NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C

Response to consultee and commentator comments on the 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
Appropriateness	AbbVie Ltd	AbbVie agrees that it is appropriate for NICE to refer this topic for appraisal	Comment noted
	British Society Of Gastroenterology: liver section	Yes	Comment noted
	Gilead Sciences	Hepatitis C Virus (HCV) remains an area of high unmet need, with an estimated 160,000 people currently infected in England. Whilst HCV is a curable disease and a number of highly efficacious treatments have become available in the past year, it remains the case that only a small proportion of diagnosed patients are treated each year. The clinical morbidity burden of chronic Hepatitis C (CHC) is growing rapidly as patients infected with HCV in the 1980s and 1990s begin to develop serious complications. Public Health England have estimated that, whilst in the year 2000 there were 4,310 people with HCV related cirrhosis, by 2010 this number had more than doubled to 9,670, and if left untreated this number is projected to reach 15,840 by 2020. These data demonstrate that there is a growing public health need and burden to the NHS from HCV.	Comment noted. If this topic is referred to NICE, it will be scheduled into the technology appraisals programme with consideration of the need for timely guidance.

		Sofosbuvir–GS-9857–velpatasvir (now designated and referred to throughout this draft scope consultation response as sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX)) is a pan-genotypic treatment (defined as high therapeutic efficacy in each of genotypes 1 through 6). This treatment represents an important advance on previous treatments in that it offers the realistic prospect of HCV cure to the small number of patients who do not achieve SVR after initial treatment with a regimen containing a direct-acting antiviral treatment ("DAA"). This small population of 'DAA-experienced' patients has a significant unmet clinical need for a highly efficacious and pan-genotypic treatment given that there are no alternative treatment options recommended by NICE for these patients. It should be noted that the EMA has adopted an accelerated regulatory process for SOF/VEL/VOX, a designation only granted to those medicines of major public health interest. Gilead fully supports timely referral to, and review of, SOF/VEL/VOX by NICE. Given the urgency of treating HCV in order to reduce the risk of long-term complications, Gilead wishes to ensure that the timing of NICE guidance aligns as closely as possible with the anticipated regulatory review timelines for SOF/VEL/VOX. We therefore strongly support an STA submission as close to anticipated CHMP decision as possible during 2017 in order to support this alignment.	
Wording	AbbVie Ltd	AbbVie has the following comments with respect to the background section in the draft scope: With respect to the statement: "A small percentage of people with chronic hepatitis and cirrhosis also develop hepatocellular carcinoma . Liver transplantation may be needed for people with decompensated cirrhosis or hepatocellular carcinoma", AbbVie wishes to point out that this percentage is actually tot so small in cirrhotic patients, as stated in the paper by Goossens et al, 2015: "' the risk of HCC, in chronic HCV infection, is associated with fibrosis stage. In cirrhotic subjects, the	Comment noted. The scope has been updated accordingly.

		annual incidence of HCC is extremely high (1-7% per year), although HCC rarely develops in livers with less fibrosis'. With respect to the statement: "The true prevalence of HCV infection is difficult to establish and likely to be underestimated because many people do not have symptoms and more than half of people with chronic hepatitis C are unaware of their infection.3 There are 6 major genotypes and several subtypes of HCV; the prevalence of each varies geographically. Recent estimates (2012) suggest that around 160,000 people have been diagnosed with chronic hepatitis C in England, and that approximately 90% of these people are infected with genotype 1 or 3.4", AbbVie wishes to point out that these patients have not necessarily been diagnosed but are chronically infected.	
	British Society Of Gastroenterology: liver section	Yes	Comment noted
	Gilead Sciences	Wording is appropriate.	Comment noted
Timing Issues	British Society Of Gastroenterology: liver section	Urgent: Pan genotypic direct acting antiviral (DAA) therapy regimes for HCV needed for treatment experienced HCV patients with previous treatment failure. Particular need is for those treatment experience (TE) patients exposed to NS5A & NS3/4A protease inhibitor containing treatment regimes. Although treatment failure with DAA is rare, the need remains.	Comment noted. If this topic is referred to NICE, it will be scheduled into the technology appraisals programme with consideration of the need for timely guidance.
	Gilead Sciences	SOF/VEL/VOX is a medicine that fulfils a significant unmet clinical need. In particular, SOF/VEL/VOX offers high and pan-genotypic efficacy for patients who do not achieve HCV cure after initial treatment with a DAA-containing regimen. For these 'DAA-experienced' patients (also referred to as a 'salvage' setting) there are no alternative treatment options recommended by NICE. The recent NHS Outcomes Framework has set a priority to reduce mortality due to liver disease in the under-75s. HCV is a significant driver for liver-related deaths (at least 296 in 2011) and a key driver for	Comment noted. If this topic is referred to NICE, it will be scheduled into the technology appraisals programme with consideration of the need for timely guidance.

