in Table S4 of the Supplementary Appendix, it reports that 4 cirrhotic Y93H patients were detected at the 1% threshold, of whom 2 of these patients relapsed and were subsequently shown to have RAVs detected at the >15% threshold. However, no data were presented to show the threshold detection rate for the remaining 2 cirrhotic Y93H patients who did achieve SVR12. So, if the remaining 2 successfully cured cirrhotic Y93H patients were actually below the 15% detection threshold (and therefore would not have been detected at a 15% detection threshold), the resultant SVR12 rate of cirrhotic Y93H patients would actually be 0% (0/2).</p> <p>AbbVie would, therefore, question the clinical validity of use of the 1% detection threshold in the model from the ASTRAL-3 trial which is different to the recommendations of the EASL Guidelines, and would like to request that results using 15% cut off are used.</p>	Thank you for your comments. Please see section 4.6 of the FAD for a summary of the committee's discussion and conclusion on this matter.
AbbVie	3. AbbVie agree with the ERG concern regarding methods used to estimate SVR for the comparators in the model, specifically the fact that single source was used for each treatment in each sub-group. Please refer to section 4.9 of ACD for further details. AbbVie would like to urge committee to request scenario	Thank you for your comments. The committee concluded that results based on the company's estimates

Commentator	Comment [sic]	Response
	analysis using mean estimates calculated from all available sources, i.e. from observational and non-randomised studies.	of sustained virological response were acceptable for its decision-making. Please see section 4.10 and 4.11 of the FAD.
AbbVie	4. On related note, AbbVie would like to note that estimates of utilities used to populate the model were not taken from the trials. Instead, the published values were used (Wright et al. 2006). Please refer to section 4.12 of ACD for further details. AbbVie appreciates the explanation given, however, in our opinion this practice represents inconsistency use of data sources and we would like to see further exploratory analysis using trial utility values.	Thank you for your comments. The committee emphasised that where available, it prefers utility values collected from the clinical trials of the intervention under evaluation to those estimated from other sources, but it was prepared to accept utility values from the literature. Please see section 4.14 of the FAD.
AbbVie	<p>References:</p> <ol style="list-style-type: none"> 1. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. Foster GR, Afdhal N, Roberts SK, et al. 2015, N Engl J Med. 2. Supplementary Appendix to Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3. Foster GR, Afdhal N, Roberts SK, et al. 2015, N Engl J Med. 3. Epclusa, Summary of Product of Characteristics, www.medicines.org [accessed October 2016] 4. EASL Recommendations on Treatment of Hepatitis C. J Hepatol, 2016. 5. Hepatitis C Virus Resistance to Direct-Acting Antiviral Drugs in Interferon-Free Regimens. Pawlotsky J-MP, 2016. Gastroenterology 151:70–86 	Noted.

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Comments received from clinical experts and patient experts

No comments were received from clinical experts and patient experts

Comments received from members of the public

No comments were received from members of the public

14th October 2016

Dear Meindert

**Appraisal Consultation Document: Sofosbuvir-velpatasvir for treating chronic hepatitis C;
comments from Gilead Sciences Ltd**

Thank you for the opportunity to comment on the ACD as above. Gilead welcomes the draft recommendation from NICE that Epclusa is a clinically- and cost-effective option for the treatment of the majority of HCV patient populations in England and Wales.

We look forward to the next appraisal committee discussion regarding this topic.

Yours sincerely

A black rectangular redaction box covering the signature of the sender.

Gilead Sciences Ltd

THE HEPATITIS C TRUST'S RESPONSE TO THE NICE ACD ON SOFOSBUVIR AND VELPATASVIR FOR THE TREATMENT OF CHRONIC HEPATITIS C

10.10.2016

We will confine our comments to a single point.

We do not believe that the provisional recommendations are sound or a reasonable basis for guidance to the NHS, for a critical reason: they are unclear.

Specifically, clause 1.2 states:

'It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.'

