GILEAD
Advancing Therapeutics.
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Single Technology Appraisal (STA)

Sofosbuvir for treating chronic hepatitis C [ID654]

Consultation on decision to amend the deferred funding

Dear Meindert,

Further to our correspondence of 14th November 2014 to Sir Andrew Dillon, a copy of which is attached (Appendix 1), we are writing in response to the consultation on the decision to defer funding for the implementation of NICE guidance recommendation on the use of sofosbuvir following a request from NHS England.

As you are aware there have already been a number of delays in the appraisal process for sofosbuvir and further delay to the actual implementation of the final recommendations will cause avoidable harm to patients and increased cost and burden on existing NHS resources.

The reasons provided by NHS England to justify delay in implementation of the current Guidance are unsupported by evidence and all information available to Gilead indicates that they are factually incorrect.

While without disclosure of the evidence, if any, which has formed the basis for NHS England's submissions, it is difficult for Gilead to respond to this consultation in a comprehensive way, we believe that the concerns expressed by NHS England are based on the predicted implications of the introduction of future treatment regimens, which will permit fully oral interferon-free regimens for the wider majority of Hepatitis C patients - and not on the implications of the implementation of the current Guidance for sofosbuvir.

This does not constitute a valid basis for extending the period for implementation of Guidance in accordance with regulation 7(5) of the 2013 Regulations. In contrast to NHS England's assertions, available evidence points to the fact that implementation of the current Guidance is very unlikely to result in substantial numbers of additional patients and will relieve rather than add to the existing burden on Hepatitis C services.

1. Introduction

An extension to the standard 90 day period for implementation of NICE Guidance is permitted only in the specific circumstances set out in regulation 7(5) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 ("the 2013 Regulations") namely:

(a) the health technology cannot be appropriately administered until—

(i) training is,

(ii) certain health service infrastructure requirements including goods, materials or other facilities are, or

(iii) other appropriate health services resources, including staff are in place; or

(b)the health technology is not yet available in England.

Other matters may not lawfully be relied upon to justify delay.

Furthermore, while Gilead recognises that the submissions made by NHS England should be taken into account by NICE in making its decision on implementation, the weight to be attached to those submissions will depend on the evidence provided by NHS England in support of its position. In particular it would not be fair, proportionate or rational for NICE to make a positive finding of any of the regulation 7(5) factors and therefore to delay implementation of Guidance based on simple assertion by NHS England (or anyone else) and in the absence of robust evidence.

Gilead strongly disagrees with NICE's preliminary view that the Guidance for sofosbuvir should be delayed by an additional 90-plus days as a result of factors within the scope of regulation 7(5)(a) of the 2013 Regulations. We firmly believe that the matters raised by NHS England and relied upon by NICE are either inconsistent with the requirements of the 2013 Regulations or contrary to the available evidence.

Furthermore, NHS England has already had at least 18 months to prepare for the introduction of sofosbuvir treatment. To suggest that they are unprepared now to implement a cost-effective treatment in circumstances where there is an unmet clinical need and therapy has already been introduced in other parts of the UK and across the EU, without the difficulties they identify, is wholly unacceptable.

In the consultation document NICE indicates its view that there is a presumption in favour of acceding to the request by NHS England for delay, stating that it "*should be cautious and sure of its judgement before requiring NHS England to provide services that it does not consider that it can provide, or provide safely and efficiently*" and that "*NICE should be wary of substituting its judgement for NHS England's in this respect*". We believe that this is the incorrect approach as a matter of fairness and does not represent a proper construction of the 2013 Regulations. The points raised by NHS England in their request for delay in implementation of the Guidance for sofosbuvir could equally apply to any Single Technology Appraisal where an innovative technology, representing a step change in treatment, is introduced and NICE should be very cautious about the implications of accepting a request for delay on the basis of what is, at most, insubstantial evidence.

We have provided below specific responses to the following points raised by NHS England and provisionally accepted by NICE as justifying delay in implementing the final Guidance;

- the perception that demand for treatment with sofosbuvir following implementation of the current Guidance, will be very substantial
- the need to establish a Hepatitis C Network prior to the implementation of NICE guidance on sofosbuvir,

In addition to the submissions set out in this letter, we rely on evidence provided by clinicians treating patients with chronic Hepatitis C infection as provided in Appendix 2. For the avoidance of doubt, Appendix 2 contains all statements and correspondence received by Gilead from clinicians, without selection or exclusion.

The additional matters raised by NHS England (a) in their letter to NICE dated 19 November 2014 and (b) prior to the meeting of the Appraisal Committee on 10th September 2014 are not addressed in detail in this response document, in view of the fact that they were not

seemingly relied upon by NICE and have not therefore formed the basis for NICE's provisional decision on implementation.

2. Response to the matters relied upon by NICE

2.1. The demand for treatment with sofosbuvir following implementation of the current Guidance,

NHS England's position

NHS England have expressed the view that the implementation of the current Guidance for sofosbuvir will result in a huge increase in patients coming forward to be tested and requesting treatment for chronic hepatitis C infection. They state in their letter of 19 November 2014:

> "*The management and treatment of Hepatitis C is an NHS England priority. The most recent national estimates suggest that around 160,000 adults*[1] *are chronically infected with hepatitis C (HCV) in England in 2012. Current numbers of patients treated are estimated at 5,000 per year in England – 3% of those currently infected but this will increase rapidly. The CRG Hepatitis C sub group have estimated that 10 - 15,000 people per year may come forward seeking HCV treatment".*

NHS England go on to say:

> *"Until last year, treatment for HCV has depended on a combination of two relatively low cost drugs – interferon and ribavirin. These have limited efficacy for some large subgroups of patients with Hepatitis C, and for many patients, cause serious side effects. There are other patients who have failed first line treatment who would now be potentially treatable with the new drugs. Patient groups are very aware that new and less toxic drugs will be available soon and there is already reported increased demand for these treatments. Over the next twelve months several directly acting anti-viral agents will be launched into the UK which will have reduced length of treatment, and side effects and increased cure / SVR rates. These drugs have different modes of action to the current treatments and allow for an interferon free (i.e. needleless) treatment strategy".*

Gilead Response

The conclusions NHS England have attributed to the CRG Hepatitis C subgroup have not been published, therefore it has not been possible to understand the basis for the figures quoted by NHS England or to test their accuracy. However, the evidence available to Gilead indicates that, while the implementation of the current Guidance will represent an important development for seriously ill patients with chronic hepatitis C infection, this will not result in a substantial increase in the numbers of patients coming forward for testing and treatment.

