**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Glecaprevir-pibrentasvir for treating chronic hepatitis C**

**Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)**

**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.

**Comment 1: the draft remit**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Appropriateness | AbbVie | Yes, it is absolutely appropriate to refer this topic to NICE, as glecaprevir-pibrentasvir addresses a range of high unmet needs in the NHS in England and Wales. It is therefore imperative that NICE appraises the clinical and cost-effectiveness evidence of glecaprevir-pibrentasvir. | Comment noted. No action required. |
| | CMO Directorate, Scottish Government. | Yes | Comment noted. No action required. |
| | Janssen Cilag | It is appropriate for NICE to this appraise this technology. | Comment noted. No action required. |
| | BASL AND BVHG | This would be an appropriate and important topic for consideration by NICE | Comment noted. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| | BSG | yes | Comment noted. No action required. |
| | Gilead | Gilead supports referral of this topic to NICE for appraisal under the STA process. | Comment noted. No action required. |
| | MSD | No comment. | No action required. |
| Wording | AbbVie | Yes | Comment noted. No action required. |
| | CMO Directorate, Scottish Government | Yes | Comment noted. No action required. |
| | Janssen Cilag | The wording of the remit is appropriate and reflects the issues of clinical and cost effectiveness of glecaprevir-pibrentasvir for treating chronic hepatitis C. | Comment noted. No action required. |
| | BASL AND BVHG | Yes | Comment noted. No action required. |
| | BSG | yes | Comment noted. No action required. |
| | Gilead | The wording appears to be appropriate. | Comment noted. No action required. |
| | MSD | No comment. | No action required. |

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| Timing Issues | AbbVie | There is clear urgency for this appraisal to start and be completed within the shortest of possible timelines by NICE, in consideration of the high unmet need existing in the NHS in England, which glecaprevir-pibrentasvir addresses. This is underpinned by the EMA's acceptance of glecaprevir-pibrentasvir for Accelerated Assessment (see also Comment 2, under "Innovation"). | Comment noted. No action required. |
| | CMO Directorate, Scottish Government | No comment | No action required. |
| | Janssen Cilag | No comments | No action required. |
| | BASL AND BVHG | There are alternative treatments for HCV available. However, this regimen provides the first interferon free option for patients with G3 on dialysis (see later). This had led to the granting of accelerated approval by both the FDA and EMEA. As such we believe that NICE should consider this appraisal in a more expedient way than normal. | Comment noted. No action required. |
| | BSG | Urgent need:<br>(i) Cost effective treatment for HCV G3 patients<br>(ii) Cost effective 8 week treatment regimes to improve compliance<br>(iii) Pangenotypic therapy for patients with chronic kidney disease (eGFR , 30ml/mim) – only regimes currently available are for HCV G1 & 4<br>(iv) Ribavirin free treatment regimes to minimise side effects of treatment | Comment noted. No action required. |

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| | Gilead | Chronic Hepatitis C is a curable disease and a number of highly efficacious treatments have become available in recent years. Following the publication of NICE TAs for direct-acting antiviral treatments, including most recently TA430 (sofosbuvir/velpatasvir), the vast majority of people with CHC in England and Wales now have access to highly efficacious, all-oral, interferon- and ribavirin-free treatment regimens with excellent tolerability and safety profiles.<br>There remain some unmet clinical needs in selected patient subgroups. | Comment noted. No action required. |
| | MSD | No comment. | No action required. |

**Comment 2: the draft scope**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Background information | AbbVie | Re: 'small percentage of people with chronic hepatitis and cirrhosis also develop hepatocellular carcinoma':<br><br>The percentage of patients with developing HCC once they have cirrhosis is relatively high, with an annual incidence of 1-7% per year.<br><br>(Reference: Goossens and Hoshida. Hepatitis C virus-induced hepatocellular carcinoma Clin Mol Hepatol. 2015 Jun; 21(2)G: 105–114).<br><br>Re: 'Recent estimates (2012) suggest that around 160,000 people have been diagnosed with chronic hepatitis C in England': | Comment noted. The background section has been amended to reflect that the estimated prevalence of HCV is 160,000 people. |

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| | | While it is estimated that 160,000 people in England are chronically infected with HCV, only a minority are diagnosed.<br><br>(Reference: Hepatitis C in the UK 2015 report. Public Health England) | |
| | CMO Directorate, Scottish Government | Appears accurate and complete | Comment noted. No action required. |
| | Janssen Cilag | No Comments | No action required. |
| | BASL AND BVHG | It is accurate and complete, except that the NICE guidance on Sofosbuvir-Velpatasvir has now been published and should be included in the list | Comment noted. NICE guidance on sofosbuvir–velpatasvir has now been added to the list. |
| | BSG | Accurate | Comment noted. No action required. |
| | Gilead | No comment. | No action required. |
| | MSD | No comment. | No action required. |
| The technology/ intervention | AbbVie | Yes | Comment noted. No action required. |

