# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single Technology Appraisal

## Ledipasvir–sofosbuvir 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 |
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| Gilead Sciences | Gilead welcomes the provisional NICE guidance for Harvoni and we are pleased that Harvoni is recommended as a treatment option for patients where Harvoni is cost-effective:<br>• GT1 treatment naïve without cirrhosis (8 weeks)<br>• GT1 and GT4 treatment experienced without cirrhosis (12 weeks)<br>• GT1 and GT4 treatment naïve with cirrhosis (12 weeks)<br>• GT1 and GT4 treatment experienced with cirrhosis (12 weeks) who meet the following criteria:<br>  ○ Child–Pugh class A<br>  ○ Platelet count of 75,000/$mm^3$ or more<br>  ○ No features of portal hypertension<br>  ○ No history of an HCV-associated decompensation episode<br>  ○ Not previously treated with an NS5A inhibitor<br><br>We set out below certain points that Gilead wishes to raise following the provisional NICE guidance: | Comments noted. |

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| | **1.** The inclusion of GT1 and 4 patients who are treatment experienced with cirrhosis is very positive, and will ensure that this group of patients with a significant unmet need has a much needed cost-effective treatment option. Feedback from clinical stakeholders has been that the treatment of patients consistent with the criteria set out at paragraph 1.1 of ACD2 and reproduced above will be readily implemented through the MDT process.<br><br>We are disappointed that GT3 interferon ineligible patients and GT4 treatment naïve non-cirrhotic patients are not eligible under this guidance for treatment with ledipasvir-sofosbuvir. While patients who are GT3 and interferon eligible have access to a highly efficacious treatment of SOF+PEG+RBV, those who cannot tolerate interferon currently have no treatment options if they have do not have cirrhosis.<br><br>**2.** NICE has included a new statement in the second ACD for ledipasvir-sofosbuvir on the implementation of its mandate for this medicine (the same statement is replicated in the ACDs for the two other medicines that were also included in the Affordability consultation with NHS England). This states that:<br><br>*"1.2 It is recommended that access to the drugs used to treat hepatitis C is managed though 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."*<br><br>Gilead considers that, as currently drafted, there is a real risk that paragraph 1.2 will | The Committee noted that the marketing authorisation for ledipasvir–sofosbuvir does not recommend the 8 week treatment duration for the genotype 4 HCV population, and therefore it could not make a recommendation for this treatment duration in people with genotype 4 HCV. The Committee highlighted its conclusions for 12 weeks of ledipasvir–sofosbuvir in people with previously untreated genotype 1 HCV without cirrhosis, and concluded that 12 weeks of ledipasvir–sofosbuvir in people with previously untreated genotype 4 HCV without cirrhosis could not be considered a cost-effective use of NHS resources. Please see section 4.18 of the FAD.<br><br>NICE has recommended sofosbuvir for specific people with genotype 3 HCV who are intolerant to or ineligible for interferon (see NICE technology appraisal guidance 330). The Committee concluded that 24 weeks of ledipasvir–sofosbuvir plus ribavirin treatment could not be considered a cost-effective use of NHS resources in people with genotype 3 HCV. Please see sections 4.23-4.28 of the FAD.<br><br>Section 1.2 of the FAD has been updated to: |

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| | result in confusion, should it be replicated in its current form in the TAG. This concern also reflects feedback we have received from clinicians and patient groups alike. In particular we are concerned that, despite the legal status of the NICE mandate - as reflected in the provisions of paragraph 5.3 of ACD2 - paragraph 1.2 will be misconstrued as purporting to remove or dilute its effect. By way of example, the suggestion that NHS England may determine access to treatments through its "specialised commissioning programme" appears to conflict with NICE's detailed recommendations at paragraph 1.1 and the description of the implications of the mandate at paragraph 5.3.<br><br>Gilead's understanding is that paragraph 1.2, properly interpreted, means that the delivery of the Hepatitis C services should be managed through the Operational Delivery Networks ("ODNs") already established by NHS England, and that treatment decisions should be determined by an MDT. Assuming this is the correct interpretation, the statement should be clarified to specifically refer to such ODNs to avoid uncertainty and the risk that "specialised commissioning programme" (not commonly used terminology) may be misinterpreted as requiring NHS England to introduce additional policies and procedures in order to give effect to the NICE recommendation.<br><br>In addition, we note that MDTs have multiple responsibilities to manage their patient cohort to best address local needs. We would therefore suggest that the inclusion of "*unmet clinical need*" is potentially overly restrictive as clinicians take into account a range of factors when considering whether a patient should be prioritised for treatment. We would therefore suggest that "clinical" be omitted from this paragraph. | "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."<br><br>For clarity on the term 'clinical need', please see section 4.31 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 |