Analysis of current Guidance and likely demand

The current Guidance recommends use of sofosbuvir as follows:

- In combination therapy with interferon and ribavirin for:

[1] Figure consistent with Report by Public Health England "Hepatitis C in the UK 2013"

- All patients with GT1
- No patients with GT2
- Treatment experienced patients with GT3 and treatment naive patients with cirrhosis
- No patients with GT4, GT5 and GT6

- In combination therapy with ribavirin alone (a fully oral regimen) for:
  - No patients with GT1
  - Treatment experienced patients with GT2 and those intolerant or ineligible for interferon
  - Patients with GT3 who have cirrhosis and are intolerant or ineligible for interferon
  - No patients with GT4, GT5 or GT6

In summary the current Guidance for sofosbuvir recommends use as part of a fully oral regimen only for patients with GT2 and GT3 hepatitis C and in limited circumstances.

Evidence from clinicians

Gilead believes, that the Hepatitis C CRG subgroup's estimate of an increase of 10,000 to 15,000 patients is unlikely to be associated with the implementation of this Guidance (which recommends sofosbuvir in combination with pegylated interferon and ribavirin in all but a very limited group of patients), but rather is associated with the introduction of future therapies that allow interferon free options for the majority of patients. This view is supported by the evidence of clinicians provided in Appendix 2; those practising in England who have identified the patients they would treat following implementation of the current Guidance for sofosuvir and those practising in Scotland who have described the impact of similar recommendations for sofosbuvir issued by the SMC in June 2014.

Thus, the evidence of clinicians in England is that whilst the regimens assessed in the current Guidance for sofosbuvir address an important unmet need by providing a high level of efficacy with a shorter duration of treatment, many patients will still wish to defer therapy until additional oral agents are available providing the anticipated fully oral options for more than a very few patients. The evidence from clinicians in England and the experience in Scotland is consistent with that from other European countries where sofosbuvir is available. (Incidentally, it is also consistent with the figures calculated by NICE themselves within the Costing Template prepared for the purposes of implementation of this particular Guidance.)

Based on the UK Ipsos HCV monitor database 2013-2014[2] the population of patients with chronic hepatitis C infection in England, may be described as follows :

- Approximately 16,000 patients are thought to be 'under treater care' in England of which:
- 10,516 (66%) are treatment naïve and 5,484 (34%) are treatment experienced
- 3,327 (21%) are cirrhotic and 12,673 are non-cirrhotic (79%)

[2] Ipsos HCV monitor Q2 2013-Q2 2014 UK datasets combined

- Approximately 14% are thought to be unsuitable or intolerant to interferon based therapy.
- Approximately 5,500 of those patients thought to be 'under treater care' are currently prescribed Hepatitis C treatment on an annual basis[14]

Data on Hepatitis C disease prevalence indicates that patients are affected by hepatitis C genotypes as follows[3]:

- 45% are genotype 1;
- 7.3% are genotype 2 (approximately 1,168 patients under treater care in England);
- 43.8% are genotype 3;
- 3.9% are genotype 4/5/6

Accordingly, clinician evidence (Appendix 2), is that the patients who will receive treatment in accordance with the current Guidance are patients who have cirrhosis and those who do not have cirrhosis but are eligible for a fully oral interferon-free regimen (i.e. treatment experienced patients with GT2 and those GT2 and GT3 patients who are intolerant or ineligible for interferon). The best estimate we can produce based on the above data constitutes approximately 800 additional patients will satisfy these criteria following implementation of the current Guidance.

Those patients who are non-cirrhotic (the majority of patients under treater care) will likely wait to commence treatment until fully oral interferon-free treatment options become available shortly. Patients most likely to opt for treatment at this stage are those with marked extra-hepatic symptoms or those with cirrhosis wishing to reduce their risk of developing cancer during the time required to make all oral treatments available.

Even if all cirrhotic patients under treater care came forward for treatment at this stage (3,327[2]), this would not represent an increase in the total numbers of current patients treated over a year (5,500)[14]

Evidence from experience following introduction of Protease Inhibitors

NHS England's statement that '*hepatitis C management has depended on two relatively low cost therapies, interferon and ribavirin'*, is factually incorrect. Protease inhibitors, boceprevir and telaprevir were approved by NICE for the treatment of GT1 hepatitis C patients in April 2012 and represented a step change in management of affected patients. (note, the drug acquisition cost of protease based inhibitor regimens range from £22,872 through to £41,210). NHS England has not suggested that the introduction of these treatments required an extended period for implementation or resulted in the increase in numbers of patients presenting for treatment as is now suggested for sofosbuvir.

Evidence from Scotland

Sofosbuvir was appraised by the Scottish Medicines Consortium earlier in this year with guidance issued in June recommending use in patients with genotypes 1 to 6. Use in

[3] Brant LJ, Ramsay ME, Tweed E et al. Planning for the healthcare burden of hepatitis C infection: Hepatitis C genotypes identified in England, 2002-2007. *J Clin Virol* 2010;48:115-119

treatment-naive patients with genotype 2 is restricted to those who are ineligible for, or are unable to tolerate, peginterferon alfa. Use of the 24-week interferon-free regimen of sofosbuvir in combination with ribavirin in patients with genotype 3 is restricted to those who are ineligible for, or are unable to tolerate, peginterferon alfa (SMC Advice Number 964/14).

NHS Scotland has a very similar service structure to England and yet has been able to implement broad access to sofosbuvir based regimens within 1 month of the SMC decision to recommend use.