		morbidity, with HCV-related cirrhosis and hepatocellular carcinoma (HCC) being life-threatening end stages of HCV disease. A substantial proportion of liver transplants performed in the UK are required as a result of advanced HCV infection. Data from recent clinical trials have shown high efficacy of SOF/VEL/VOX in all HCV genotypes, with a side-effect profile similar to placebo. All of this means that there is an urgent need for patient access to SOF/VEL/VOX, re-iterating the need for timely NICE review and guidance. Gilead wishes to ensure that the timing of NICE guidance aligns with the anticipated accelerated regulatory review timelines for SOF/VEL/VOX. We therefore strongly support an STA submission as close to CHMP as possible to facilitate this alignment.	
Additional comments on the draft remit	British HIV Association on behalf of the BHIVA/BASHH Consultation Group on Hepatitis Topics	Any additional comments on the draft remit Many thanks for asking us to review the Scoping Document for the TA for Sofosbuvir-voxilaprevir-velpatasvir (sof-vox-vel). We have a few specific comments that might influence the remit and the scope for the proposed TA. a) The committee will be well aware that the dual combination sof-vel TA and guidance for use (ID921) will be available soon b) Whilst we still await the formal EMA approval and indications for use for this triple DAA combination, the committee should be mindful that 8 weeks of sof-vox-vel did not meet it's primary non-inferiority endpoint versus 12 weeks of sof-vel in DAA-naive non-cirrhotic and cirrhotic patients with genotype 1-6 HCV infection c) Patients failing first-line DAA therapies (with or without pegIFN and ribavirin) are beginning to emerge, and data from the registration trial of sof-vox-vel (with sof-vel or placebo as a comparator) suggest efficacy in these populations. We would, therefore, suggest that the remit and the scope of this TA to reflect	Thank you for your comments. The appraisal committee will appraise this treatment within its marketing authorisation based on the evidence presented to it. The remit is kept broad to avoid excluding potential populations that could be covered by the anticipated marketing authorisation. However subgroups according to the type of previous treatment has been included in the 'other considerations' section of the scope.

		a) Emerging groups of patients with failure after DAA-based treatment, both with and without pegIFN/Ribavirin containing regimens and the need to re-treat this group of patients b) Groups with de-compensated liver cirrhosis where current NICE approved treatments are either contra-indicated (PegIFN, SImeprevir, Paritaprevir/ritonavir/ombitasvir containing regimens) or sub-optimal (all others, especially genotype 3 decompensated cirrhotics) b) a small minority of patients where shortening the duration of therapy to 8 weeks may be of benefit (only sof-ledipasvir approved for 8 weeks currently) - such group of patients may include Prison populations, patients with chaotic lifestyles who may be difficult to engage in care (current intravenous drug users for example)	Subgroups according to cirrhosis status is specified in the scope and is assumed to include people with decompensated cirrhosis if covered by the marketing authorisation. The committee will take into account any evidence presented on short treatment duration during the appraisal. No changes required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AbbVie Ltd	No comments on this section	Comment noted
	British Society Of Gastroenterology: liver section	Accurate	Comment noted
	Gilead Sciences	Background information is generally accurate and complete. However, it should be noted that there is no clinical evidence to suggest that a 'watchful waiting' strategy is effective in the current context of CHC management. This is especially true at the present time, when all-oral, interferon-free treatments with short treatment durations and excellent tolerability profiles have been recommended for use in the NHS for all patients with CHC. CHC is a progressive disease, and the best opportunity for cure with any patient is to treat as early as possible, as increased fibrosis/cirrhosis correlates to poorer treatment outcomes. It should also be noted that if patients are engaged in clinical care but not treated, there remains the potential risk for onward transmission of HCV. This is	Comment noted. This statement has now been removed from the background section.