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| | Our recommendation for the wording of this paragraph is (changes highlighted in bold):<br>*"It is recommended that access to the drugs used to treat hepatitis C is managed through the **Operational Delivery Networks** 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."*<br><br>Alternatively, if NICE does not agree that paragraph 1.2 should be clarified as we have suggested above, Gilead requests that NICE include a clarification statement that paragraph 1.2 does not impact on paragraph 5.3 which refers to the NICE mandate. | 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 this in mind, people with chronic hepatitis C may accept treatment being prioritised for those with highest unmet clinical need (including some people without cirrhosis), potentially determined by multidisciplinary teams". |
| | **3.** In section 4.3, we are pleased that NICE recognised that the budget impact estimates provided by NHS England were "significantly overestimated" and "not robust". The budget impact figures presented by NHS England were inflated primarily due to their assumption around patient number coming forward for treatment. We are in agreement with the consensus of the other stakeholders involved in the affordability consultation, who stated that the most likely estimate of patient numbers treated per year is 7,000-10,000. With the experience of the ODN networks since the 1st August, the estimates of 7000-10,000 may be overly ambitious.<br><br>Gilead also notes NICE's comment at paragraph 4.34 that further work should be initiated "*sooner rather than later*" to consider "*whether there are combinations or* | Comment noted. No action required.<br><br>All technology appraisal guidance recently developed by NICE for chronic hepatitis C will be considered for inclusion in the NICE guideline on |

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| | *sequences of treatment … that could be of particular value to patients*". While we recognise that this is not subject to formal consultation at this stage, we would note that this is a rapidly developing treatment area and would suggest that the resource implications of a review at this stage should be considered in light of potential barriers to delivering a comprehensive consideration of treatment pathways that will provide the greatest benefits to patients with hepatitis C infection.<br><br>We note that there are a number of additional treatments that are expected to become available in the near future; the development of treatment combinations or sequences will clearly need to take account of these, if the resulting recommendations are to be useful. In addition, there may be significant benefit in leaving sufficient time to assess the impact of the tendering process implemented by the NHS to increase competition (as referenced by NICE at paragraph 4.32 of ACD2). If it is intended that the proposed consideration of combinations or sequences of treatment would take into account the cost of treatments, it would be important for stakeholders to understand how that would be achieved in circumstances where the tendering procedures are likely to cause the pricing environment to develop over relatively short periods and also to vary from region to region at any given time. In these circumstances, it may be challenging for NICE to draw conclusions that are comprehensive and are not quickly superseded by events outside the NICE process. | hepatitis C: diagnosis and management of hepatitis C. Please see section 7 of the FAD. |
| British Association for the Study of the Liver | Many thanks for allowing the 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 Ledipasvir/Sofosbuvir. | |

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| | 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.<br><br>We are however unclear on the wording in section 1.2. NHSE does not have specific "specialised commissioning programmes" it prepares 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.<br><br>In reference to the more specific detail related to the Ledipasvir/Sofosbuvir ACD we generally support the conclusions reached by NICE.<br><br>We are especially supportive of the positive assessment of an 8 week regimen length in non-cirrhotic treatment naïve genotype 1 patients.<br><br>We agree with the conclusions on a 12 week course for genotype 1 non-cirrhotic treatment experienced patients.<br><br>For genotype 1 and 4 cirrhotic treatment-experienced patients we are unclear as to the solidity of the evidence-based behind the thresholds for acceptance (particularly the platelet count and the presence of portal hypertension) and would have welcomed the more general statement given for the cirrhotic naïve patients (with the | Comments noted. Section 1.2 of the FAD has been updated to:<br>"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."<br><br>The Committee considered that there was a need to define 'low risk of clinical disease progression and subsequent retreatment options' that could be used to identify people with previously treated genotype 1 or 4 HCV with cirrhosis eligible for 12 weeks' treatment with ledipasvir–sofosbuvir in clinical practice. The Committee understood from the clinical experts at the third Appraisal Committee |

