Gilead response to NICE questions 8th April 2015

NICE Question 1.

The clinical guideline that was published in March/April 2015 referred to by Gilead Sciences during the Appraisal Committee meeting. Would it be possible to send this clinical guideline to NICE, as well as, the associated links to where the publication is shared and referenced online? The Committee heard from Gilead Sciences and the clinical experts that this guideline made a number of recommendations relating to the use/duration of ledipasvir-sofosbuvir treatment for specific populations.

Gilead Response

The enclosed draft set of clinical recommendations was discussed at a Consensus Meeting on Therapy for Chronic Hepatitis C held in London on 3rd March, also attended by two members of NICE (Elizabeth George and Richard Diaz). This meeting was attended by physicians representing the major treatment centres and professional bodies (BASL, Liver Network, BVHG etc).The draft document is out for consultation and is published on the BASL (British Association for the Study of Liver Diseases) website:

http://www.basl.org.uk/news/136/Consensus-Meeting-Report-Therapy-for-Chronic-Hepatitis-C---03-March-2015/index.cfm

The discussion around treated duration for ledipasvir/sofosbuvir (LDV/SOF) focused solely on the 8 and 12 week duration, as is evident from the recommendations. Based on experience with the NHS England expanded access programme as well as additional data presented at AASLD, the addition of RBV to the 12 week regimen was also discussed as an option for certain patients on the understanding that this would be based on discussion at the Multidisciplinary Team (MDT) meeting to determine the appropriate treatment regimen.

NICE Question 2.

For people with treatment-experienced genotype 1 or 4 HCV with cirrhosis, please can Gilead Sciences confirm how this population can be identified and operationalised in clinical practice (in line with the marketing authorisation)?

Gilead Response

NHS England have stated that individual treatment decisions for patients with HCV will be decided in England through the MDT process. The delay of the implementation for the Sovaldi NICE TAG was put in place to allow NHS England adequate opportunity to commission clinical networks with MDTs to ensure specialist expertise was available to make these decisions. We believe that via the MDT process clinical judgement will determine if LDV/SOF for 12 weeks is an appropriate treatment option for a treatment experienced patient with cirrhosis.

To aid clinical decision making for LDV/SOF, Gilead Sciences sought advice from clinical experts in the UK, Germany, France, Spain and Italy as to how best to further define those patients that should be considered to be "at low risk of clinical disease progression" and having "subsequent retreatment options" in line with the LDV/SOF marketing authorisation. The consensus opinion of these European clinical experts is that treatment experienced patients with cirrhosis should be considered for 12 weeks therapy with LDV/SOF if they meet the following criteria:

- Child-Pugh A
- Platelets ≥75,000/mm^3
- No features of portal hypertension (e.g. absence of oesophageal varices)
- No previous history of a HCV-associated decompensation episode
- Not previously treated with an NS5A inhibitor

To provide background to these criteria, the following information is provided:

a) Low risk of clinical disease progression

Child–Pugh A is a commonly used method of identifying cirrhotic patients at lower risk of imminent disease progression, as described by Dr. Charles Millson, one of the clinical experts at the second LDV/SOF appraisal meeting. In addition, the consensus amongst European HCV clinical experts is that GT1 or GT4 patients meeting all the following criteria are at low risk of clinical disease progression and would be appropriate for the 12 week duration:

- Child-Pugh A
- Platelets ≥75,000/mm^3
- No features of portal hypertension (e.g. absence of oesophageal varices)
- No previous history of a HCV-associated decompensation episode

All of these criteria are routinely assessed as part of normal clinical practice for patients with cirrhosis and platelet count in particular is often seen as a clinical marker of 'how cirrhotic' a patient can be considered to be. Therefore these metrics provide hard, clinically appropriate decision measures that can be easily operationalised.

b) Subsequent retreatment options

The European clinical experts indicated that the subset of treatment experienced cirrhotic patients that should not be considered for 12 weeks LDV/SOF are those that have previously been treated with an NS5A inhibitor. This would include those previously treated with LDV, daclatasvir (DCV) or ombitasvir (OBV).