		likely to contribute to future healthcare resource costs and work against efforts to reduce and ultimately eliminate the burden of disease represented by CHC. Taking these points into account, a 'watchful waiting' strategy is inappropriate and should not be included within the background as a reasonable option for patients with mild disease.	
The technology/ intervention	AbbVie Ltd	No comments on this section	Comment noted
	British Society Of Gastroenterology: liver section	Yes	Comment noted
	Gilead Sciences	The description of the technology is accurate. As noted above, the INN for GS-9857 has been assigned as voxilaprevir (VOX).	Comment noted. The scope has been amended accordingly.
	MSD UK	MSD understands that the compound GS-9857 is now known as voxilaprevir.	Comment noted. The scope has been amended accordingly.
Population	AbbVie Ltd	No comments on this section	Comment noted
	British Society Of Gastroenterology: liver section	Groups & subgroups accurate	Comment noted
	Gilead Sciences	The population is comprehensive and appears appropriate at this stage. However, it should again be noted that SOF/VEL/VOX is expected particularly to fulfil an unmet clinical need for the treatment of patients who do not achieve SVR after initial treatment with a DAA-containing regimen. This is referred to as a 'salvage' treatment setting. There are currently no alternative treatment options recommended by NICE for these 'DAA-experienced' patients. This subgroup of patients should be considered separately within the 'treatment-experienced' group. Gilead therefore suggests the following revision to the wording of the population in order to make this subgroup clear:	Comment noted. Subgroups according to the type of previous treatment has been included in the 'other considerations' section of the scope.

		Adults with chronic hepatitis C: □ who have not had treatment for chronic hepatitis C before (treatment-naive) □ who have had treatment for chronic hepatitis C before (treatment-experienced): • Previously treated with peginterferon alfa with ribavirin with or without telaprevir, boceprevir or simeprevir • Previously treated with all-oral DAA regimens or with sofosbuvir in combination with peginterferon alfa and ribavirin	
	MSD UK	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. MSD would also seek clarity on the inclusion of treatment-naïve individuals in this scope in light of the recently-presented POLARIS-2 study, which failed to meet its primary endpoint in a study population predominantly comprising treatment-naïve patients.	Comment noted. Subgroups according to the type of previous treatment has been included in the 'other considerations' section of the scope. The population section is kept broad to include all possible populations that could be covered by the anticipated marketing authorisation. However, the technology will only be appraised in line with the marketing authorisation.
Comparators	AbbVie Ltd	No comments on this section	Comment noted.
	British Society Of Gastroenterology: liver section	Comparators should include Sofosbuvir & velpatasvir treatment with ribavirin (not studied directly in Polaris studies) Also cost effectiveness comparison of 8 week treatment regimes should be made stratified by genotype & cirrhosis stage	Comment noted. Sofosburvir-velpatasvir is included as a comparator. The actual duration of each treatment will be presented as part of the evidence base if this topic is referred for appraisal. No action required.