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| | exception of insisting on no prior NS5a exposure).<br><br>Having made these comments however we feel that the current guidance is a fair reflection of the data and would welcome early completion of this assessment process and therefore access to these important medications for our patients.<br><br>Many thanks for allowing us to comment on this ACD and we would like to congratulate NICE on balanced and thorough processes and conclusions. | meeting that all of the company's criteria were routinely assessed in clinical practice in England (for example, Child–Pugh score, platelet count, features of portal hypertension). Please see section 4.7 of the FAD. |
| British HIV Association & British Association for Sexual Health and HIV | Many thanks for asking us to comment on the ACD for the STA for Ledipasvir-sofosbuvir for treating chronic HCV (ID742).<br><br>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.<br><br>We have no further comments on this ACD at this stage. | Comments noted. No action required. |
| British Society of Gastroenterology | In relation to the above ACD 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:<br>"It is recommended that in England the decision to treat and the prescribing | Comments noted. Section 1.2 of the FAD has been updated to:<br>"It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary |

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| | decisions are made by the multidisciplinary teams in the operational delivery networks now established by NHS England. This should be in partnership with and supported by NHS England" | teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.” |
| Department of Health | No comments. | Comments noted. No action required. |
| Haemophilia Society | 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.<br><br>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 | Comments noted. Section 1.2 of the FAD has been updated to:<br>“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.”<br><br>The Committee agreed that its recommendations were fair and did not constitute an equality issue. Please see section 4.37 of the FAD. |

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| | would significantly outweigh the cost of Hepatitis C treatment if bleeding were to occur due to delayed treatment.<br><br>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. | |
| Hepatitis C Trust | The Hepatitis C Trust very much welcomes the fact that NICE is proposing to treat this as a technology appraisal on Ledipasvir-Sofosbuvir in the usual way on the basis of cost-effectiveness, 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.<br><br>We do however have some concerns around clause 1.2, which states:<br>"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."<br><br>After requesting clarification, we have received assurances from NICE that 'prioritisation' as referred to in this context should only be necessary where there are constraints caused by capacity, and should not be dictated by NHS England's | Comments noted.<br><br>Section 1.2 of the FAD has been updated to:<br>"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." |

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| | 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.<br><br>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:<br>• The desire not to infect others (e.g. through maternal transmission)<br>• Significant symptoms that may impact on work, relationships, emotional well-being, indeed all aspects of life<br>• Experience of discrimination, such as losing a job as a result of disclosing hepatitis C infection.<br><br>We would ideally like need to be defined as it is in the draft Scottish Sexual Health and Blood-borne Virus Framework 2015-2020, as:<br>• patients with F3/F4 hepatic fibrosis;<br>• and/or patients with severe extra-hepatic manifestations of hepatitis C;<br>• and/or patients with significant psychosocial morbidity as a consequence of hepatitis C. | For clarity on the term 'clinical need', please see section 4.31 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 this in mind, people with chronic hepatitis C may accept treatment being prioritised for those with highest unmet clinical need (including some people without cirrhosis), potentially determined by multidisciplinary teams. |

