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Executive Summary

AbbVie is grateful for the opportunity to comment on NHS England's submission to questions raised by NICE following consultation responses to hepatitis C drug appraisals. Given the nature of the response and the proposals put forward by NHS England, AbbVie welcomes that NICE are conducting this consultation and hopes stakeholders will have an opportunity to put forward additional viewpoints during the specific session on this topic at the NICE committee meetings of 23 June.

We note at the outset that NHS England have confirmed their comments do not describe a consensus view from the Clinical Reference Group. AbbVie thus recognises that the stated position throughout the entirety of the NHS England's response does not represent a consensus of opinion and requests that a clarification is provided concerning the supporters of the CRG statement as well as the context in which these comments were made.

While AbbVie's position on NHS England's proposals is articulated below, AbbVie would like to make clear our willingness to work with all relevant stakeholders including NHS England to ensure that patients can gain access to cost-effective medicines. AbbVie welcomes NHS England's recent interim commissioning policies and recognises that this represents an appropriate way to provide patients for whom a delay to treatment could impair their health with access to clinically suitable medicines prior to NICE guidance. But such interim policies should not be used as a reason to delay NICE appraisal or influence the remit of NICE.

AbbVie's response falls into the following three broad categories which are explored in further detail below:

1. *The **principle** of NICE technology appraisals and NICE's remit*

It is AbbVie's view that the response of NHS England raises a number of principles of fundamental importance to the process of technology appraisals undertaken by NICE. This has potential implications beyond the specific medicine appraisals to which they are directed. Such fundamental changes to the established NICE remit will create a precedent and therefore cannot be taken without the involvement of the Secretary of State for Health following extensive public and stakeholder consultation separately and without prejudice to this appraisal

2. *The **process** by which AbbVie's hepatitis C regimen is being appraised*

This includes, but is not limited to, the proposal to halt the current STA process for a number of medicines, which NICE has already commenced. In any event, a request for a pause in STA (or for the products to be assessed under an MTA) undermines the Ministerial Direction to NICE to assess AbbVie's product under the STA process.

3. *The **robustness of the evidence** presented by NHS England*

The evidence base provided by NHS England contains, in AbbVie's view, multiple areas of confusion and possible errors of fact and/or methodology which therefore cast doubt on a number of projections and conclusions drawn from them.

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Matters for consideration by the NICE Committee

1. The principle of NICE technology appraisals and NICE's remit

The proposals put forward by NHS England within its response give rise to a number of issues of principle that seek to fundamentally alter many of the recognised aspects of technology appraisals undertaken by NICE. These are outlined in more detail below. As NHS England states, in response to question three on page eight of its response, it is *"seeking a more substantial revision to the strategy to deliver care for hepatitis C that includes a managed market entry and a cost effective approach to implementation for each patient cohort"*.

It is AbbVie's position that such substantial revisions of practice and principle cannot be made on an 'ad hoc' basis, in relation to one specific disease area or to any specific appraisal or set of appraisals. Revisions to such principles are the matter for relevant decision makers, for example Government, the Department of Health and Parliament, following the usual processes for such fundamental changes. Processes which allow for appropriate scrutiny and which should be undertaken completely independently of this (or any) ongoing appraisal.

The five areas of broad principle are as follows:

1.1 The role of NICE in reviewing budget impact and cost-effectiveness

NHS England has called into question NICE's general duties to have regard to the broad balance between benefits and costs of the provision of health services or social care in England. NHS England has requested that NICE have regard of the potential budget impact of its possible positive recommendations of the hepatitis C medicines currently under review. In response, it is AbbVie's view that the remit of NICE is to review the clinical and cost-effectiveness of any particular medicine during its appraisal and not its budget impact, the nature of which is determined on a case by case basis. At a more general level, it is inappropriate for NHS England to impose itself on the NICE process and its role when this is clearly established by law. Such an approach also undermines the decision of the Secretary of State to refer STA topics, including [ID731], to NICE.

This position is clearly supported by the Health & Social Care Act 2012 (**the Act**), the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013, and the NICE Guide to the methods of Technology Appraisal 2013 (**the NICE Guide**). In particular, NICE is required to take into account how its advice may enable the more efficient use of available healthcare resources but *"the potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision"* (section 6.2.14 of the NICE Guide[1]).

As set out in the Act, NICE's role is to review and consider the clinical and cost-effectiveness of a medicine. The NHS Constitution then allows for medicines which are deemed cost effective and a good use of NHS resource to be made available to patients subject to the medicine being deemed clinically appropriate. Thus, the decision making criteria that NICE use when developing guidance for new medicines is based on the estimated cost-effectiveness of a medicine and not on its potential budget impact.