Based on Scottish Health protection data 2013,[4] Scotland has approximately 5100 patients under treater care of which in 2013, 1050 were treated. Since positive Sovaldi SMC guidance in June of this year approximately XXX-XXX patients have been initiated on treatment with Sovaldi based regimens over a six month time period[5]. This means that the number of patients treated with a sofosbuvir based regimen over this time period did not exceed the number of patients typically treated over a 6 month period i.e. the availability of Sofosbuvir does not appear to have driven the 2 to 3 fold growth in treatment that NHS England suggest. (Appendix 2)

The experience in Scotland has therefore confirmed that a substantial increase in patients presenting for testing and treatment after implementation of this Guidance is unlikely and provides no support for NHS England's concerns. Furthermore, in circumstances where NHS Scotland was able to implement a similar recommendation within a month of issue, the delay proposed by NHS England is unjustified and wholly unacceptable.

In summary therefore, while there seems likely to be a substantial increase in patients with chronic hepatitis C infection presenting for testing and treatment once fully oral interferon-free regimens for the predominant non-cirrhotic category of patients are available, Gilead is aware of no evidence which validates NHS England's concerns regarding an increase in numbers following implementation of <u>this</u> Guidance relating to sofosbuvir only, whilst having available substantial evidence indicating the contrary position.

2.2 Need to establish a Hepatitis C network

<u>NHS England's position</u>

NHS England state that there is a need to establish a Hepatitis C Network prior to implementation with this involving the set up a series of centres with the staff and the other resources and systems necessary to provide a multi-disciplinary team (MDT) approach to care. They say in their letter of 19 November 2014:

> "*A Hepatitis C network model will be formally commissioned comprising specialised centres with a caseload to develop and maintain expertise in the treatment of the condition working in partnership with a range of providers across the health and justice system. The Centres will encompass MDT decision-making by experienced teams on the appropriateness of initiation of treatment or continued surveillance of infected patients. MDT decision-making by experienced teams will support selection of the optimal treatment regimen for each patient. MDTs offer clinical and cost*

[4] McHutchinson, S. Epidemiology of Hepatitis B and C in Scotland, Hepatitis Monethematic meeting, Health Protection Scotland data 2013

[5] Gilead ex factory sales data (June 2014-Dec 2014)

effective prescribing of high cost drug treatments in accordance with NHS England policy / NICE TAs. The network will support access to treatment services locally through formal partnership and outreach models. This will optimise partnership working and utilisation of local expertise in engaging hard to reach groups in completing treatment programmes. NHS England would be required to commission Hepatitis C Networks through a competitive procurement route. This process would take about 9 months. A key part of the model is partnership working and the preferred procurement model would be to allow bidders additional time to develop their proposals jointly with others e.g. prison health, LAs etc.

Gilead's response

Whilst Gilead welcomes any opportunity to improve the current Hepatitis C service model that may further enhance patient access and outcomes, the submission by NHS England provides no evidence that the proposed Hepatitis C network is required for the implementation of the current Guidance. In particular, whilst a more sophisticated approach may be preferred in the context of the increase in the number of patients with chronic Hepatitis C infection who would be expected to present for testing and treatment after implementation of fully oral interferon-free regimens for the non-cirrhotic group, Gilead believes there is no requirement for this approach for the implementation of the current Guidance relating solely to sofosbuvir - and NHS England has provided no evidence indicating that this would be the case. Importantly we are not aware of any suggestion that implementing this guidance under the current service framework would result in ineffective, unsafe treatment.

Currently the majority of hepatitis C treatments (circa 80%) are managed by approximately 60 tertiary treatment centres across the UK.[6] .We are not aware of any drug or alcohol services initiating hepatitis C treatment without affiliation to one these tertiary centres[6]. (Appendix 2)

The current service has historically treated around 5,500 chronic hepatitis C patients on an annualised basis[14]

The following two main treatment options providing the standard of care[7]:

- Protease inhibitors telaprevir and boceprevir in combination with peginterferon and ribavirin for patients with genotype GT1 for 24 to 48 weeks dependent on patient profile and response.
- Peginterferon plus ribavirin (PEG-IFN + RBV) for GT 2 – 6 and GT1 where PIs are contra-indicated for 24 to 48 weeks.

Services are therefore already set up to initiate patients on complex therapies involving direct-acting antivirals (DAAs) as well as PEG-IFN and RBV. In order to initiate current NICE-approved therapies, centres already have in place:

- The ability to screen for drug – drug interactions (input from speciality pharmacy)

[6] IMS Hospital profiler data 2014

[7] European Association for the Study of the Liver. EASL clinical practice guidelines: Management of hepatitis C virus infection. J Hepatol. 60, 392-420. 2014

- Understanding of resistance considerations for choice of DAA
- Ability to use on treatment measurements of response to guide duration (Response guided therapy, RGT)
- MDT approach suitable for the prescribing of high cost drugs (treatment with currently NICE approved combinations could cost from £5,000 to £39,000)
- Throughout treatment patients must have regular appointments to monitor viral load and safety. In particular PIs have been associated with life-threatening skin reactions and anaemia meaning that rapid referral to dermatology clinics needs to be in place and admissions may be required to manage anaemia

The implementation of the current Guidance for sofosbuvir will have the following impact on the Hepatitis C service and is further evidenced in Appendix 2:

1) Reduction in treatment duration of interferon based therapy from 24-48 weeks down to 12 weeks for the majority of patients. The reduction of treatment duration will free-up significant capacity as current treatments require regular checks and interventions.
2) Reduction in time required to manage DDI and resistance profile due to an improved safety and tolerability profile of sofosbuvir vs. majority of existing treatments
3) No need for on treatment viral load testing and adjustments as duration of therapy is ascertained at the start of treatment

Therefore for every patient treated it is anticipated that the service capacity required will be substantially lower following the introduction of sofosbuvir. Furthermore, there seems to be no basis for concluding that a service capable of delivering treatment of currently NICE approved options safely and efficiently would not be more than able to implement the current Guidance for sofosbuvir safely and efficiently. NHS England has provided no evidence whatsoever to the contrary or for its conclusion that the introduction of a Hepatitis C network is necessary before the current Guidance for sofosbuvir may be implemented.