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| | CMO Directorate, Scottish Government | Yes | Comment noted. No action required. |
| | Janssen Cilag | No Comments | No action required. |
| | BASL AND BVHG | It is accurate | Comment noted. No action required. |
| | BSG | Yes | Comment noted. No action required. |
| | Gilead | No comment. | No action required. |
| | MSD | No comment. | No action required. |
| Population | AbbVie | Yes, the population is defined in an appropriate way. | Comment noted. No action required. |
| | CMO Directorate, Scottish Government | The population appears to be defined appropriately | Comment noted. No action required. |
| | Janssen Cilag | Yes, the population is consistent with previous NICE appraisals in the disease area. | Comment noted. No action required. |
| | BASL AND BVHG | The population is well defined and accurate. If data allows considering further subsets – especially those with decompensated liver disease and those with impaired renal function would be appropriate | Comment noted.<br>A subgroup for people with and without renal |

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| | | | impairment has been added to the scope.<br>A subgroup for people with and without cirrhosis is included in the scope. |
| | BSG | Groups & subgroups accurate | Comment noted. No action required. |
| | Gilead | The population is comprehensive and appears appropriate. | Comment noted. No action required. |
| | MSD | MSD would seek clarity on whether a distinction should be made between individuals previously treated with a DAA-based regimen versus those who have previously received interferon-based treatment for chronic hepatitis C. | Comment noted. The subgroup section has been amended to include 'previous treatment received (with or without direct-acting antiviral-containing regimens)' |
| Comparators | AbbVie | Daclatasvir in combination with peginterferon alfa and ribavirin is not accepted standard of practice for patients with genotype 4 in the NHS in England and should not be considered as a comparator to glecaprevir-pibrentasvir<br>Daclatasvir in combination with sofosbuvir, with or without ribavirin, is not standard of care in England for patients with genotypes 1 and 4 but just for genotype 3. | Comment noted. The comparators in the scope have been amended to reflect that peginterferon alfa and ribavirin in combination with daclatasvir or simeprevir are not used to treat genotype 1 and |

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| | | With the more widespread use of DAAs, peginterferon alfa with ribavirin is not a relevant comparator for GT1 and GT4<br>Simeprevir in combination with peginterferon alfa and ribavirin should not be included among the comparators as it does not represent standard of care for patients with genotype 4 in the NHS in England.<br>Sofosbuvir in combination with ribavirin, with or without peginterferon alfa should only be considered as SOC for patients with genotype 2, 3, 5 and 6 | 4 HCV because there are several interferon-free regimens available for this population. The remaining comparators were considered to appropriately reflect current clinical practice in the NHS. |
| | CMO Directorate, Scottish Government | Cannot comment on whether these are standard treatments in NHS England or not | No action required. |
| | Janssen Cilag | All appropriate comparators have been included. | Comment noted. No action required. |
| | BASL AND BVHG | The treatment current utilised on the NHS are genotype specific and therefore there is no single 'best alternative care'.<br>Of the list of comparators some are no longer utilised or relevant to the NHS – specifically daclatasvir in combination with peginterferon and ribavirin; and simeprevir in combination with peginterferon alfa and ribavirin (for genotype 4). It would also now be rare to utilise peginterferon alfa with ribavirin except in genotype 2 non-cirrhotic patients and 'best supportive care (watchful waiting)' has been largely superseded by the newer medications. | Comment noted. The comparators in the scope have been amended to reflect that peginterferon alfa and ribavirin in combination with daclatasvir or simeprevir are not used to treat genotype 1 and 4 HCV because there are several interferon-free regimens available for this population. The |

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| | | | remaining comparators were considered to appropriately reflect current clinical practice in the NHS. |
| | BSG | Cost effectiveness comparison of 8 week treatment of non HCV G1 regimes should specifically be made. | Comment noted. Cost-effectiveness analyses will be considered from the perspective of the current standard of care in the NHS. No action required. |
| | Gilead | As stated in response to the NICE draft scope consultation for proposed appraisal 1055, given that all-oral, interferon-free regimens are now recommended for the treatment of the vast majority of patients with CHC on the basis of previous NICE appraisals, the majority of interferon-containing regimens are now obsolete and irrelevant to usual NHS practice. | Comment noted. The comparators in the scope have been amended to reflect that peginterferon alfa and ribavirin in combination with daclatasvir or simeprevir are not used to treat genotype 1 and 4 HCV because there are several interferon-free regimens available for this population. The remaining comparators were considered to appropriately reflect |