In view of the above, there is no legal basis or precedent for NHS England to request a broader budget impact review. Any change to NICE's role would require formal consultation and legislative reform.

1.2 The Pharmaceutical Price Regulation Scheme (PPRS)

As outlined in point 1 above, it is AbbVie's view that it is not the remit of NICE to take into account the budget impact of HCV medicines in the way NHS England is proposing. Without prejudice to this position, one factor which is relevant but seemingly overlooked by NHSE is the role of the PPRS. NICE has a position statement on the PPRS where it states the PPRS "*should not, as a matter of course, be regarded as relevant consideration to*

the cost effectiveness of branded medicines".[2] However, because NHS England is seeking to introduce elements of budget impact beyond the mandated NICE principles of cost-effectiveness, AbbVie feels the PPRS must be highlighted, because it is critical in the considerations of the models and projections of cost put forward by NHS England. Indeed, any review of budget impact in the way being suggested cannot be made without reference to the PPRS.

Throughout its response NHS England highlights its projections of budget impact of between £285 and £772 million per year starting in the next 12 months and summarises that *"there is no spare capacity in the system to afford increased hepatitis C expenditure at the scale potentially suggested by forthcoming NICE appraisal decisions"*. Given the current PPRS agreement provides for a medicines bill cap, it is AbbVie's view that this is not accurate given the mechanism by which the current scheme is designed to operate.

It should be stressed that the PPRS affords for expenditure on medicines manufactured by companies who are a member of the current voluntary scheme (which AbbVie is) above the agreed medicines bill cap will be repaid / rebated to the UK Government. It is estimated this will be almost £1 billion in 2015/16.[3] As NICE makes clear in its position statement on the PPRS, this encompasses new products, which are *"included in the calculation of the growth rate of sales for all medicines, that is, they are taken into account in determining whether the agreed growth level has been exceeded and a PPRS payment will be required, and determining the size of the percentage"*.

It is AbbVie's view that there can be no ambiguity on this point. The medicines bill is capped to provide assurance to the UK Government of its expenditure on such medicines. Any increase to the hepatitis C medicines expenditure manufactured by companies within the PPRS scheme will therefore not contribute to increased medicines bill growth beyond what is already forecasted. This is particularly the case given one of the aims of the PPRS is to improve patient access to clinically- and cost-effective medicines. Indeed, section 1.4 of the NHS Mandate also references the PPRS as follows, *"in ensuring people have access to the right treatment when they need it, including drugs and treatments recommended by the National Institute for Health and Care Excellence (taking account of the Pharmaceutical Price Regulation Scheme agreement),…"* [4]

1.3 The transparency and predictability of the NICE Single Technology Appraisal process

There is no legal basis for NHS England's intervention. AbbVie believes it is unprecedented for a STA which has already commenced and already had its first Committee Meeting to be paused and merged into a MTA with unknown and uncertain timelines. The request by NHS England to stop STAs for HCV drugs already underway undermines the well-established NICE STA process and the principles of valuing innovation in new medicines, as set out under the 2014 PPRS. The PPRS emphasises the need for a prompt appraisal by NICE and this is fundamental and an important element in Government's approach to ensuring that patients access innovative and cost-effective medicines rapidly and the rationale for conducting STAs rather than MTAs. As we have already emphasised, NHS England's intervention also undermines the direction issued by Ministers requiring NICE to assess the HCV drugs pursuant to an STA. We note that the Department of Health did not have any comments on the scope of the ID731 appraisal, which was finalised, approved by Health Ministers and referred to NICE for a single technology assessment.

1.4 The proposed introduction of alternative cost-effective thresholds

In answer to NICE's question number two, NHS England response makes reference to the recent academic work and conceptual framework proposed by Claxton et al. (2015). Under this framework, the incremental cost-effectiveness ratios for NICE recommended therapies should not exceed a £13,000/QALY threshold and such a threshold should inform NICE decisions moving forward.