	Gilead Sciences	The comparators listed in the draft scope are comprehensive, given that the list comprises all treatment regimens historically offered to people with CHC in the NHS setting. However, given that all-oral, interferon-free regimens are now recommended for the treatment of all patients with CHC on the basis of previous NICE appraisals, it should be recognised that the majority of interferon-containing regimens are now obsolete and irrelevant to usual NHS practice. The removal of interferon-containing regimens from clinical practice is recommended by the "EASL (European Association for the Study of the Liver) Recommendations on Treatment of Hepatitis C 2016", which state: "In 2016 and onwards, IFN-free regimens are the best options in treatment-naïve and treatment-experienced, DAA-naïve patients with compensated and decompensated liver disease, because of their virological efficacy, ease of use and tolerability." Given that the vast majority of patients now have access to all-oral interferon-free treatments with superior efficacy, safety and tolerability profile, the following treatments are no longer routinely offered for the treatment of patients with CHC in NHS practice: • Combination therapy with ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b for people with chronic hepatitis C regardless of disease severity, genotype or treatment experience. • Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended for people who are unable to tolerate ribavirin or for whom ribavirin is contraindicated • Telaprevir in combination with peginterferon alfa and ribavirin for people with genotype 1 chronic hepatitis C. • Boceprevir in combination with peginterferon alfa and ribavirin for people with genotype 1 chronic hepatitis C. • Simeprevir in combination with peginterferon alfa and ribavirin as an option for people with genotype 1 or 4 chronic hepatitis C	Telaprevir and boceprevir have not been included as comparators. Daclatasvir and simeprevir (both in combination with peginterferon alfa plus ribavirin) have been removed as comparators given the comments from the clinical experts in TA430 that they are not used to treat genotype 4 HCV because there are several interferon-free regimens available for this population. Simeprevir has also been excluded as a comparator in genotype 1 for the same reason. Although the use of peginterferon alfa plus ribavirin is reducing for some HCV genotypes in clinical practice, the clinical experts in TA430 stated that its use has not completely stopped. Therefore no change has been made to this comparator in the scope.

		• Daclatasvir in combination with peginterferon alfa and ribavirin, as an option for specific people with genotype 4 chronic hepatitis C With these points in mind, and with the wish to simplify STAs as far as is reasonable, Gilead suggests that all of the aforementioned comparators are not relevant to this appraisal and should be removed. While the remaining all-oral, interferon-free treatments included in the draft scope represent appropriate comparators at this stage, it should again be noted that SOF/VEL/VOX is expected particularly to fulfil an unmet clinical need for the treatment of those patients who do not achieve HCV cure after initial treatment with a DAA-containing regimen, and for whom there are no alternative treatment options recommended by NICE (also known as a 'salvage' treatment setting). It should be noted that none of the comparators listed in the draft scope are recommended by NICE for use in the 'salvage' setting i.e. for the treatment of patients who have failed to achieve SVR following treatment with a DAA-containing regimen.	
	MSD UK	Further clarity is needed to define best supportive care (BSC) (watchful waiting); MSD recommend the wording: "no active pharmacological treatment".	Comment noted. Scope updated accordingly.
Outcomes	Gilead Sciences	The outcomes are appropriate.	Comment noted.
Economic analysis	AbbVie Ltd	No comments on this section	Comment noted.
	British Society Of Gastroenterology: liver section	Correct	Comment noted.
	Gilead Sciences	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.
	AbbVie Ltd	No comments on this section	Comment noted.

Equality and Diversity	British Society Of Gastroenterology: liver section	No issues regarding equality	Comment noted.
	Gilead Sciences	In addressing the appraisal, NICE should be aware that CHC adversely affects certain populations who could be considered at risk of being disadvantaged in terms of accessing the healthcare system and therefore at risk of inequity of access to innovative new treatments. For example: - Certain immigrant populations - Prison inmate population - Intravenous drug users	Comment noted. The appraisal committee have previously discussed these issues in previous hepatitis C appraisals, for example TA430, and concluded that its recommendations were fair regarding these groups of people.
Innovation	AbbVie Ltd	No comments on this section	Comment noted.
	British Society Of Gastroenterology: liver section	Yes for following reasons: (i) Thus far most effective ribavirin free (RBV) treatment option for HCV G3 cirrhotic & those treatment experienced to previous DAA therapy (ii) Approximately 15% improvement overall in SVR rate over current NICE approved treatment Sofosbuvir (SOF) , interferon (IFN) and RBV or second line treatment of SOF & daclatasvir (DCV) (iii) Most efficacious 8 week treatment option for HCV G3 with or without cirrhosis (iv) Efficacious pangenotypic therapy 8 week regime with slight reduction in SVR rate for HCV g1a and those with cirrhosis (SVR still > 90%) (v) Moderately improved SVR rate for G3 treatment experienced cirrhotic patients compared SOF & velpatasvir (VEL) with no ribavirin, although more modest improvement when compared to SOF/VEL/RBV (vi) May be most cost effective 8 week treatment for pangenotypic HCV non-cirrhotic and cirrhotic patients	Comment noted. The innovative aspects of this technology will be considered by the appraisal committee based on evidence presented to it, if this topic is referred for appraisal. Therefore consultees are encouraged to include their views on the innovative aspects of this treatment in their evidence submissions and expert statements.