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| NHS England | **Background**<br><br>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.<br><br>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'.<br><br>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:<br>a) the early access scheme for patients with decompensated cirrhosis;<br>b) the expansion of access for all patients with cirrhosis; and<br>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 | Comments noted. The Committee was aware that the final protocol has not been agreed and STOP-HCV-1 has not started. It considered that the clinical effectiveness evidence available for ledipasvir–sofosbuvir for people with untreated genotype 1 HCV without cirrhosis was more robust than the evidence available for other populations considered in this technology appraisal. The Committee noted that it had recommended only the shortest duration included in the marketing authorisation for this population (8 weeks and not 12 weeks) and that the ICER was considerably 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 ledipasvir–sofosbuvir in people with untreated genotype 1 HCV without cirrhosis. Please see section 4.35 of the FAD. |

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| | patients and a focus on the specific needs of the complex patient groups with hepatitis C.<br><br>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.<br><br>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.<br><br>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.<br><br>**The STOP-HCV-1 trial and implementation of NICE guidance for interferon-free hepatitis C treatment** | |

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| | 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.<br><br>**Rationale for the trial design**<br>• Several new, interferon-free, treatments for hepatitis C look set to be recommended as cost-effective by NICE.<br>• Two new combinations (Abbvie 3D, Harvoni®) treat Genotype 1 infection, the most prevalent in England (and Wales)<br>• The efficacy of these treatments is very high (>90% cure)<br>• The cost of a standard 12 week treatment is very high (currently> £30k)<br>• 12 weeks of treatment is more than most patients with mild disease need to be cured<br>• 12 weeks treatment, although a major improvement on current treatment options, is still a long course<br>• 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<br>• There is strong evidence that both human and viral genetics play a role in the response to treatment<br>• 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 | |

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| | disease<br>• If NICE recommendations are implemented as they stand the opportunity to collect the data required to use the treatments more rationally will be lost<br><br>**An approach through stratified medicine**<br>• 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.<br>• 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<br>• This study as it currently stands will enrol 408 patients with mild (non-fibrotic) genotype 1 infection<br>• 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<br>• 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.<br>• 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 | |

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| | **Potential benefits in supporting the study**<br>• The data gathered will provide vital information for clinicians managing hepatitis C with limited resources allowing more precise selection of treatments for patients<br>• This, in turn, should allow many more patients to be treated within fixed budgets<br>• 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<br>• 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<br>• 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<br><br>**Summary**<br>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.<br><br>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). | |

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| | 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.<br><br>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. | |
| 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.<br><br>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. | Comments noted. 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.<br><br>Due to the confidential nature of the NHSE comments the committee response is | Comments noted. No action required. |

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| | based on my overall senior opinion and discussion themes which we as a group have had since the previous documents were received.<br><br>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.<br><br>Our feedback is brief and includes the following;<br>• 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.<br>• 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. | Section 1.2 of the FAD has been updated:<br>"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." |

## Comments received from commentators

| Commentator | Comment [sic] | Response |
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| Janssen | No comments. | Comments noted. No action required. |
| Merck Sharp & Dohme | No comments. | Comments noted. No action required. |
| Roche Products | No comments. | Comments noted. No action required. |

## Comments received from clinical experts and patient experts

| Nominating organisation | Comment [sic] | Response |
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| Gilead Sciences (clinical expert) | Thank you for asking me to comment on the above document. I welcome and agree with all the recommendations for the use of sofosbuvir / ledipasvir in genotype 1 infection with eight weeks for treatment naive non-cirrhotic patients and twelve weeks for others.<br><br>Getting on and treating patients with hepatitis C with these new highly effective oral drugs is important and having confirmed NICE approval without further delay will be of considerable benefit in achieving this.<br><br>With regard to point 1.2, it remains slightly unclear how the last part of point 1.2 "…with prescribing decisions made by multidisciplinary teams/centres to ensure that treatment is prioritised for patients with the highest unmet clinical need" sits with point 5.3 suggesting that NICE approved treatment should be made available for all those meeting the criteria. However, the | Comments noted.<br><br>Section 1.2 of the FAD has been updated to:<br>"It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in |