The Department of Health outline makes reference to the 2014 PPRS in relation to the NICE technology appraisals programme.[5] Paragraphs 4.5 to 4.9 make it clear that NICE should continue to appraise the clinical

and cost effectiveness of new technologies. In particular, the Government has agreed with the Industry that the baseline cost-effectiveness threshold should be kept at a level consistent with the current range (£20,000-£30,000/QALY), subject to the application, in individual cases, to a number of modifying factors, for the duration of the 2014 PPRS scheme. Any modifying factors which may be considered within individual appraisals would only result in an increase in the threshold and not a reduction. *Paragraph 4.9 states: 'The basic cost effectiveness threshold used by NICE will be retained at a level consistent with the current range and not changed for the duration of the scheme'.* Therefore, the application of the £13,000 figure referenced[6] in the NHS England's response is not consistent with the current agreement or the methodological principles that manufacturers have to consider when submitting evidence to the Technology Appraisal programme.

1.5 The NHS Constitution and improving public health

NHS England propose that for F0 to F2 chronically infected hepatitis C patients a *watchful waiting* strategy should be adopted by NICE whereby patients would be monitored until their disease progresses to a more severe stage and then treated. NHS England further suggests a *watchful waiting* strategy may be particularly cost-effective for patients with mild disease and a low likelihood of onward transmission, although they do not discuss how this would be ascertained. Therefore, the proposed strategy would likely lead to new infections in previously uninfected individuals due to continued transmission of chronic hepatitis C by the large cohort of patients who would be left untreated. Thus in AbbVie's view, such a poorly defined strategy represents a dangerous pitfall.

In our cost-effectiveness analysis, AbbVie demonstrated that offering Viekirax® and Exvirea® to non-cirrhotic patients (patients with histologically mild chronic hepatitis C) is fully cost-effective, even more cost-effective than treating patients with histologically advanced hepatitis C. Therefore, the proposed NHS England *watchful waiting* strategy would represent placing individuals with mild and moderate hepatitis C at a health disadvantage compared to patients with more advanced hepatitis C. This is given that restoring the health of this patient group by offering treatment with Viekirax® and Exvirea® has been shown to be of comparable value to that of patients with more advanced disease.

2. The process by which AbbVie's hepatitis C regimen is currently being appraised

2.1 The proposed Multiple Technology Appraisal

The request by NHS England to halt this STA and pursue an alternative MTA has been addressed above. However, there are outstanding areas of concern in relation to this specific request.

If implemented, this approach would unfairly impact upon AbbVie's hepatitis C medicine and it is unclear what the practical effects of halting a half complete STA are. The information already submitted has been presented in good faith and at significant cost. It is unclear to us how a manufacturer's submission dossier would be used and what position AbbVie's hepatitis C regimen would have within the market place should this STA be halted. For example, how would this affect the ability to secure parity with NICE approved products through the Commercial Medicines Unit HCV therapeutic tender process, underwritten by NHS England's proposed commission policy?

The future timing and scope of a possible MTA are also unclear and have not been adequately explained by NHS England in their response. Furthermore, as NICE and NHS England will be aware, there are a number of hepatitis C medicines in development by a number of companies which are expected to reach regulatory approval beyond the point at which a future MTA would be underway. In other words, the hepatitis C treatment landscape continues to evolve as improvements are made to the benefit of patients. It is unclear how NHS England's proposed MTA would account for these and a question mark would hang over whether their imminent arrival would be the justification for a further pause in future. NICE is well-used to issuing STAs

in a number of rapidly evolving fields and then at an appropriate moment in time re-evaluating that guidance, perhaps in the context of an MTA.

AbbVie believe this approach is neither fair nor consistent with the Government's supportive approach to improving the adoption of innovative cost-effective medicines in the UK as articulated most recently in the principles behind the Accelerated Access Review.[7] After much resource and time has already been expended on the current STA appraisal, the halting of this process would lead to unnecessary and, in AbbVie's view, unjust delays. Furthermore, there is no guarantee that products currently under clinical development would be approved by the European Medicines Agency (EMA) due to the well documented uncertainties associated with the development of new medicines.

2.2 NHS England's alternative "evaluative" approach to access is not clear

The stepwise approach articulated by NHS England as a proposal to manage access to new hepatitis C medicines in the absence of NICE guidance is not transparent. It is difficult for AbbVie to support a process which is not clear and the details of which have not been formally provided to us or placed into the public domain. Questions will be raised as to its implementation, effect, operation and the principles that will underpin it. Furthermore, it is unclear as to how this approach might be amended, altered or disregarded at a future point in time given it is not underpinned in the same way the NHS Constitution underpins a patients' rights to NICE approved medicines for example.[8] AbbVie believes this is an understandable cause of concern to stakeholders and patients.