2.3 Service implications and sofosbuvir

There are no specific service implications for sofosbuvir. As described in section 2.2 above, treating patients with sofosbuvir based regimens will simplify treatment, reduce pressure on the existing MDT service and significantly reduce impact on current NHS service provision given. Compared with the existing protease inhibitor standard of care sofosbuvir is associated with a:

- significantly lower duration of treatment (12 weeks vs. 24 to 48 wks down to 12)
- lower number of adverse events leading to increased hospital admissions (e.g.; lower risk of severe anaemia and severe rash) and outpatient stays
- lower number of drug-drug interactions to manage

In addition there is no requirement for response-guided therapy with sofosbuvir. Patients treated with current standards of care are managed using a response guided therapy approach, where virologic response measured at specific on-treatment time points is used to

determine the likelihood of SVR and the required treatment duration (Incivo SmPC[8], Pegasys SmPC[9], Victrelis SmPC[10], Viraferon SmPC[11]). By comparison the high proportion of patients achieving both a rapid virologic response (after 4 weeks of treatment) and an end of treatment response means that on-treatment monitoring of HCV RNA and response-guided therapy are not required for sofosbuvir-based regimens. This will simplify patient management considerably relative to standards of care and also reduce the need for frequent on-treatment viral load monitoring and clinic visits.

The benefits of introducing sofosbuvir within the existing infrastructure are supported by clinical bodies and Dr Michael Jacobs, on behalf of the Royal College of Physicians and a clinical specialist in this appraisal, stated:

"*... introduction of sofosbuvir would tend to simplify treatment regimes for chronic HCV infections. Centres with experience in managing patients with Hepatitis C will be able to deliver this intervention without additional training. There is a need to improve accessibility of HCV treatment ... and simpler treatment regimes are an important component of this".*

Furthermore, as indicated above, two new hepatitis C treatments (boceprevir and telaprevir) were introduced successfully in 2012, without substantial additional investment in infrastructure, supporting Gilead's case that no additional measures are required in order to implement the current Guidance.

3 Impact of delaying implementation

Delaying access to sofosbuvir effectively prohibits those patients who are either cirrhotic or have bridging fibrosis from accessing the best possible treatment now in order to avoid the longer terms complications of this disease. These patients will have no option but to commence treatment using current standards of care (which, as outlined above, are less efficacious, more burdensome to patients and require significant NHS resource given the treatment durations and adverse event profiles). Each of these patients is exposed to an increased risk of liver cancer (approximately 6% per year[12]). This risk is reduced significantly if the HCV virus is removed to around 1% per year[12]. The consequence of this is that for every month that these cirrhotic patients continue untreated, approximately 40 people will develop a preventable cancer that is likely to be incurable. Furthermore every non cirrhotic patient who achieves an SVR is likely to avoid these future complications altogether.

The burden placed on these patients is unacceptable when sofosbuvir is available, particularly as the cost of treating these negative patient outcomes far outweighs the shorter term costs for this curative therapy and where sofosbuvir has been demonstrated to be highly cost-effective (NICE provisional guidance). It should be noted:

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[8] Janssen-Cilag Ltd. Incivo (telaprevir) Summary of product characteristics. 2013

[9] Roche Products Limited. Pegasys (Peginterferon alfa-2a) Summary of product characteristics. 2013

[10] Merck Sharp and Dohme Ltd. Victrelis (boceprevir). Summary of product characteristics. 2013

[11] Merck Sharp & Dohme Ltd. ViraferonPeg (peginterferon alfa-2b). Summary of product characteristics. 2013

[12] Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol. 2010;52(5):652–657

- Liver disease costs the UK National Health Service in excess of £500 million per annum, a cost that is rising by 10% annually[13]
- Hospital admissions for hepatitis C-related end stage liver disease and hepatocellular carcinoma have risen year-on-year, almost quadrupling between 1998 and 2012[14]
- Analysis of hospital statistics in England between 2011 and 2012, reveals around half (10,691, 49%) of all recorded hospital admissions for hepatitis C are non-elective (The Hepatitis C Trust. October 2013.). The average cost of a non-elective in-patient admission, including both short and long stays, is £1,436, excluding excess bed days, and £2,052 including excess bed days.[13]

Importantly, delaying access for those patients who require treatment now effectively increases future NHS service burden due to the effective 'warehousing' of a significant proportion of patients who would otherwise seek treatment now. In addition, the burden in terms of lifetime tertiary care follow up for patients (who have either progressed to cirrhotic, decompensated cirrhotic or hepatocellular carcinoma health states) should also be considered as there are potentially significant secondary care resource efficiencies and financial savings to be made for the NHS with the introduction of sofosbuvir.

In addition, we would like to highlight our concerns that the request from NHS England to extend the implementation period for this Guidance is significantly at odds with the NHS Five Year Forward Review within which Simon Stevens stressed the need for 'getting serious about prevention' and the benefits that this can bring to both patient outcomes and NHS resource over the longer term.[15]

Finally and for completeness, whilst we welcome any extension to the NHS England interim access policy regarding access to sofosbuvir it should be noted that this does not provide an appropriate substitute for prompt implementation of NICE Guidance for sofosbuvir (and the 2013 Regulations do not indicate that it does). NHS England's interim policy only covers treatment for those few hundred patients who are already severely decompensated and for whom liver transplant is the only available treatment option. There is no policy in place to treat those patients who could actually avoid these negative outcomes associated with chronic liver disease and reduce future service burden if they were offered treatment now. (i.e. in particular the cirrhotic population and those with bridging fibrosis).

Conclusion

As stated in our introduction there have already been a number of delays in the appraisal process for sofosbuvir and further delay to the actual implementation of the final recommendations will cause avoidable harm to patients and increased cost and burden on existing NHS resources.

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[13] The Hepatitis C Trust. Hospital Admissions where Hepatitis C is the primary diagnosis. Hepatitis C in England: The State of the Nation – Technical Appendix. Available at: http://www.hepctrust.org.uk/News_Resources/resources/reports (Last accessed 18 October 2013). October 2013

[14] Public Health England. Hepatitis C in the UK, 2013 Report. July 2013

[15] http://www.england.nhs.uk/ourwork/futurenhs/

The reasons provided by NHS England to justify delay in implementation of the current Guidance are unsupported by evidence and all information available to Gilead indicates that they are factually incorrect.