		(vii)Apparent high barrier to viral resistance compared to other HCV DAA treatment regimes (viii) Possible option to avoid need to genotype or stage pre HCV treatment in treatment naïve patients with associated total cost reduction	
	Gilead Sciences	SOF/VEL/VOX fulfils a number of criteria identified by the Kennedy Report as constituting innovation: - SOF/VEL/VOX meets a need which the NHS has identified as being important, as evidenced by the recent NHS Outcomes Framework that reflects the government commitment to reducing mortality due to liver disease in people under 75 - SOF/VEL/VOX has a robust and extensive evidence base, and has demonstrated an appropriate level of effectiveness in clinical trials (greater than 90% efficacy in all patient groups treated) - SOF/VEL/VOX will have a marketing authorisation for the indication under review As HCV is an infectious disease with the potential for cure, by improving cure rates together with increasing numbers of patients eligible for treatment, there is the potential to positively impact on the overall epidemiology and long-term burden of CHC to the NHS. In particular and as stated previously, there remains a significant unmet clinical need for highly efficacious treatments for patients who have not achieved cure after initial treatment with a DAA-containing regimen, for whom there are no alternative treatment options recommended by NICE. SOF/VEL/VOX is expected particularly to address this unmet clinical need. This re-iterates the urgent need for timely patient access to SOF/VEL/VOX and timely NICE review and guidance. Gilead wishes to ensure that the timing of NICE guidance aligns with the anticipated accelerated regulatory review timelines for SOF/VEL/VOX. We therefore strongly support an STA submission close to anticipated CHMP opinion in 2017 to support this alignment.	Comment noted. The innovative aspects of this technology will be considered by the appraisal committee based on evidence presented to it, if this topic is referred for appraisal. Therefore consultees are encouraged to include their views on the innovative aspects of this treatment in their evidence submissions and expert statements.

Other considerations	AbbVie Ltd	No comments on this section	Comment noted.
	Gilead Sciences	In line with the suggested amendment to the wording of the 'treatment-experienced' population in this appraisal, Gilead suggests that the cost-effectiveness of SOF/VEL/VOX 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) should be considered. In addition, Gilead is mindful of comments and suggestions made in the context of previous NICE Single Technology Appraisals in CHC, which identified a potential area for improvement in economic modelling in CHC by incorporation of dynamic re-infection and transmission effects. With this in mind, Gilead is assessing how to leverage and incorporate current research in this area within the proposed STA for SOF/VEL/VOX, as far as is feasible and appropriate.	Comment noted. Subgroups according to the type of previous treatment has been included in this section.
Questions for consultation	British Society Of Gastroenterology: liver section	1] Is this the best current option for re DAA treatment failure pangenotypic HCV? 2] Is this the most cost effective 8 week HCV treatment regime? 3] Is this the most cost effective treatment for HCV G3 cirrhotic patients?	Comment noted. The appraisal committee will consider the cost-effectiveness of this treatment based on the evidence presented.
	Gilead Sciences	Data from the Phase III POLARIS clinical trial programme has been presented at the AASLD annual conference (November 2016, with anticipated peer reviewed publication within Q1 2017). These data are expected to form the principal clinical evidence base supporting the clinical efficacy and safety of SOF/VEL/VOX within its proposed marketing authorisation and within the proposed remit outlined by NICE for this appraisal.	Comment noted.
	MSD UK	Are the subgroups suggested in 'other considerations appropriate? MSD would welcome clarity on whether the following subgroups should also be considered: people with advanced liver disease	Comment noted. Subgroups according to the type of previous treatment has been included in this section.

		people who received a prior DAA people with haemoglobinopathies (for example, sickle cell disease, thalassaemia major) MSD would also suggest differentiating between prior DAA treatment and prior interferon-based treatment, as per our comments above.	Subgroups according to advanced liver disease and haemoglobinopathies have been included in previous scopes but have not been a key consideration in those appraisals. However, the company is welcomed to present evidence for any other subgroups not included in the scope. No further action taken.

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

British Infection Association