AbbVie welcomes and supports NHS England's approach to treating those in most need through an interim commissioning policy where those patients' health may be negatively impaired by a delay, e.g. the commissioning policy for hepatitis C patients with cirrhosis. AbbVie believes this is the correct approach supported by a consensus view amongst the relevant Clinical Reference Groups. However, this should not form an alternative model to the proper assessment of cost-effectiveness through the existing procedures.

The third stage of NHS England's proposed stepwise approach envisages the formation of the work programme to establish access to all oral drugs for patients with F3 liver fibrosis. AbbVie is not aware of the plans behind this commissioning policy. This means the timing of this policy is not clear and the medicines that would be made available within it are also not clear. It is therefore difficult to comment on the appropriateness of this policy in securing access to treatments for patients who need them and, certainly, difficult to support this process as a suitable alternative to the recognised process of a NICE STA.

2.3 NHS England infrastructure

In answer to NICE question number three, NHS England express their concern that a work rate of 20,000 patients per year could not be absorbed by the current hepatology services necessitating a new service delivery model. In response, AbbVie highlights that NHS England articulated this objection and the need for a new service specification in its unprecedented request to NICE in January to delay the implementation of sofosbuvir + pegylated interferon and ribavirin guidance.[9] At that point, NHS England requested the delay (an additional 90 days) to put this service specification in place. It would therefore be expected that the service specification will be in place by the expiration of those 180 days (July 2015)and therefore is an issue that should have already been addressed and in accordance with this commitment.

As it was pointed out by stakeholders when this request was made, the new all oral treatments under consideration here will require less direct and regular patient interventions because of the absence of interferon injections and the more favourable side effect profiles when compared to the historical controls. The introduction of company funded patient support programmes will also reduce pressure on hospital based services significantly whilst serving to enhance home based patient care, an important consideration for NHS

England as it endeavours to deliver its proposed service specification for hepatology services across the country.

2.4 The request for real world evidence collection

AbbVie is fully supportive of real world data generation but does not agree that this is would be required in order to establish cost-effectiveness of Viekirax® and Exvirea®. This is particularly relevant given the large clinical trial programme that has studied these regimens in over 2000 patients worldwide, which has established a set of narrow confidence intervals for efficacy across different patient subgroups. Therefore, 'waiting' to generate additional real world evidence as opposed to accepting or rejecting a technology based on the provided clinical and cost effectiveness evidence available at the time of the appraisal is considered unacceptable.

3. The robustness of the evidence presented by NHS England

In the section below (see AbbVie's comments to the specific aspects of NHS England's responses), AbbVie challenges the evidence presented and relied upon by NHS England for their budget impact projections.

Fundamentally, it is difficult to satisfactorily address points raised by NHS England when the evidence has not been fully referenced. When the provenance is unclear it is not possible to make an informed comment. It is unclear in many areas what methodology has been adopted and what assumptions have been made as they are often not articulated (please see examples below). This has limited our ability to systematically address the points that have been made.

AbbVie understands NHS England has provided budget impact modelling for illustrative purposes only. In preparing an evidence submission for clinical and cost-effectiveness review by NICE, a manufacturer would be expected to provide rich detail regarding the assumptions, methodology and data used so as to guide the reviewers in their analysis. AbbVie believes it is reasonable therefore to suggest that similar scrutiny is applied by NICE to the grade of the evidence offered by NHS England's in its analyses as would be applied to a manufacturer's submission.

AbbVie's comments to the specific aspects of NHS England's responses to NICE clarification questions

Question 1. Confirmation as to the extent of the impact on its budget

NHS England states*: "The budget impact of the annual costs covering all drugs, all genotypes and all stages of disease for diagnosed patients is estimated to be between £285-£772 million per year. However, if a hypothetical, but unrealistic 100% of the estimated 80,000 population with confirmed chronic HCV comes forward for treatment our analysis suggests budget impact up to circa £1.9 billion."*

NHS England is projecting a hypothetical, but potential budget impact of £1.9 billion if a total diagnosed 80,000 individuals living with chronic HCV all came forward for treatment. No reference is supplied for the figure of 80,000 patients known to be infected with chronic HCV, and therefore it is impossible for AbbVie to ascertain its validity, nor the validity of the associated, hypothetical budget impact of £1.9 billion.

NHS England further states:
"If there is access to all patients of all stages of disease (F0-F4) with chronic HCV, NHS England estimated this could move patient treatment numbers to range from 7,000 (manageable but not currently affordable within current clinical services) to 20,000 patients per annum which will require significant service transformation along the entire pathway (from diagnosis to treatment) in order to meet expectation generated by the

guidance even if this were affordable, which it is currently not. NHS England believes it is unlikely that calls for treatment access will exceed 20,000 per annum, but there are international examples where annual access rates have increased to 40% of the 80,000 known infected patients (which would be 32,000 per annum).