While without disclosure of the evidence, if any, which has formed the basis for NHS England's submissions, it is difficult for Gilead to respond to this consultation in a comprehensive way, we believe that the concerns expressed by NHS England are based on the predicted implications of the introduction of future treatment regimens, which will permit fully oral interferon-free regimens for the wider majority of Hepatitis C patients - and not on the implications of the implementation of the current Guidance for sofosbuvir. This does not constitute a valid basis for extending the period for implementation of Guidance in accordance with regulation 7(5) of the 2013 Regulations. In contrast to NHS England's assertions, available evidence points to the fact that implementation of the current Guidance is very unlikely to result in substantial numbers of additional patients and will relieve rather than add to the existing burden on Hepatitis C services.

In these circumstances, in the absence of any robust evidence supporting NHS England's request for delay and in the context of the presumption under the 2013 Regulations that Guidance will be implemented within the standard 90 day period, Gilead believes that any delay in implementation of Guidance for sofosbuvir would be procedurally unfair, unreasonable and disproportionate. Accordingly any such delay will, in our view, be susceptible to legal challenge.

Yours sincerely

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Director Market Access and Reimbursement

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Appendix 1

Andrew Dillon

Chief Executive

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Dear Sir Andrew

NICE appraisal of sofosbuvir for the treatment of chronic hepatitis C infection

Following our letter of 10th October regarding the period for implementation of NICE's Guidance for sofosbuvir, we understand that NICE is considering a further submission by NHS England in support of their request for delayed implementation of the Guidance (180 days, rather than 90 days). This information is a matter of serious concern; not only has this appraisal already been subject to substantial and unjustified delays, the apparent acceptance and consideration of further submissions by a consultee at this stage in the procedure does not form part of the appraisal process and all evidence available to Gilead indicates convincingly that an extension to the standard 90 day period for implementation of guidance is inappropriate in this case.

<u>The period for implementation of Guidance: legal provisions</u>

As you know, the National Health Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 ("the 2013 Regulations") require NICE to specify, in relation to any technology appraisal recommendation, the period within which the recommendation should be complied with. Regulation 7(3) states that this period

> ".....must be a period that begins on the date the recommendation is published by NICE and ends on the date 3 months from that date, unless [one of the circumstances at Regulation 7(5) applies]"

Accordingly, in the absence of clear evidence of a Regulation 7(5) circumstance, NICE is required to specify that guidance should be implemented within the standard 3 month time period.

The circumstances set out at Regulation 7(5), in which NICE is required to specify a period longer than 90 days for implementation of technology appraisal guidance, are follows:

"(a) The health technology cannot be appropriately administered until -

(i) training is,
(ii) certain health service infrastructure requirements including goods, materials or other facilities are, or
(iii) other appropriate health service resources including staff,

are, in place; or

(b) the health technology is not yet available in England."

NHS England's request for delay

While NHS England's response to the first ACD had raised no concerns about implementation, during the meeting of NICE's Appraisal Committee on 10 September 2014, a summary of comments on the second ACD was presented. This presentation provided the first indication that NHS England had requested an extension of time for implementation of Guidance for sofosbuvir. The reasons for that request, as presented during the meeting were:

- "need appropriate health service resources, including staff in place;
- technology is not affordable at the quantum of new expenditure it would represent;
- other therapies for Hepatitis C are likely to become available in the future and NHS wants to compare cost-effectiveness before choosing one option for investment."

Since that time, Gilead has sought clarification in relation to the reasons for the request by NHS England for delay. While we have not seen the submissions by NHS England to NICE, the information provided to us is consistent with the presentation given at the September meeting of the Appraisal Committee, to which no reference was made at the October Appraisal Committee meeting and indicate that NHS England's reasons for seeking a delay in implementation do not constitute permitted circumstances as defined by Regulation 7(5) of the 2013 Regulations. Our current understanding of NHS England's reasons is as follows:

a) Overall affordability

Gilead strongly believes that the principal motivation underpinning the request by NHS England for delay, is concern over the overall cost of implementation. This view is consistent with the inflated figures proposed by NHS England at the September meeting of the Appraisal Committee, those numbers 'leaked' to HSJ early October and addressed by Gilead in our letter of 10th October 2014.

While therefore Gilead refutes the estimations proposed by NHS England, in terms of the numbers of patients who will receive treatment with sofosbuvir, in accordance with NICE's proposed guidance, the appraisal committee has concluded that such use of sofosbuvir constitutes cost-effective treatment - and, most importantly, concerns over affordability do not constitute a valid basis for delay in implementation as determined by the 2013 Regulations.

b) NHS England's intention to conduct a comparison between current and future treatments for hepatitis C infection

NHS England has stated, both during the September meeting of the Appraisal Committee and in correspondence with Gilead, that it intends to conduct further cost-effectiveness analyses including comparisons with new hepatitis C treatments, not yet assessed by NICE and to consider a "Hepatitis C network approach".
It is not, however, the role of NHS England to conduct additional cost-effectiveness assessments, duplicating the work of NICE - but without the experience, procedural safeguards and regulatory framework of the Institute's processes. Such an approach would be procedurally unfair and a substantial waste of the time and cost associated with a double assessment process.
Furthermore, it is NICE that is required to determine the time for implementation of its recommendations in accordance with the 2013 Regulations and a wish by NHS England to conduct additional analyses outside the NICE process does not constitute a permitted reason for delay in implementation.

c) NHS England's assertion that a particular "service specification" and "staff in place" are required prior to implementation of guidance

While NHS England have claimed, belatedly, that the NHS may not be able to implement the guidance effectively within the standard period, the simple assertions made by NHS England and seen by Gilead are unconvincing and counter-intuitive.