This same sentence formed part of TAs 363, 364 and 365. At a meeting on May 18, 2016 between The Hepatitis C Trust and NICE, in the presence of solicitors, NICE said that this clause was inserted only in response to the concern of clinicians that they might be overwhelmed by demand and was to give them comfort that they could prioritise patients according to clinical need in that circumstance and that circumstance only. NICE was clear that the clause was only concerned with system capacity and that it was wholly unconnected to the cost or the affordability of the drugs.

NHS England, however, chose to interpret the clause to mean it could cap the number of people being treated at an arbitrary 10,011 on the grounds that it wished only to spend a certain amount of money on the drugs. Furthermore in the High Court on September 21, 2016 Mr Justice Blake said in a judgement, referring to this clause: 'the plain words of the policy are inconsistent with a treatment as of right approach.'

It is, therefore, clear that this clause is being used to mean something other than NICE, by its own admission, intended. We feel that, now that NICE is aware of this issue, it is absolutely essential that NICE clarifies the meaning of clause 1.2.

If NICE wishes to limit access of Sofosbuvir-Velpatasvir to however many NHS England decides it will treat, then it should be clear. Equally, if NICE wishes this drug to be available to everyone for whom it is clinically appropriate – since it is cost-effective – then this should be stated in language that is unambiguous and not open to misinterpretation.

PATRONS

Ms Sadie Frost
Boy George
Mr Robbie Williams
Mr Tim Westwood

Miss Emilia Fox
The Marchioness of Bute
Mr Alan McGee

The Lord Mancroft
Mr Andrew Loog Oldham
Ms Justine Roddick

TRUSTEES

Sir Adrian Baillie
Mr David Enthoven
Ms Magdalena Harris
Prof Noreena Hertz

Peter Holt
Mr Edward Mead
Dr Iain Murray-Lyon

The Hon Mary Parkinson
Mr Charles Walsh
Prof Graham Foster

This is extremely important because the way that NHS England has chosen to interpret Clause 1.2 broadly speaking means that people with advanced liver disease get treatment, while those with mild disease have to wait for an indeterminate amount of time. In terms of preventing mortality this assumes that people made to wait will be available next year or the year after or whenever treatment becomes available. Unfortunately, many of the most disadvantaged people with hepatitis C are only infrequently in touch with services, for example those with mental health or substance use issues. If we fail to treat and cure them now when we have them in front of us, we risk that they will not be in services again until they have conditions such as liver cancer for which anti-viral treatment is too late. Furthermore the system of CQUINs NHS England has put in place to support its 'run rate' approach removes money from Operational Delivery Networks if they are not able to follow up patients 48-60 weeks after the end of treatment, further disincentivising the treatment of those less likely to remain in contact with services.

We are completely aware of NHS England's need to balance its books. We simply do not want people with hepatitis C, an already disadvantaged group, to be singled out for what amounts to rationing, while people with other conditions get full access to NICE-approved drugs. The current position is that NICE-approved drugs have to be fully funded by the NHS. That may well change in the future under the proposals put forward today by NICE and NHSE. However, this TA must be considered under the existing arrangement.

The question we would ask the committee to consider is whether NICE would recommend rationing of cost-effective drugs or by being vague in its recommendation permit NHS England to ration cost-effective drugs if the drugs were to cure young women with breast cancer, or indeed whether NHS England would seize on an apparently unclear clause to undertake such rationing. Surely fairness and equity must underlie all that NICE does.

We consider the principle here to be so important that we ask NICE in the strongest possible terms to publish this response in full.

PATRONS

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Mr David Enthoven
Ms Magdalena Harris
Prof Noreena Hertz

Peter Holt
Mr Edward Mead
Dr Iain Murray-Lyon

The Hon Mary Parkinson
Mr Charles Walsh
Prof Graham Foster

11 October 2016

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): Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921] – Appraisal consultation document

Thank you for asking us to comment on the TA document Sofosbuvir-Velpatasvir for the treatment of chronic HCV.

We would like to congratulate the Appraisal Committee for their timely and thorough review of this recently licensed DAA regimen and are in complete agreement with the draft recommendations.

We sincerely hope that NHS England will adopt this technology as soon as feasible, as it will add to the currently available therapies, and with the recently approved Grazoprevir-Elbasvir will increase competition in the market with reducing prices. We hope that this will enable more patients than the current cap of 10,000 patients per year to clear HCV.