The model and the figures presented are based on the following assumptions:
In the NICE ACD, the total population figure of 167,000 is used, within which it has been taken that 28,500 are known to the health system. 21% of the known patients have cirrhosis of which one third are decompensated cirrhotics. 14% of non cirrhotic patients are F3, 14% pf patients are interferon unsuitable. Similar proportions have been applied to the unknown (de novo) patients."

Estimated budget impact

	Patient numbers	*Cost £m*	*Patient numbers*	*Cost £m*	*Patient numbers*	*Cost £m*
Decompensated Cirrhosis	*1,100*	*60*	*1,100*	*60*	*1,100*	*60*
Compensated cirrhotic	*3,500*	*153*	*3,922*	*172*	*3,922*	*172*
Non cirrhotic (known to the system)	*2,400*	*72*	*14,978*	*286*	*22,095*	*422*
De Novo					*4,883*	*119*
Total	*7,000*	*285*	*20,000*	*518*	*32,000*	*772*

It is very difficult for AbbVie to establish a relationship between the patient numbers provided in the above budget impact table and NHS England's working assumptions supporting the budget impact calculations. NHS England has not provided any references for different patient numbers they have estimated or for the assumptions and key variables forming the basis for the stated range of budget impact scenarios presented above.

For example, it is unclear where the first figure of 7000 patients comes from. This number does not appear to have been calculated based on the epidemiology assumptions listed above. Further, the number of patients with compensated cirrhosis (3,500 patients) does not tally with the stated 21%, with a third of all cirrhotics representing patients with decompensated cirrhosis (1,100). 2,400 non-cirrhotic patients are stated to be known to the system, but no reference has been supplied for this estimate either.

The same applies to the estimate of 20,000 patients. It is possible that this figure has been borrowed from the manufacturers' submission (MS) for sofosbuivir + peginterferon + ribavirin, where the manufacturer states that *"20,000 patients are thought to be under care" (page 301 of the MS, TA 330)*[9]. However, the source for this figure is also unclear. The 20,000 patients figure is once again at odds with the above stated 28,500 patients which are quoted to be known to the health system.

Further, a reference has been made to international examples where the demand for treatment amongst patients has increased 40%. Countries or markets where such increases have been observed have different health systems with different capacities. However, without a reference to these actual markets, comparability and the relevance to the UK market cannot be established.

Lastly, NHS England estimated 1,100 patients with decompensated cirrhosis feed into the budget impact. However, AbbVie questions this patient estimate given our understanding that the majority of patients with

decompensated cirrhosis have already been treated under the early access scheme launched in 2013/2014 Therefore this number appears to be far too large an estimate. Again, without a proper reference, the entire budget impact statement is questionable.

Question 2. What other areas of treatment would be impacted by the need to find the cost of this technology?

a. The opportunity costs from funding new interventions

In response to this question, NHS England highlights recent empirical research by Claxton et al., 2015[6] on the cost-effectiveness threshold whereby "*the additional cost which results in 1 QALY being forgone by NHS patients is approximately £13,000.*" AbbVie wishes to re-iterate that the referenced work represents academic theory which has not been endorsed by the Department of Health, NICE, health economists, academics, industry or other interested parties. It is not relevant to the methodological approaches of current NICE processes. Therefore, the opportunity cost considered by NICE is represented by the NICE threshold range between £20,000 to £30,000 per QALY, below which technologies are generally considered cost-effective to justify use of NHS resources (the NICE Guide)[1].

b. The opportunity costs for the new treatments for chronic hepatitis C

Please see the above response. It is important to highlight that even the authors of the above referenced work state in their summary that "the limitation of currently available data means there is substantial uncertainty associated with the estimate of the overall threshold".[6] As already highlighted under the point 1.4, the 2014 PPRS agreement between the industry and the DoH does not support any decrease in the current cost-effectiveness threshold range. The suggested threshold of £13,000/QALY should not be mistaken for a guiding principle for NICE technology assessments.

c. The ability to undertake further research to support future care of HCV

"Until a NICE multiple technology appraisal can be carried out, NHS England would support with their Access Scheme Programmes a NICE 'Recommended with Research' position for patients without cirrhosis. This would harness substantial 'real world data on effectiveness of treatments and their combinations to deliver much greater value for money for the NHS than proceeding with a NICE recommendation through a single technology appraisal at this stage."