- There are no specific service implications for sofosbuvir – patients are already being treated and use of sofosbuvir actually reduces the duration of treatment (by around 4-fold) and simplifies treatment (by reducing adverse events) compared with alternative therapies;

- The overwhelming evidence from clinicians, is that there will be no increased service impact as demonstrated by evidence presented to NICE during the appraisal process, including:

  a) Dr Michael Jacobs, on behalf of the Royal College of Physicians and a clinical specialist in this appraisal, stated:
  "... introduction of sofosbuvir would tend to simplify treatment regimes for chronic HCV infections. Centres with experience in managing patients with Hepatitis C will be able to deliver this intervention without additional training. There is a need to improve accessibility of HCV treatment ... and simpler treatment regimes are an important component of this".
  b) Dr Richard Aspinall, on behalf of the British Gastroenterology Society and a clinical specialist in this appraisal, stated:
  "*Implementation of this technology should be relatively straightforward, given its ease of use. The major training requirement would be to ensure optimum personalisation of therapy in individual patients and it is recommended that HCV treatment centres should hold minuted MDT meetings to discuss choice of antiviral therapy. NHS England is currently proposing specialist commissioning standards that would include such arrangements and treatment units should be in a position to adopt sofosbuvir without too much difficulty if approved".*

- Indeed it is also appears that in its assertion regarding a lack of service infrastructure, NHS England has disregarded the specific advice of members of the relevant Clinical Reference Group (CRG) – members whose sole purpose within this context is to advise NHS England on matters relating to HCV.

- While Gilead refutes the numbers of patients who would receive treatment with sofosbuvir, as proposed by NHS England, we understand from discussions with numerous clinicians (including members of the CRG as noted above) that there will be no impact on the ability of the existing service to manage patients appropriately.

- Appropriately trained staff are already available. All relevant resources, infrastructure and resources required for implementation of sofosbuvir treatment are already in place. In fact the abbreviated and simplified treatment duration and, in some cases, use of an all oral treatment compared with alternative parenteral therapies will require less resources and avoid the need for training and personnel to manage the side effects of alternative treatments.

- A specific service specification has not been required to date for existing hepatitis C therapies generally and there is accordingly no requirement for such a specification specifically for sofosbuvir.

In summary, Gilead does not accept that there is any genuine need for training and infrastructure that may permit delay in implementation of guidance for sofosbuvir in accordance with Regulation 7(5) of the 2013 Regulations. It would, in fact be surprising if a need for training were permitted to delay implementation of NICE guidance, in circumstances where administration of sofosbuvir is substantially more straightforward than alternative therapies and where NHS England and its predecessor organisations have had over 18 months in which to prepare for the introduction of this treatment.

Procedural issues in relation to NHS England's request for delay

As indicated above, we understand that NHS England has provided supplementary submissions to NICE in relation to its case for delay in implementation of guidance and that these submissions have been considered and discussed with NHS England outside the technology appraisal process published by NICE, in private and without transparency.

If this is the case, such an approach is fundamentally unfair not only as a matter of domestic law, but also in accordance with the requirements of the Transparency Directive.

Clinical implications of delay in implementation of guidance

Hepatitis C is a progressive disease in which the virus attacks the liver causing scarring (fibrosis and eventually cirrhosis). This can lead to failure of the liver with impaired function (decompensation) and further increases the risk of the liver cancer hepatocellular carcinoma (HCC). Whilst a certain degree of fibrosis is reversible it is as yet unclear the extent to which cirrhosis can be reversed, if at all, following successful treatment of the hepatitis C. According to Public Health England's 2014 report on HCV there are approximately 10,000 patients with HCV related cirrhosis in the UK. Each of these patients is exposed to an increased risk of liver cancer (approximately 6% per year) which reduces significantly if the HCV virus is removed to around 1% per year. The consequence of this is that for every month that these cirrhotic patients continue untreated, approximately 40 people will develop a preventable cancer that is likely to be incurable. In addition of the 10,000 cirrhotic patients

over one year approximately 440 will decompensate. With treatment this number would be expected to reduce to around 60, therefore for every month's delay approximately 30 patients unnecessarily progress to decompensation that could be prevented by treatment. Whilst liver decompensation and HCC would make patients eligible for the current interim policy, the outcomes of these patients once they have developed end stage liver disease is still uncertain and these patients would be much better treated ahead of this preventable event. Late treatment also increases the burden to the NHS in terms of liver transplant and care for endstage patients.

Finally for those patients who have not yet developed cirrhosis but have rapidly progressing fibrosis a delay to treatment may lead to the development of cirrhosis. Current understanding based on other liver disease suggests that these patients will have an irreversible risk of liver cancer which can be reduced but not completely eliminated by subsequent treatment of their HCV. This would not only add to the lifelong anxiety for these patients but they would also require bi-annual liver imaging and blood tests within the NHS for the remainder of their lives.

Overall it would be is erroneous to assume that a further delay to access for these patients will not have severe clinical implications.

Request for consultation

If, despite this letter and the provisions of Regulation 7(5) of the 2013 Regulations, NICE extends the period for implementation of guidance for sofosbuvir beyond the standard 3 month period, fairness will require that NICE provides an opportunity for stakeholders to respond to this determination. However, while consultation on such a proposal would be necessary, it is essential that the consultation period itself is not used to extend the time for guidance to be issued in this case.

The issues surrounding the time for implementation of guidance are discrete and, Gilead believes that the issues have generally been rehearsed. In these circumstances we suggest that consultation should properly be limited to the question of delay and that the consultation period should be no longer than strictly necessary for this purpose.

Conclusion

In summary, Gilead does not believe that there is any valid reason in accordance with the 2013 Regulations to justify delay in implementation of guidance for sofosbuvir. Accordingly any such delay will, in our view, be susceptible to legal challenge.

Finally, we are concerned that the process followed in relation to NHS England's request has not been conducted in accordance with NICE's procedures, the requirements of the Transparency Directive or standards of fairness under English Administrative Law.

Please confirm that this letter will be taken into account by NICE before a decision on the time for implementation of NICE's recommendations for sofosbuvir is made. We look forward to hearing from you as a matter of urgency.

Yours faithfully

XXXXXX XXXXXXXXXX

General Manager

Gilead Sciences UK & Ireland

Cc Professor Carole Longson, Health Technology Evaluation Centre Director, NICE

Meindert Boysen, Programme Director Technology Appraisals, NICE

Helen Knight, Associate Director NICE Project Team, NICE

Appendix 2

8th December 2014

To Whom It May Concern

RE: NICE APPRAISAL OF SOFOSBUVIR [ID 654]

I am a full-time NHS Consultant Hepatologist working in an academic Liver Unit and tertiary referral centre in West London. I have been treating patients with hepatitis C for more than twenty years and have been actively involved in clinical research into novel therapies for at least the past ten years.