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| | | | current clinical practice in the NHS. |
| | MSD | Further clarity is needed to define best supportive care (BSC) (watchful waiting). MSD recommend the wording “no active drug treatment”. | Comment noted. The wording has been amended to ‘Best supportive care (no active pharmacological treatment)’ |
| Outcomes | AbbVie | AbbVie agrees that the outcome measures proposed capture the most important health related benefits of the technology | Comment noted. No action required. |
| | CMO Directorate, Scottish Government | Yes | Comment noted. No action required. |
| | Janssen Cilag | All appropriate outcomes have been included. | Comment noted. No action required. |
| | BASL AND BVHG | These are correct but we would add that the sustained virological response currently utilised is at 12 weeks post-therapy (SVR12) and this should be the primary SVR outcome (not SVR24) | Comment noted. The most appropriate outcome for decision-making may be considered by the committee during the course of the appraisal. No action required. |

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| | BSG | Yes | Comment noted. No action required. |
| | Gilead | The outcomes are appropriate. | Comment noted. No action required. |
| | MSD | As a point of accuracy, MSD would suggest using the wording “treatment-emergent resistant substitutions to glecaprevir-pibrentasvir”. This reflects that patients do not develop resistance, but rather resistant isolates are selected for. | Comment noted. In line with previous scopes for chronic hepatitis C, the outcome ‘development of resistance to treatment’ has not been changed in the scope. |
| Economic analysis | AbbVie | AbbVie agrees with the proposed approach to economic analysis, including time horizon. | Comment noted. No action required. |
| | CMO Directorate, Scottish Government | Appropriate time horizon should be in keeping with previous NICE Technology Appraisals for similar products | Comment noted. No action required. |
| | Janssen Cilag | No comments | No action required. |
| | BASL AND BVHG | We are pleased to see acknowledgement of, and congratulate NICE on planning to consider, the ‘Personal Social Services’ costs – however would advise that the data is not currently easily obtainable to determine this | Comment noted. No action required. |
| | BSG | Correct | Comment noted. No action required. |

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| | Gilead | Described elements of the economic analysis appear appropriate. Gilead agrees that the time horizon should be such as to capture the full differences in costs and outcomes between the technologies being compared, and given the long-term consequences of HCV infection, a lifetime analysis is likely to be required. | Comment noted. No action required. |
| | MSD | No comment. | No action required. |
| Equality and Diversity | AbbVie | AbbVie does not think that the proposed remit or scope need to be changed in order to address specific equality issues. | Comment noted. No action required. |
| | CMO Directorate, Scottish Government | No changes suggested | No action required. |
| | Janssen Cilag | No comments | No action required. |
| | BASL AND BVHG | No specific issues expected<br>The different genotypes affect different racial groups disproportionately, however the availability of the other medications for hepatitis C and the plan to review this technology according to its marketing authorisation mean that we do not foresee any particular equality issues | Comment noted. The committee will consider this comment, together with others on potential equality issues, during the course of the appraisal. No action required. |
| | BSG | No issues regarding equality | Comment noted. No action required. |
| | Gilead | No comments. | No action required. |

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| | MSD | No comment. | No action required. |
| Innovation | AbbVie | Glecaprevir/pibrentasvir is an innovative treatment for chronic hepatitis C, in that:<br><br>1) It addresses a particular unmet need for interferon-free treatment for:<br>- Genotype 1-6 infected patients who have failed prior treatment with an NS5A<br>- Patients with genotype 2,3,5 or 6 with chronic kidney disease (stage 4/5)<br>- GT3 infected patients with compensated cirrhosis<br><br>2) It meets the need to reduce mortality due to liver disease in people under 75 years of age, as identified by the NHS Outcomes Framework<br><br>3) It generates a range of benefits not captured by QALYs, such as a reduction in onward transmission of the HCV virus, thanks to the high SVRs achieved across all genotypes<br><br>Reference: The NHS Outcomes Framework 2015/16, NHS Group, Department of Health FN-NHSG-NHSCPS. | Comment noted. AbbVie is encouraged to describe the innovative nature of glecaprevir-pibrentasvir in its submission to NICE. No action required. |
| | CMO Directorate, Scottish Government | Unable to comment on this aspect | No action required. |