In accordance with the NICE Guide, when the evidence of clinical effectiveness or impact of a technology on other health outcomes is either absent, weak or uncertain, the Appraisal Committee may recommend that the technology is used only in the context of research or while the technology is recommended as an option, research is also conducted. As discussed under point 2.4 above, whilst in full support of the collection of real world evidence on clinical effectiveness, AbbVie do not agree that this is required for Viekirax® and Exvirea® to demonstrate their cost-effectiveness and the value they deliver to the NHS and, most importantly, to patients. In fact the manufacturer submission for Viekirax® and Exvirea® presents robust SVR12 results with six phase III trials repeatedly and consistently resulting in an SVR of around 97%, with tight confidence intervals (95%CI 95.16 to 97.94 for 611/631 GT1, non-cirrhotic, treatment-naive patients), across a broad spectrum of over 2,000 HCV GT1 patients. In the context of this evidence base it is unclear what area of clinical uncertainty would need to be addressed through a "Recommended with Research" decision.

AbbVie further believes that NICE currently has the appropriate mechanisms in place to evaluate evolving evidence bases over time through its current technology appraisal review processes. Uncertainty in the evidence base for any new medicine can be considered in this way rather than by recourse to 'recommended in research' which has the potential to limit the availability of treatments to only a small number of patients who would otherwise benefit from a cost-effective treatment across the NHS.

"The evaluations NHS England suggests should be carried out by a 'recommended with research' appraisal include:

- *A direct comparison of all relevant treatment options, including new treatments, watchful waiting and treatment sequences"*

While advising patients on management options, it is AbbVie's understanding that clinicians weigh the individual's chance of a sustained virological response, the stage and rate of progression of their disease as well as patient preference. Although a strategy of *watchful waiting* may appear rational and logical, there are many issues associated with it which do not appear to have been discussed or acknowledged by NHS England. These issues are summarised as follows:

1. It is important to note that AbbVie presented its cost-effectiveness analyses against a large number of comparators, all of which were considered by NICE to be in routine (i.e. established) practice in the NHS at the time of our submission. A *watchful waiting* strategy, defined by NHS England as monitoring of patients until their disease progresses to a more severe stage of the disease and then treating does not constitute established clinical practice or a standard of care. As such, it has not been considered in our cost-effectiveness analysis. AbbVie's view is that it should not be considered in the future as it does not represent an effective clinical management of patients with chronic hepatitis C.

2. Individual clinical decisions about treatment for HCV infection are complicated by the limited understanding of the natural history of a disease, inconsistent patient progression and the lack of reliable risk factors to assess patient probability of progression to advanced liver disease. While age and sex help explain some of the variation in progression, other sources of heterogeneity exist, but remain poorly defined. Therefore, until factors and sources of heterogeneity associated with progression to cirrhosis are better understood (to be able to truly distinguish between a patient that is more likely going to progress versus the one that will not), AbbVie believes that discrimination regarding treatment eligibility should not be based on a flawed and unethical treatment strategy.

3. In comparison to mild/moderate liver fibrosis (F0-F2), reaching F3 fibrosis is associated with a significant loss in health-related quality of life, lower SVR rates (associated with interferon-based regimens), greater on going monitoring costs and in general higher health burden and greater health care costs. In order to prevent liver complications and substantial loss in quality of life, patients logically should be treated before they reach advanced stages of liver disease. Therefore, for patients to most benefit from a treatment's enhanced efficacy, they should be treated before they progress to more severe health states such as F3 fibrosis. Therefore *watchful waiting* would deprive patients of significant benefits they could have had with earlier therapy.

4. Further, monitoring strategies and individualised treatment plans based on careful evaluation of the histological severity of the disease and patient need versus the expected outcome (efficacy) would have to be developed and implemented for the watchful waiting strategy to be successful. Studies have shown that a more reassuring histological presentation associated with the absence of cirrhosis does not necessarily correlate with a lower depression rate or perceived illness uncertainty in patients with chronic hepatitis C on *watchful waiting*.[10,11] NHS England do not appear to have given due regard to implications that *watchful waiting* or treatment sequencing may have for patients themselves nor have they defined in their response what the optimal strategy for patient monitoring and effective clinical management would look like (for example the frequency of fibroscans or biopsies). Different strategies have differential costs, efficacy and associative risks which would have to be appropriately assessed, but no such work appears to have been done by NHS England. In addition, there are real, practical concerns associated with the wait to treat strategy which appear to have been overlooked, for example, there are known measurement error issues associated with fibroscan testing. This means that an F2 patient cannot be reliably differentiated from an F3 patient using this diagnostic test. The

measurement error issue associated with fibroscan will be "inefficient" regardless of the direction of the error. Therefore, *watchful waiting* would potentially necessitate routine liver biopsies to be conducted on all non-cirrhotic patients to establish whether they are candidates for antiviral therapy. However, its expense and a risk of side-effects reduce its utility for frequent fibrosis screening.