Sadly due to a general lack of awareness of the condition both among the public and the medical profession a significant proportion of patients continue to present in late stages of disease which places a heavy burden on the patient and the health service. I am also seeing patients presenting late with decompensation of their liver disease who have been aware of their condition for some time but have previously declined the offer of treatment because of the perceived arduous nature of long interferon-containing regimens.

While the majority of patients are currently treated in specialist centres it is clear that in order to reach those who need treatment, (and to treat the numbers that need to be treated in order to reverse the current epidemic), we are going to need to change the ways in which we deliver service. To this end we have already established a number of outreach clinics in community drug-treatment units and plan to establish more in the future. I am observing a steady increase in those infected through drug use coming forward for treatment. In addition I am being referred increasing numbers of patients who have migrated to the UK and who have been infected iatrogenically in their country of birth.

The majority of our patients continue to receive interferon-based therapies though I am fortunate in being able to offer clinical trials of interferon-free treatment to a significant number of our patients. I have witnessed first-hand the benefit these new drugs bring to these patients. We also have a large number of patients with advanced liver disease on the government's early access programme which has made a real difference to those patients in whom interferon is contraindicated.

If NICE guidance for Sofosbuvir were to be implemented, I would not anticipate a huge increase in patients coming forward for treatment. There are still a considerable number of patients who are deferring treatment until all-oral therapies are available. However for those who are willing to accept IFN-containing regimens, the availability of sofosbuvir will offer them shorter duration treatments with significantly improved outcomes (thereby reducing the number of patients who will require retreatment in the future). The shorter duration of treatment (and fewer adverse events) will mean that we will be able to treat more patients with the same resources – something that will ultimately begin to make an impact on the huge task we have set ourselves to eventually eliminate HCV.

innovation respect
care
achievement
pride

I therefore sincerely hope that NHS England will implement the recommendations of NICE on Appraisal ID654.

Yours faithfully

Date: 08 December 2014

TO WHOM IT MAY CONCERN

I am the Clinical Lead for Hepatology & Hepatitis and I am a Transplant Physician at the Institute of Liver Studies, King's College Hospital. I lead the largest viral hepatitis service in the UK and incorporating tertiary, outpatient, outreach, co-infection and complex populations.

We have the infrastructure to deliver new therapies post-NICE appraisal of sofosbuvir, simeprevir, daclatasvir and combination therapies with and without pegylated interferon. We have specialist nurses, clinical trials nurses, a dedicated pharmacist, on-site CPA-accredited hard diagnostics and liaison psychiatry. We have run a large outreach population and are keen to get patients into therapy as we see the spectrum of patients from those with mild disease to those who have advanced disease and the requirement for liver transplantation.

I do not believe that patients will take up interferon-based therapy and as a clinician with significant trial experience experience would prefer to 'fast-track' patients with more advanced disease through to newer innovative peg-free therapies. I do not believe that current infrastructure issues will constrain therapy to those with advanced

disease/cirrhosis as the duration of 12 weeks' therapy with targeted adherence education and simpler on- treatment monitoring will allow appropriate patients to be treated and to achieve a significant 'step-up' in clinical outcomes and cure.

In addition, we have various programmes focusing on screening and education for GPs and there is no doubt that liver disease *in toto* (as seen by the LANCET Liver Commission) is an important Public Health agenda item.

With kind regards,

Yours sincerely

4th December 2014

To Whom It May Concern:

I am a Consultant Physician in Infectious Diseases and HIV Medicine at the Royal Free Hospital and lead a large tertiary referral HIV/hepatitis co-infection service.

I have been in involved in the care of co-infected patients for over twenty years. We have a cohort of over 450 co-infected patients we look after locally and are the referral centre for North Central London and parts of Hertfordshire for the treatment of 'complex' HCV in HIV-infected patients. Patients not deemed to be complex (non-advanced fibrosis, no other co-morbidities, no significant drug-drug interactions) are managed by the local HIV services (in collaboration with hepatology/gastroenterology services).

Up to 10% of co-infected patients have advanced fibrosis/cirrhosis (metavir F3/F3 disease). The rest have early HCV (post-acute) or mild/moderate (metavir F0-F2) fibrosis, although fibrosis progression rates are faster in this population. About 65% have Genotype 1 (majority 1a) disease, with 25% Genotype 4 and 8% Genotype 3 infection. Current treatment (outside of clinical trials) is mostly PegIFN-alpha, ribavirin and either telaprevir or boceprevir. Most treatments currently are for patients with acute HCV who express a preference for treatment in the cute phase of illness.

Most patients with mild/moderate fibrosis prefer to wait for IFN-free therapy. Patients with CP-B/C cirrhosis have been treated in the NHSE EAS with sofosbuvir/ledipasvir or daclatasvir.

Once sofosbuvir becomes available in accordance with NICE guidance ID654 (preliminary recommendations August 2014), we anticipate treatment mainly for patients with advanced fibrosis/compensated cirrhosis in 'urgent' need of therapy. Since the vast majority of patients have G1 and G4 infections, this would be 12 weeks of therapy with PegIFN and ribavirin.

As indicated above, we don't anticipate large numbers of patients taking on IFN-based therapy and certainly would want to prioritise patients with F3/F4 disease willing to take-up therapy.

As a tertiary referral centre, we already have the resources (specialist nurses, pharmacists, on-site virology, etc) to treat patients with PegIFN and ribavirin and have been a treatment centre for the expanded access programme. Implementation of this guidance would not require further resources. Furthermore, reducing the treatment length down to 12 weeks would help stretch current resources to make treatments available for more patients.

In the context of HIV patients, testing for HCV is universal and there is a high-level of awareness amongst clinicians looking after HIV+ patients regarding annual screening for those at high-risk of HCV acquisition. Availability of DAAs will not change that.

With best wishes,

8th December 2014

To Whom It May Concern:

I have read with interest the NICE Health Technology Assessment for Sofosbuvir. As the clinical lead for one of the country's leading centres for the treatment of hepatitis C I eagerly await access to this highly effective drug for patients of the NHS.

I am confident that the introduction of Sofosbuvir, along with pegylated interferon and ribavirin, will not have an adverse impact on our service's ability to deliver treatment to patients. The improved side-effect profile and shorter duration of treatment will enable us to provide care for more patients with our existing resources.