There are four classes of direct acting anti-viral (DAA) drugs in development and in use in the treatment of Hep C: NS3A, NS5A, non-nucleotide NS5B and nucleotide NS5B inhibitors. It has been established that NS5A inhibitors (LDV, DCV, OBV), NS3A inhibitors (boceprevir, BOC; telaprevir, TVR; simeprevir, SMV; paritaprevir, PTV), and non-nucleotide NS5B inhibitors (dasabuvir, DBV) can select resistant variants that remain present for some period after the completion of therapy if the patient does not achieve SVR. By contrast nucleotide NS5B inhibitors have a high genetic barrier to resistance – at present SOF is the only licensed drug in this class. Resistance to SOF has been very rarely observed even in patients not achieving SVR and patients have been quickly and successfully retreated with a SOF based regimen.

Data were presented in 2014 at the EASL (April 2014, London, U.K.) and AASLD (November 2014, Boston, U.S.A.) conferences providing evidence for the re-treatment of patients previously exposed to SOF or a PI with SOF-based regimens such as SOF+SMV. These data are available should NICE wish to review them. Table 1 demonstrates the subsequent retreatment options for treatment experienced patients who do not achieve an SVR with LDV/SOF, based upon their previous treatment regimen.

Table 1: Illustration of subsequent retreatment options following treatment with LDV/SOF in a treatment experienced population

Previous Treatment Regimen	LDV/SOF treatment duration	Subsequent retreatment Options
Pegylated-interferon + ribavirin (PR)	LDV/SOF 12 weeks	SOF + SMV SOF + PR SMV + PR
PI (BOC, TVR or SMV) + PR	LDV/SOF 12 weeks	SOF + PR SOF + SMV
SOF + PR	LDV/SOF 12 weeks	SOF + SMV SMV + PR
NS5A (DCV or LDV) + SOF	LDV/SOF 24 weeks	SOF + SMV SOF + PR
Abbvie 3D (PTV/OBV/DBV) + RBV	LDV/SOF 24 weeks	SOF + SMV SOF + PR

NICE Question 3.

a) Please confirm the marketing position of Gilead Sciences relating to 12 weeks' treatment in people with treatment-experienced genotype 1 or 4 HCV with cirrhosis?
b) Are Gilead Sciences intending to promote the use of the 12 week regimen in *all* people with treatment-experienced genotype 1 or 4 HCV with cirrhosis?
c) The NICE technical team note that the clinical-effectiveness and cost-effectiveness evidence submitted by the company for this regimen includes all people with treatment-experienced genotype 1 or 4 HCV with cirrhosis – data in a population corresponding to marketing authorisation has not been provided (that is, those deemed 'at low risk for clinical disease progression and for whom have subsequent retreatment options').

3 a+b) Gilead has a legal obligation to promote in line with the marketing authorisation. The marketing authorisation written by the EMA has been deliberately non-specific to leave duration of treatment choice for patients with cirrhosis down to the prescribing clinician. However, in order to support consistent decision making and effective implementation of NICE guidance, Gilead will communicate the feedback from clinical experts on the criteria to help clinicians interpret the label as described above.

In addition Gilead will focus activities on supporting clinicians to prescribe those regimens made available for those patients where NICE or NHS England have made a recommendation.

3 c) Gilead has conducted analyses comparing SVR12 rates observed with the 12 and 24 week duration of LDV/SOF stratified by low risk of clinical disease progression. These data show that in treatment experienced patients with cirrhosis and platelets ≥75,000 mm^3, a 12 week duration results in similar efficacy to 24 weeks duration. This data is available on request. Patients with prior history of HCV-related decompensation episodes, or who were previously treated with an NS5A inhibitor, were excluded from the LDV/SOF ION Phase III trials; information on patients with features of portal hypertension (in the absence of a historic or current decompensation event) in the trials was not collected.

The ICERs for 12 weeks LDV/SOF in treatment experienced patients with cirrhosis that were considered by the Appraisal Committee at the 2nd meeting were £5,435 and £6,432, based on Cardoso et al. and Fattovich et al. respectively. This is a conservative analysis for the subgroup of these patients who are at low risk of clinical disease progression and have subsequent retreatment options. The reason for this is that the SVR rate for the overall treatment experienced cirrhotic population is lower compared to the SVR for the population meeting the criteria defined above. Furthermore, these ICERs used transitions based on both Cardoso et al. and Fattovich et al., which assess the impact of a slower transition from compensated cirrhosis to decompensated cirrhosis (i.e. for patients defined at lower risk of clinical disease progression). Given the similarity in the resulting ICERs for the treatment experienced population with cirrhosis, the cost-effectiveness is not sensitive to changes in the assumptions on the risk of clinical disease progression.

A cost-effectiveness analysis has been undertaken using the SVR12 rates stratified by low risk of clinical disease progression. This is available on request.