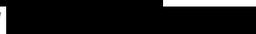
We particularly welcome the option of Sofosbuvir-Velpatasvir as the only interferon-free option for the treatment of chronic genotype 3 HCV in patients with milder forms of liver disease, and for patients with genotype 5 and 6 infections.

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


; *BHIVA Hepatitis
Society Subcommittee*

BASHH 

Dear Kate,

Please see below the BSG's response to the ACD on sofosbuvir and velapatasvir for treating hepatitis C. I would be grateful if you could acknowledge receipt of [REDACTED] statement.

Dear Sir/Madam

I have reviewed the NICE appraisal and find the comments fair and balanced. The major issue of the data concerning cost effectiveness is the rate of reinfection in HCV patients, which as stated in the report is at best debatable and probably too high at 2.4% for the UK population based on clinical experience.

In answer to specific questions:

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

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

· Are the recommendations sound and a suitable basis for guidance to the NHS? :YES

· 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?: No

Best wishes

[REDACTED]

On Behalf of BSG liver section

[REDACTED]
British Society of Gastroenterology
3 St Andrews Place
Regent's Park
London NW1 4LB

<http://www.bsg.org.uk>

BVHG and BASL would like to congratulate the committee on their robust, extensive and comprehensive review of Sofosbuvir/Velpatasvir, and support all the main conclusions reached and the recommendations proposed.

We have some minor comments only on the September 2016 Appraisal Consultation Document.

- In section 4.8 we would like to congratulate the committee on considering the potential impacts upon onward transmission to others. It is important that such appraisals analyse either the impacts of both re-infections and transmission, or analyse neither (as in this case). Including the impact of one, but not the other, would result in an unbalanced assessment.
- In section 4.9 there is the comment that 'the company should have included other study types such as uncontrolled and non-randomised studies'. We are not aware that any such extra data exists for the company to provide.

Company response to the Appraisal consultation document for Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID921]

AbbVie welcomes the opportunity to be invited to comment on Appraisal Consultation Document for Sofosbuvir-velpatasvir for treating chronic hepatitis C.

AbbVie would like to make the following comments to be considered by the committee.

1. **SVR₁₂ estimates in patients with genotype 3 with resistance-associated variants (RAVs).** This population was involved in ASTRAL-3 trial and demonstrated overall SVR₁₂ at 95%. However, when split by sub-groups, a range of different outcomes are observed (see Table 1 below).

1	SVR ₁₂ Non-cirrhotic, Treatment-naïve	160/163	98%
2	SVR ₁₂ Non-cirrhotic, Treatment-experienced	31/34	91%
3	SVR ₁₂ Cirrhotic, treatment-naïve	40/43	93%
4	SVR ₁₂ Cirrhotic, treatment-experienced	33/37	89%

Table 1: SVR₁₂ in GT3 patients from ASTRAL-3 (1) (2) (3)

However, when specifically considering patients with Y93H variants, the rates of SVR₁₂ are as follows:

1	Non-cirrhotic, no Y93H	171/173	98.8%
2	Non-cirrhotic, + Y93H	19/21	90.5%
3	Cirrhotic, no Y93H	71/76	93.4%
4	Cirrhotic, + Y93H	2/4	50.0%

Table 2: SVR₁₂ in GT3 Y93H patients (1) (2) (3)

Considering the population enrolled into ASTRAL-3 (1) (2) (3), it was demonstrated that of the GT3 non-cirrhotics (194 patients), 11% had the Y93H variant (²¹/₁₉₄).

Also, it was demonstrated that of the GT3 cirrhotic population (80 patients), 5% had the Y93H variant (⁴/₈₀).

Therefore, the prevalence of Y93H in GT3 patients, as presented in the ASTRAL-3 paper, is in the region of 9.1% (²⁵/₂₇₄).

In the data presented for ASTRAL-3, of those who have the Y93H variant (total 25 patients), only 21 (i.e. 19 + 2) of these patients achieve an SVR₁₂, resulting in a pooled SVR₁₂ rate of 84.0% (²¹/₂₅).