| Nominating organisation | Comment [sic] | Response |
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| | recently established Hepatitis C Virus Operational Delivery Networks (HCV ODNs) will be well placed for overseeing treatment decisions, and treatment prioritisation based upon disease severity / clinical need and their networks clinical capacity to treat individuals. | place by NHS England, to prioritise treatment for people with the highest unmet clinical need." |
| Bristol-Myers Squibb (clinical expert) | 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.<br><br>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.<br><br>I note clause 1.2 which is taken to mean that NHS England will engage with | Comments noted.<br><br>The Committee understood from NHS England that a clinical trial, STOP-HCV-1, will assess SVR rates in people with untreated genotype 1 HCV without cirrhosis who have direct-acting antiviral drugs, including ledipasvir–sofosbuvir, for shorter durations than stipulated in the marketing authorisation. Please see section 4.35 of the FAD.<br><br>Section 1.2 of the FAD has been updated to: |

| Nominating organisation | Comment [sic] | Response |
|---|---|---|
| | 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.<br><br>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. | "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." |

## Comments received from members of the public

| Role* | Section | Comment [sic] | Response |
|---|---|---|---|
| Health professional (within NHS) | General | This is an important NICE assessment that I support in its entirety. The committee has provided an independent, evidence-based review of the data on sofosbuvir/ledipasvir and their robust conclusions will allow patients to access this very significant therapeutic advance. I note that NICE has recommended that patients access drugs via the NHSE "network approach" and this system of delivering and monitoring expensive new therapeutics for HCV has already been shown to allow access to treatment without unacceptable budgetary impacts. | Comments noted. No action required. |

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

**Gilead response to ACD2 for ledipasvir-sofosbuvir**

Gilead welcomes the provisional NICE guidance for Harvoni and we are pleased that Harvoni is recommended as a treatment option for patients where Harvoni is cost-effective:

- GT1 treatment naïve without cirrhosis (8 weeks)
- GT1 and GT4 treatment experienced without cirrhosis (12 weeks)
- GT1 and GT4 treatment naïve with cirrhosis (12 weeks)
- GT1 and GT4 treatment experienced with cirrhosis (12 weeks) who meet the following criteria:
    - Child–Pugh class A
    - Platelet count of 75,000/$mm^3$ or more
    - No features of portal hypertension
    - No history of an HCV-associated decompensation episode
    - Not previously treated with an NS5A inhibitor

We set out below certain points that Gilead wishes to raise following the provisional NICE guidance:

**1.** The inclusion of GT1 and 4 patients who are treatment experienced with cirrhosis is very positive, and will ensure that this group of patients with a significant unmet need has a much needed cost-effective treatment option. Feedback from clinical stakeholders has been that the treatment of patients consistent with the criteria set out at paragraph 1.1 of ACD2 and reproduced above will be readily implemented through the MDT process.

We are disappointed that GT3 interferon ineligible patients and GT4 treatment naïve non-cirrhotic patients are not eligible under this guidance for treatment with ledipasvir-sofosbuvir. While patients who are GT3 and interferon eligible have access to a highly efficacious treatment of SOF+PEG+RBV, those who cannot tolerate interferon currently have no treatment options if they have do not have cirrhosis.

**2.** NICE has included a new statement in the second ACD for ledipasvir-sofosbuvir on the implementation of its mandate for this medicine (the same statement is replicated in the ACDs for the two other medicines that were also included in the Affordability consultation with NHS England). This states that:

*"1.2 It is recommended that access to the drugs used to treat hepatitis C is managed though 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."*

Gilead considers that, as currently drafted, there is a real risk that paragraph 1.2 will result in confusion, should it be replicated in its current form in the TAG. This concern also reflects feedback we have received from clinicians and patient groups alike. In particular we are concerned that, despite the legal status of the NICE mandate - as reflected in the provisions of paragraph 5.3 of ACD2 - paragraph 1.2 will be misconstrued as purporting to remove or dilute its effect. By way of example, the

suggestion that NHS England may determine access to treatments through its "specialised commissioning programme" appears to conflict with NICE's detailed recommendations at paragraph 1.1 and the description of the implications of the mandate at paragraph 5.3.