5. There is evidence of an increased mortality associated with F4 fibrosis stage, with or without achievement of an SVR given an increased probability of transition into the hepatocellular carcinoma (HCC).[12] In other words, achieving an SVR in patients with advanced cirrhosis represents virologic "cure" but does not universally prevent decompensation or completely abolish the risk of hepatocellular carcinoma development. Thus, patients with advanced cirrhosis still need to be monitored after SVR for hepatic decompensation and must undergo regular HCC screening. Due to the above described measurement error, waiting to treat until a patient reaches F3 fibrosis would mean that some patients would progress to F4 quicker than expected and would be unnecessarily faced with an excess lifetime risk of death. Further, due to lack of the appropriate surveillance systems, and the socio-demographic backgrounds of many infected patients, there is a significant risk that patients undergoing *watchful waiting* would be lost to follow up and only re-engaging in healthcare once symptomatic and having progressed to F4 fibrosis. One could imagine a disparate recourse concerning disadvantaged minorities who carry the potential to be the most adversely affected by this strategy.

6. Lastly, as demonstrated in AbbVie's cost-effectiveness analysis, an antiviral treatment of non-cirrhotic patients (patients with histologically mild chronic hepatitis C) with Viekirax® and Exvirea®is fully cost-effective and thus represents an efficient use of NHS resources. Therefore, a *watchful waiting* strategy would fundamentally place individuals with mild and moderate hepatitis C at a disadvantage given that the quality and length of life restored to this patient group through treatment with Viekirax® and Exvirea® demonstrated a comparable value to that of patients with more advanced disease. For ICERs for GT1 and GT4 non-cirrhotic patients, please refer to AbbVie's response to ID731 specification for further work NACIC 17 April 2015.

- *Subgroup analyses by patients characteristics that affect the costs and benefits of treatment, such as genotype, prior treatment, prior treatment experience, interferon eligibility and severity of disease*

As already discussed under question 2c, the clinical trial programme for Viekirax and Exviera has studied these regimens in over 2000 patients worldwide, and has established a set of narrow confidence intervals for efficacy across different patient subgroups. As detailed in our evidence submission (please see Table 58 of the MS), 96.8% of HCV GT1 treatment naïve non-cirrhotic patients and 95.5% of HCV GT1 cirrhotic prior null responders achieved an SVR. Further, stepwise logistic-regression analysis showed that characteristics such as age, sex, race, ethnic group, IL28B genotype, fibrosis score, and baseline viral load (all historically associated with poor response) did not have a significant effect on the sustained virologic responses at post-treatment week 12 (please refer to section 6.5, page 153 of the MS). The efficacy of Viekirax and Exviera do not appear to depend on the majority of the above stated patient characteristics and therefore the utility of the suggested subgroup analyses is unclear in the context of AbbVie's licensed regimens.

- *The impact of uncertainty in the effects of treatment on the costs and benefits of the optimal strategies*

Please refer to the answers provided under question 2c and the bullet point above.

- *The costs and benefits of reducing onward transmission and reinfection*

As detailed in AbbVie's evidence submission, we assumed that individuals are not immune from being re-infected (please see page 245 of the MS). Reinfection after achieving SVR is represented in our cost-effectiveness model by a small, but constant risk irrespective of the stage of liver fibrosis if individuals continue to expose themselves to potential HCV infection or conduct risk-taking behaviours. Although the effect of re-infection on the ICERs is relatively small, its inclusion in the cost-effectiveness model means that the overall health gain associated with Viekirax and Exviera has diminished for factors outside of our control (i.e. individual behaviour). While a decrease in health effects arising from the inclusion of re-infection has been included in our analysis, an increase in health effects arising from a reduced onward transmission has been omitted, making our analysis a conservative one. One of the clinical benefits of being able to achieve high SVR rates with Viekirax and Exviera is a considerable reduction in the likelihood of onward transmission, especially amongst socially or geographically isolated communities. Not accounting for onward transmission has potentially underestimated the overall health benefit and the public health gain resulting from the very high levels of sustained virological response afforded by Viekirax and Exviera.