I believe that Sofosbuvir and other directly acting antiviral agents represent a major advance in the management of patients with hepatitis C and look forward to their introduction into clinical care with the opportunity to cure many more patients.

Yours faithfully

07/12/2014

To whom it may concern,

I am writing to outline my experience of the effects of the introduction of Sofosbuvir (SOF) post SMC recommendation in June 2014.

I am a Consultant Gastroenterologist, and have been involved in treating patients with hepatitis C for over 5 years. Patients under my care are assessed in a liver outpatient clinic, and if appropriate treated under the supervision of a liver nurse specialist.

For comparison, in the 6 months June to November 2013 we initiated treatment in 44 patients (24 GT1 (54.5%), 18 GT3 (41%), 2 GT2 (4.5)). 23/44 (52%) of whom had a diagnosis of cirrhosis. During this period GT3 patients were treated with pegylated Interferon (IFN) and Ribavirin (RBV) for 24 weeks, GT1 patients were treated with IFN/RBV and a first generation protease inhibitor (PI, Boceprevir or Telaprevir) for 24 to 48 weeks. Those GT 1 patients not suitable for a PI, predominantly due to ongoing drug use (opiods or benzodiazepenes), were treated with IFN/RBV for 48 weeks. Overall 27/44 (61%) received IFN/Ribavirin (RBV), 9/44 (20.5%) IFN/RBV/Telaprevir (TVR) and 8/44 (18.1%) IFN/RBV/Boceprevir (BOC).

In the current financial year we are prioritising treating SOF based regimens to those with advanced fibrosis (F3/4, defined as liver stiffness ≥9.5 kPa). Requests to treat with IFN free regimens, or to use SOF regimens for non F3/4 patients are made to a peer scrutiny panel (single A4 form, evaluated by 2 treating consultants out with of requestor's clinic, form sent to pharmacist by email).

No additional resources were required to implement the SMC recommendations for Sofosbuvir. For GT1 patients, the use of Sofosbuvir reduced pharmacy involvement in screening for drug-drug interactions, which are infrequent and rarely clinically significant compared to PIs. Simpler once daily dosing, and improved tolerability, in particular the absence of life threatening rash, have likewise substantially reduced the nursing time taken for pre-treatment counselling and on treatment toxicity management.

The net result of these improvements has an increase in clinic throughput, without the requirement for any additional resources:

In the 6 months June to November 2014 inclusive, we treated 77 patients (43 GT3 (55.8%), 26 GT1 (33.7%), 4 GT4 (5.2%) and 3 GT2 (3.9%)). 43/77 (55.8%) had a diagnosis of cirrhosis. The majority of patients were infected through intravenous drug use.

65/77 (85.4%) of patients received IFN based regimens; 40/77(51%) Sofosbuvir/IFN/RBV for 12 weeks, 15 (19.5%) IFN/RBV for 24 to 48 weeks, 6 (7.8%), BOC/IFN/RBV for 28to 48 weeks, 3 (3.9%) Simeprevir/IFN/RBV for 24 weeks (post SMC approval in October), 1 (1.3%) TVR/IFN/Ribavirin.

12/77 (15.6%) of patients received an IFN free regimen; 7 (9%) Sofsbuvir/RBV, 3 (3.9%) Sofosbuvir/Daclatasvir, 1 (1.3%) Sofosbuvir/Ledipasvir 1, (1.3%) Sofosbuvir/Simeprevir.

In marked comparison to longer treatment regimens, and in particular PI regimens, we have yet to have any premature discontinuation of treatment in our Sofosbuvir treated patients, and all patients who completed treatment have had an end of treatment response.

In summary, the impact of the SMC guidance of Sofsobuvir has been to reduce the amount of nursing and pharmacy input required per patient which, in combination with the shorter duration of treatment, has significantly increased the treatment capacity of our clinic without additional clinic resource. Treatment in a "real life" setting has been well tolerated, with on treatment response in line with that expected from the phase 3 clinical trials.

Yours Faithfully,

8 December 2014

To whom it may concern,

I understand that there are concerns about the impact of the introduction of new DAAs on the ability of clinical units to deliver HCV treatment with the new HCV DAAs.

I am a consultant physician managing Hepatitis C since 1989. I work in an ID unit in Edinburgh, which has a HCV treatment target of 90 patients per year. We have a multidisciplinary team of ID doctors, HCV nurse specialist, dietician, social worker and mental health team. We also treat HCV in 2 local prisons.

Last year we treated 94 patients; 50 were GT 1 and the rest mostly genotype 3. Twenty five per cent of patients treated were cirrhotic of which 60% were genotype 1 and the rest non-GT1. 9 patients were enrolled in a sofosbuvir study.

We started using Sofosbuvir once the Formulary committee approved its use in our trust. In five months, we have initiated 52 patients on treatment; 21 were cirrhotic and 75% were Genotype 1; 10 were on an all-oral HCV treatment. This increase in numbers is because some patients have delayed treatment until the introduction of sofosbuvir. In our local protocol, sofosbuvir can only be used in patients with advanced fibrosis. We are hopeful that in the next financial year we will be able to use it according to the SMC approval. Sofosbuvir was used in 32 patients in the last 5 months.

Our staff were well prepared since the advent of HCV protease inhibitors, as we had access to them through clinical trials prior to SMC approval.

Patients are now aware of the new DAAs but there has not been a significant increase in the number of patients identified with HCV infection. We are in the process of contacting HCV infected patients who have been lost to follow up to ensure that those with advanced fibrosis are reassessed and initiated on HCV treatment.

The HCV action plan in Scotland has over the years provided funding for the infrastructure to enable more testing and treatment and this happened well before the introduction of sofosbuvir. Our unit has been undertaking clinical trials for antivirals for several decades and the introduction of new antiviral agents into the clinics has been smooth. All our staff are kept up to date with the new drugs

through education meetings and are also involved with certain aspects of clinical trial at an early stage. We also have a weekly MDT meeting where patients are discussed and treatment is planned.

In view of these factors, we did not have any difficulties introducing the new DAAs in the clinic

Yours sincerely