Gilead's understanding is that paragraph 1.2, properly interpreted, means that the delivery of the Hepatitis C services should be managed through the Operational Delivery Networks ("ODNs") already established by NHS England, and that treatment decisions should be determined by an MDT. Assuming this is the correct interpretation, the statement should be clarified to specifically refer to such ODNs to avoid uncertainty and the risk that "specialised commissioning programme" (not commonly used terminology) may be misinterpreted as requiring NHS England to introduce additional policies and procedures in order to give effect to the NICE recommendation.

In addition, we note that MDTs have multiple responsibilities to manage their patient cohort to best address local needs. We would therefore suggest that the inclusion of "*unmet clinical need*" is potentially overly restrictive as clinicians take into account a range of factors when considering whether a patient should be prioritised for treatment. We would therefore suggest that "clinical" be omitted from this paragraph.

Our recommendation for the wording of this paragraph is (changes highlighted in yellow):

*"It is recommended that access to the drugs used to treat hepatitis C is managed through the Operational Delivery Networks 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."*

Alternatively, if NICE does not agree that paragraph 1.2 should be clarified as we have suggested above, Gilead requests that NICE include a clarification statement that paragraph 1.2 does not impact on paragraph 5.3 which refers to the NICE mandate.

**3.** In section 4.3, we are pleased that NICE recognised that the budget impact estimates provided by NHS England were "significantly overestimated" and "not robust". The budget impact figures presented by NHS England were inflated primarily due to their assumption around patient number coming forward for treatment. We are in agreement with the consensus of the other stakeholders involved in the affordability consultation, who stated that the most likely estimate of patient numbers treated per year is 7,000-10,000. With the experience of the ODN networks since the 1st August, the estimates of 7000-10,000 may be overly ambitious.

Gilead also notes NICE's comment at paragraph 4.34 that further work should be initiated "*sooner rather than later*" to consider "*whether there are combinations or sequences of treatment … that could be of particular value to patients*". While we recognise that this is not subject to formal consultation at this stage, we would note that this is a rapidly developing treatment area and would suggest that the resource implications of a review at this stage should be considered in light of potential barriers to delivering a comprehensive consideration of treatment pathways that will provide the greatest benefits to patients with hepatitis C infection.

We note that there are a number of additional treatments that are expected to become available in the near future; the development of treatment combinations or sequences will clearly need to take account of these, if the resulting recommendations are to be useful. In addition, there may be significant benefit in leaving sufficient time to assess the impact of the tendering process implemented by the NHS to increase competition (as referenced by NICE at paragraph 4.32 of ACD2). If it is intended that the proposed consideration of combinations or sequences of treatment would take into account the cost of treatments, it would be important for stakeholders to understand how that would be achieved in circumstances where the tendering procedures are likely to cause the pricing environment to develop over relatively short periods and also to vary from region to region at any given time. In these circumstances, it may be challenging for NICE to draw conclusions that are comprehensive and are not quickly superseded by events outside the NICE process.

**The comments below relate to minor factual inaccuracies reported in the ACD document (numbers corresponding to the relevant paragraph or table):**

**2.3** The prices presented in this paragraph are for the 12 and 24 week regimens. As NICE has only recommended the 8 and 12 week regimens, we suggest that only these prices are included. Suggested wording is:

*"The cost of ledipasvir–sofosbuvir is £12,993.33 per 28-tablet pack (excluding VAT; company's evidence submission). The cost of an 8-week course of treatment is £25,986.66 and a 12-week course is £38,979.99 (both excluding VAT), not including the cost for ribavirin. Costs may vary in different settings because of negotiated procurement discounts."*

**3.16:** Within this paragraph it states:

"*Most adverse reactions were mild to moderate in severity (grade 1 or 2, the range reported across all treatment groups was 90.2% to more than 99%)*."

The percentages reported above are not provided in the company submission for LDV/SOF. Please could the following text be used:

*"Most adverse events were mild to moderate in severity (grade 1 or 2), with 67% to 93% of patients across all treatment groups reporting at least one adverse event."*

**Table 10** To avoid any confusion, please could '*Dominated*' be replaced with '*LDV/SOF dominates*' throughout this table. In addition, the ICER for LDV/SOF versus SOF+PR in previously untreated genotype 1 HCV patients should be £1,349 (current incorrect value in the ACD is £149).