AbbVie would therefore question validity of the current cost-effectiveness recommendation for this subset of patients with GT3 + the Y93H variant - irrespective of cirrhosis status - and would like further to seek additional clarification analysis on this matter. In addition, the said population in question could be presenting a failure treatment rate of ~16.0%, which may result in subsequent harder-to-treat patients with possible development of additional RAVs.

2. Resistance testing in ASTRAL-3 study.

Further discussing the presentation of ASTRAL-3 study results, AbbVie would like to note that the deep sequencing for resistance-testing was conducted with a cut-off at 1%. However, a 15% cut-off better predicts treatment failure due to the selection of resistant viruses (5). Indeed, as documented in the most recent European Association for the Study of the Liver (EASL) Guidelines 2016 (4), it is clearly recommended that HCV resistance testing should be based on population sequencing, or deep sequencing with a cut-off of 15% (only RAVs that are present in more than 15% of the sequences generated should be considered).

For example, in Table 7 of the Summary of Product Characteristics for Eplclusa (3), it shows that in ASTRAL 3, it shows that there were a total of 21 GT3 patients who were non-cirrhotic with a baseline Y93H variant, and of this cohort, 2 non-cirrhotic Y93H patients relapsed, which gave an overall SVR₁₂ of 90.5% (¹⁹/₂₁). As further shown in Table S4 in the ASTRAL-3's supplementary appendix (2), one of these relapsed patients was detected at a 2.8% detection threshold (i.e. below the clinically relevant 15% detection threshold). However, it is unclear in Gilead's presentation of their data, as to how many of these 21 patients were detected at a <15% threshold. It is clear that in this instance, that the inclusion of subjects with clinically irrelevant resistance levels could inflate the overall SVR₁₂ rate

However, it is unclear in Gilead's presentation of their data, as to how many of these 21 patients were detected at a <15% threshold. It is clear that in this instance, that the inclusion of subjects with clinically irrelevant resistance levels could inflate the overall SVR₁₂ rate

The reason why this is important is that the SVR₁₂ response rate at a 15% cut off could theoretically be 0% in GT3 cirrhotic patients with a baseline Y93H RAV. For example, in Table S4 of the Supplementary Appendix, it reports that 4 cirrhotic Y93H patients were detected at the 1% threshold, of whom 2 of these patients relapsed and were subsequently shown to have RAVs detected at the >15% threshold. However, no data were presented to show the threshold detection rate for the remaining 2 cirrhotic Y93H patients who did achieve SVR₁₂. So, if the remaining 2 successfully cured cirrhotic Y93H patients were actually below the 15% detection threshold (and therefore would not have been detected at a 15% detection threshold), the resultant SVR₁₂ rate of cirrhotic Y93H patients would actually be 0% (0/2).

AbbVie would, therefore, question the clinical validity of use of the 1% detection threshold in the model from the ASTRAL-3 trial which is different to the recommendations of the EASL Guidelines, and would like to request that results using 15% cut off are used.

3. AbbVie agree with the ERG concern regarding methods used to estimate SVR for the comparators in the model, specifically the fact that single source was used for each treatment in each sub-group. Please refer to section 4.9 of ACD for further details. AbbVie would like to urge committee to request scenario analysis using mean estimates calculated from all available sources, i.e. from observational and non-randomised studies.
4. On related note, AbbVie would like to note that estimates of utilities used to populate the model were not taken from the trials. Instead, the published values were used (Wright et al. 2006). Please refer to section 4.12 of ACD for further details. AbbVie appreciates the

explanation given, however, in our opinion this practice represents inconsistency use of data sources and we would like to see further exploratory analysis using trial utility values.

References:

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3. *Epclusa, Summary of Product of Characteristics*, www.medicines.org [accessed October 2016]
4. *EASL Recommendations on Treatment of Hepatitis C*. J Hepatol, 2016.
5. *Hepatitis C Virus Resistance to Direct-Acting Antiviral Drugs in Interferon-Free Regimens*. **Pawlotsky J-MP, 2016**. *Gastroenterology* 151:70–86