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| | Janssen Cilag | No comments | No action required. |
| | BASL AND BVHG | Because of the fact that the regimen is purely metabolised by the liver this regimen can be used in patients on dialysis. There are currently very few options for patients with genotype 3 HCV on dialysis and this regimen provides potentially the only treatment option for this currently disadvantaged group.<br>There are other potential advantages in terms of broad pan-genotypic cover (and therefore simplification), drug interactions and the potential to treat individuals who harbour resistant hepatitis C virus and/or who have failed previous directly-acting antiviral regimens.<br>In these regards this technology could be an improvement/step-change in our ability to treat patients within the NHS. | Comment noted. A subgroup for people with and without renal impairment has been added to the scope. |
| | BSG | Yes for following reasons:<br>(i) Effective RBV free sustained viral response rate (SVR >99%) 8 week treatment for **HCV non cirrhotic genotype 1** (Endurance 1)<br>(ii) Effective ribavirin free (RBV) 12 treatment option for **all non cirrhotic, non HCV G3 genotypes** with SVR of > 99% (Endurance phase III studies 1, 2 & 4)<br>(iii) Effective RBV free sustained viral response rate (SVR 97%) 8 week treatment for **HCV non cirrhotic genotype 2, 4,5,6 (**Phase II data only Surveyor II part 4, thus further data needed)<br>(iv) Effective RBV free treatment (SVR > 99%) for **all non cirrhotic, non HCV G3 genotypes previously failed treatment with interferon containing regimes** (Endurance studies 1, 2 & 4).<br>(v) Effective RBV free treatment of **non cirrhotic, cirrhotic and non protease treatment experienced patients HCV G3 with** SVR | Comment noted. BSG is encouraged to describe the innovative nature of glecaprevir-pibrentasvir in its submission to NICE. No action required. |

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| | | 91-98% after 12-16 weeks treatment. (Phase II data only Surveyor II part 3, thus further data needed)<br>(vi) Effective RBV free treatment of **non cirrhotic , cirrhotic and non protease treatment experienced patients pan genotypic HCV with chronic kidney disease (eGFR < 30 ml/min) with** SVR 98% after 12 weeks treatment (Phase III Expedition study)<br>**Caveats on data** –<br>(i) Endurance studies have relatively small numbers of HIV co-infected patients only in G1 patients<br>(ii) No data on treatment experienced patients with protease inhibitors as yet<br>(iii) Some data Phase II studies | |
| | Gilead | Following the publication of NICE TAs for direct-acting antiviral regimens, including most recently TA 430 (sofosbuvir/velpatasvir), the vast majority of people with CHC in England and Wales now have access to highly efficacious, all-oral, interferon- and ribavirin-free treatment regimens with excellent tolerability and safety profiles.<br>There remain some unmet clinical needs in selected patient subgroups. | Comment noted. No action required. |
| | MSD | No comment. | No action required. |
| Other considerations | CMO Directorate, Scottish Government | Nil suggested | No action required. |
| | Janssen Cilag | No comments | No action required. |

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| | BASL AND BVHG | We welcome the plan to analyse, if evidence allows, the impacts on those who have failed the older therapies or the newer sofosbuvir/all-oral regimens separately as this correlates with clinical considerations and utility<br>Equally we very much welcome the proposal of NICE to assess the impact on reduced onward HCV transmission, as this is a very important potential factor largely missing from previous appraisals | Comment noted. No action required. |
| | Gilead | Reflecting comments made to the draft NICE scope consultation for proposed appraisal 1055, Gilead is supportive of appraising the cost-effectiveness of glecaprevir-pibrentasvir after treatment with older therapies (mainly, peginterferon alfa with ribavirin with or without telaprevir, boceprevir or simeprevir) and separately, after treatment with newer therapies (sofosbuvir in combination with peginterferon alfa and ribavirin, or all-oral regimens). | Comment noted. No action required. |
| | MSD | No comment. | No action required. |
| Questions for consultation | Janssen Cilag | Best supportive care (watchful waiting) is an appropriate comparator, however, all patients should receive treatment as soon as possible to reduce the risk of transmission and loss to follow up. This will be dependent on the price, but we anticipate that glecaprevir-pibrentasvir may be positioned in treatment naïve patients (first line) as available clinical evidence suggest similar of better outcomes with 8 weeks of treatment. | Comment noted. The wording has been amended to 'Best supportive care (no active pharmacological treatment)' |
| | BSG | 1] Is this the best current treatment option for HCV patients with advanced chronic kidney disease?<br>2] Is this the most cost effective 8 week HCV treatment regime for non cirrhotic HCV G1 (& possibly HCV G2, 4, 5 & 6)?<br>3] Is this the most cost effective treatment for all HCV G3 patients? | Comment noted. These questions may be considered during the course of the appraisal. No action required. |
| | MSD | **Are the subgroups suggested in 'other considerations' appropriate?** | Comment noted. |

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| | | MSD would welcome clarity on whether the following subgroups should also be considered:<br>• people with renal impairment<br>• people who received a prior DAA<br><br>MSD would also suggest differentiating between prior DAA treatment and prior interferon-based treatment, as per our comments above. | A subgroup for people with and without renal impairment has been added to the scope.<br><br>The subgroup section has been amended to include 'previous treatment received (with or without direct-acting antiviral-containing regimens)' |
| Additional comments on the draft scope | Gilead | NICE TA 430 (sofosbuvir-velpatasvir) should be included in the bullet point list on page 2 of the draft scope for glecaprevir-pibrentasvir. | Comment noted. NICE guidance on sofosbuvir–velpatasvir has now been added to the list. |

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**

Department of Health