**3.31** Under the bullet point for people who had treatment before and after liver transplant, please could it be specified that this subgroup was not modelled due to a lack of clinical data specifically on the outcomes, costs and quality of life of patients who either a) achieve post-transplant virologic response following pre-transplant treatment or b) who achieve SVR

following treatment post-transplant, due to the fact that these patients have not historically been treated. There are also high levels of uncertainty about the transition probabilities for patients post-transplant with graft re-infection of HCV. The current wording could be interpreted as meaning that there are no clinical data on the efficacy of LDV/SOF in this population where, in fact, the SOLAR-1 trial studied this. In addition, could the bold text for this bullet point be amended to '*People who had treatment before/after liver transplant*'. The current text may suggest that this would be an analysis of patients who receive treatment both before and after a liver transplant rather than one or the other.

Please could the bold text for the third bullet point be amended to '*Analysis of patients according to response to prior treatment (i.e. null response, partial response, relapse)*'. The current wording may be interpreted as meaning that people whose HCV had responded to previous treatment (but who, subsequently, relapsed) were excluded from the analysis, whereas the assumption made was that prior response to IFN treatment is no indicator of response to SOF-based regimens i.e. that all treatment experienced patients can be modelled together.

**3.49** Please specify that the 79%:21% split of treatment durations was used in people with previously untreated genotype 1 HCV **who are non-cirrhotic**.

**4.13** Please amend the following sentence: *'The Committee also highlighted that there was further uncertainty relating to the company's assumption that the transition probabilities were independent of genotype.'*

to the following *'The Committee also highlighted that there was further uncertainty relating to the company's assumption that **these particular** transition probabilities were independent of genotype.'*

This amend is requested since different transition probabilities are applied for the transition from non-cirrhotic disease to compensated cirrhosis in the model, based on a patient's genotype.

| | |
|---|---|
| **Name** | [redacted] |
| **Organisation** | British Association for the Study of the Liver |
| **Role** | NHS Professional |
| **Job title** | BASL [redacted] |
| **Location** | England |
| **Conflict** | n/a |
| **Disclosure** | |
| **Comments** | 702<br>BASL/BVHG response to NICE ACD for Hepatitis C (chronic) - ledipasvir-sofosbuvir [ID742]<br><br>Many thanks for allowing the British Association for the Study of the Liver) and BVHG (British Viral Hepatitis Group â€“ a Special Interest Group within BASL) to respond to the ACD for Ledipasvir/Sofosbuvir.<br><br>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.<br><br>We are however unclear on the wording in section 1.2. NHSE does not have specific â€˜specialised commissioning programmesâ€™ â€“ it prepares and delivers policies, and commissions operational delivery networks, and the term â€˜programmeâ€™ is not one which is clear when used in reference to NHSE. Clarity on what NICE are suggesting would be useful.<br><br>In reference to the more specific detail related to the Ledipasvir/Sofosbuvir ACD we generally support the conclusions reached by NICE.<br><br>We are especially supportive of the positive assessment of an 8 week regimen length in non-cirrhotic treatment naÃ¯ve genotype 1 patients.<br><br>We agree with the conclusions on a 12 week course for genotype 1 non-cirrhotic treatment experienced patients.<br><br>For genotype 1 and 4 cirrhotic treatment-experienced patients we are unclear as to the solidity of the evidence-based behind the thresholds for acceptance (particularly the platelet count and the presence of portal hypertension) and would have welcomed the more general statement given for the cirrhotic naÃ¯ve patients (with the exception of insisting on no prior NS5a exposure).<br><br>Having made these comments however we feel that the current guidance is a fair reflection of the data and would welcome |

| | |
|---|---|
| | early completion of this assessment process and therefore access to these important medications for our patients.<br><br>Many thanks for allowing us to comment on this ACD and we would like to congratulate NICE on balanced and thorough processes and conclusions.<br>_____<br><br>Comments collated by [redacted] BVHG [redacted] and BASL [redacted] |
| **Submission date** | 19/08/2015 |

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

**NICE consultation on Single Technology Appraisal (STA): Ledipasvir-sofosbuvir for treating chronic hepatitis C [ID742]: Appraisal consultation document**

Many thanks for asking us to comment on the ACD for the STA for Ledipasvir-sofosbuvir for treating chronic HCV (ID742).