- *The level of investment to increase treatment uptake that is warranted alongside the optimal strategies in each of the patients groups*

AbbVie is not sure why this is relevant. NHS England's proposal seems to advocate restricting access to a cost-effective therapy in order to allow for the time required to assess how much additional resources would be needed to increase diagnosis and treatment uptake. If NHS England believes that the capacity and infrastructure of the current system to treat the projected number of patients is an issue, it would seem prudent to start using cost-effective therapies on patients known to the system whilst assessing and implementing programmes to increase diagnosis.

- *The characteristics required of any further new treatment in order for it to offer value to the NHS (threshold levels of effectiveness and costs)*

This point is unclear and requires further clarification in order to be addressed.

Question 3. What difference would it make if the timeframe was extended?

NHS England has not specifically asked for the timeframe for implementation to be extended, contrary to their request for a deferred funding period for NICE guidance on sofosbuvir for treating chronic hepatitis C (TA330).[9] However, NHS England requested "a pause" in the current STAs which would allow a re-working of the cost-effectiveness models to include watchful waiting and the formation of MTAs. AbbVie's position on watchful waiting and potential MTA has been discussed at length within this document (please refer to process issue 2.1 and our answer to NICE question 2c). In summary, whilst watchful waiting may have been considered an acceptable option for some people in the context of the peginterferon based antiviral treatments, watchful waiting should not be regarded as an acceptable treatment choice in the era of cost-effective all-oral, interferon-free treatment regimens such as Viekirax and Exviera.

Question 4. Whether there is a possibility of the overall budget being increased to meet the recommendation?

N/A

Question 5. Is NHSE's key point the % of the budget, which would be required to meet an unrestricted positive recommendation (for all eligible patients)? If so, what %?

Please refer to AbbVie's response detailed under section 1.2.

We trust that the detailed nature of this response underscores the concerns that AbbVie has about NHS England's proposals.

AbbVie would be pleased to provide any clarification or further information on any of the points raised within this consultation response and looks forward to further engagement with NICE during our appraisal.

References:

[1] NICE Guide to the Methods of Technology Appraisal. https://www.nice.org.uk/article/pmg9/chapter/6-the-appraisal-of-the-evidence-and-structured-decision-making Last accessed 10 June 2015

[2] Pharmaceutical Price Regulation Scheme 2014 – NICE position statement https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance Last Accessed 01 June 2015

[3] Pharmaceutical Price Regulation Scheme PPRS Payment for 2015:Written statement - HCWS90 http://www.parliament.uk/business/publications/written-questions-answers-statements/written-statement/Commons/2014-12-11/HCWS90/ Last accessed 10 June 2015

[4] A mandate from the Government to NHS England: April 2014 to March 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/383495/2902896_DoH_Mandate_Accessible_v0.2.pdf

[5] The Pharmaceutical Price Regulation Scheme 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/282523/Pharmaceutical_Price_Regulation.pdf Last accessed 10 June 2015.

[6] Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, Devlin N, Smith PC, Sculpher M. Methods for the estimation of the National Institute for health and Care Excellence cost-effectiveness threshold. *Health Technol Assess.* 2015; **19**(14)

[7] Accelerated Access Review. https://www.gov.uk/government/organisations/accelerated-access-review Last accessed 10 June 2015

[8] The NHS Constitution. http://www.nhs.uk/choiceintheNHS/Rightsandpledges/NHSConstitution/Documents/2013/the-nhs-constitution-for-england-2013.pdf Last accessed 10 June 2015

[9] Sofosbuvir for treating chronic hepatitis C. NICE technology appraisal guidance [TA330] https://www.nice.org.uk/guidance/ta330

[10] Bailey DE Jr(1), Landerman L, Barroso J, Bixby P, Mishel MH, Muir AJ, Strickland L, Clipp E. Uncertainty, symptoms, and quality of life in persons with chronic hepatitis C. 2009 Mar-Apr;50(2):138-46

[11] Colagreco JP(1), Bailey DE, Fitzpatrick JJ, Musil CM, Afdhal NH, Lai M. Watchful waiting: role of disease progression on uncertainty and depressive symptoms in patients with chronic hepatitis C. J Viral Hepat. 2014 Oct;21(10):727-33

[12] Cardoso et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: Incidence and survival in hepatitis C patients with advanced fibrosis. *Journal of Hepatology* 2010;**52**:652-657.