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*

*BASHH* [redacted]

# The Haemophilia Society response to NICE consultation on Ledipasvir–sofosbuvir for treating chronic hepatitis C

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 Ledipasvir-Sofosbuvir for treating hepatitis C**

The Hepatitis C Trust very much welcomes the fact that NICE is proposing to treat this as a technology appraisal on Ledipasvir-Sofosbuvir in the usual way on the basis of cost-effectiveness, 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 where 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 it is in the draft Scottish Sexual Health and Blood-borne Virus Framework 2015-2020, as:

- 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

**Final Response to Appraisal Consultation Document 'Hepatitis C (chronic) - ledipasvir-sofosbuvir'**

**On behalf of the British Society of Gastroenterology,**

In relation to the above ACD 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. This should be in partnership with and supported by NHS England"

**ACD2 - Consultees & Commentators: (Hepatitis C (chronic) - ledipasvir-sofosbuvir) [ID742]**

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] | [redacted]
**Membership Support and Global Engagement Department| Royal College of Physicians**
**11 St Andrews Place | Regent's Park | London NW1 4LE**

**Direct line** [redacted] | www.rcplondon.ac.uk | facebook | twitter | linkedin

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 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 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**

## 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.

Plymouth Hospitals NHS
NHS Trust

South West Liver Unit
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Consultant Hepatologists
[redacted] MD FRCP
[redacted] PhD MRCP
[redacted], MD MRCP
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[redacted], PhD FRCS
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[redacted], MB ChB MD FRCS

**Hepatology Nurse Specialists**: [redacted] HPB Cancer Nurse Specialist
**Alcohol Liaison Service:** [redacted]

**Prof Cramp/** [redacted] **Sec**: [redacted]
[redacted] **Sec:** [redacted]

**Surgical Secretaries**:
[redacted]

Dictated: 7th August 2015
Date: 19th August 2015

**RE: Ledipasvir/sofosbuvir - Appraisal Consultation Document ID742**

Thank you for asking me to comment on the above document. I welcome and agree with all the recommendations for the use of sofosbuvir / ledipasvir in genotype 1 infection with eight weeks for treatment naive non-cirrhotic patients and twelve weeks for others.

Getting on and treating patients with hepatitis C with these new highly effective oral drugs is important and having confirmed NICE approval without further delay will be of considerable benefit in achieving this.

With regard to point 1.2, it remains slightly unclear how the last part of point 1.2 "…with prescribing decisions made by multidisciplinary teams/centres to ensure that treatment is prioritised for patients with the highest unmet clinical need" sits with point 5.3 suggesting that NICE approved treatment should be made available for all those meeting the criteria. However, the recently established Hepatitis C Virus Operational Delivery Networks (HCV ODNs) will be well placed for overseeing treatment decisions, and treatment prioritisation based upon disease severity / clinical need and their networks clinical capacity to treat individuals.

Yours sincerely

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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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| | |
|---|---|
| **Name** | [redacted] |
| **Organisation** | |
| **Role** | NHS Professional |
| **Job title** | [redacted] |
| **Location** | England |
| **Conflict** | No |
| **Disclosure** | I have received consultancy and speaker fees from Gilead |
| **Comments** | 701<br>This is an important NICE assessment that I support in its entirety. The committee has provided an independent, evidence-based review of the data on sofosbuvir/ledipasvir and their robust conclusions will allow patients to access this very significant therapeutic advance. I note that NICE has recommended that patients access drugs via the NHSE â€˜network approachâ€™ and this system of delivering and monitoring expensive new therapeutics for HCV has already been shown to allow access to treatment without unacceptable budgetary impacts. |
| **Submission date** | 19/08/2015 |