Daclatasvir for treating chronic hepatitis C

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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 Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
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1 Guidance

1.1 Daclatasvir is recommended as an option for treating chronic hepatitis C in adults, as specified in table 1, only if the company provides daclatasvir at the same price or lower than that agreed with the Commercial Medicines Unit.

Table 1 Daclatasvir for treating adults with chronic hepatitis C

<table>
<thead>
<tr>
<th>HCV genotype, liver disease stage</th>
<th>Treatment</th>
<th>Duration (weeks)</th>
<th>Recommendation according to treatment history</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Untreated</td>
</tr>
<tr>
<td>1, without cirrhosis</td>
<td>Daclatasvir + sofosbuvir</td>
<td>12</td>
<td>Recommended only if the person has significant fibrosis</td>
</tr>
<tr>
<td>4, without cirrhosis</td>
<td>Daclatasvir + sofosbuvir</td>
<td>12</td>
<td>Not recommended</td>
</tr>
<tr>
<td>1 or 4, with compensated cirrhosis</td>
<td>Daclatasvir + sofosbuvir (with or without ribavirin)</td>
<td>24</td>
<td>Not recommended</td>
</tr>
<tr>
<td>3, without cirrhosis</td>
<td>Daclatasvir + sofosbuvir</td>
<td>12</td>
<td>Not recommended</td>
</tr>
<tr>
<td>3, with compensated cirrhosis</td>
<td>Daclatasvir + sofosbuvir + ribavirin</td>
<td>24</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir + peginterferon alfa + ribavirin</td>
<td>24</td>
<td>Recommended only if the person has significant fibrosis or compensated cirrhosis</td>
</tr>
<tr>
<td>---</td>
<td>------------------------------------------</td>
<td>----</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>

Abbreviation: HCV, hepatitis C virus.

Significant fibrosis is defined as METAVIR fibrosis stages F3 and F4.

Treated – the person's hepatitis C has not adequately responded to interferon-based treatment.

1.2 It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.

1.3 People whose treatment with daclatasvir is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
2 The technology

2.1 Daclatasvir (Daklinza, Bristol-Myers Squibb) is an oral inhibitor of non-structural protein 5A, a multifunctional protein that is a component of the hepatitis C virus (HCV) replication complex. It inhibits both viral replication and assembly. Daclatasvir, in combination with other medicinal products, has a marketing authorisation in the UK for treating chronic hepatitis C virus infection in adults. The marketing authorisation recommends specific treatment combinations and durations, as follows:

- For genotype 1 or 4 HCV without cirrhosis: daclatasvir plus sofosbuvir for 12 weeks.
  - Prolonging treatment to 24 weeks may be considered for people who have had previous treatment including a NS3/4A protease inhibitor.

- For genotype 1 or 4 HCV with compensated cirrhosis: daclatasvir plus sofosbuvir for 24 weeks.
  - Shortening treatment to 12 weeks may be considered for untreated people with cirrhosis and positive prognostic factors.
  - Adding ribavirin may be considered for people with very advanced liver disease or with other negative prognostic factors.

- For genotype 3 HCV without cirrhosis: daclatasvir plus sofosbuvir for 12 weeks.

- For genotype 3 HCV with cirrhosis: daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks.

- For genotype 4 HCV: daclatasvir for 24 weeks plus peginterferon alfa and ribavirin for 24–48 weeks.

  The recommended dose of daclatasvir is 60 mg once daily.

2.2 The marketing authorisation recommendation for genotype 3 HCV was updated during the course of this appraisal to include a 12-week treatment in people without cirrhosis (see section 2.1). Formerly, the summary of product characteristics had recommended a 24-week treatment with daclatasvir plus sofosbuvir and ribavirin for genotype 3 HCV in people with compensated cirrhosis and/or who have had previous treatment.
2.3 Frequently reported adverse reactions with daclatasvir include fatigue, headache, and nausea. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The price of daclatasvir is £8172.61 per 28-tablet pack of 60 mg daclatasvir (excluding VAT; 'British national formulary' [BNF] March 2015). The average cost of daclatasvir plus sofosbuvir is £59,501 for a 12-week course and £119,002 for a 24-week course; when ribavirin is added these costs increase to £60,304 and £120,608 respectively. The average cost of a course of treatment with daclatasvir in combination with peginterferon alfa and ribavirin ranges from £53,628 to £58,221 (depending on whether peginterferon alfa and ribavirin are taken for 24 or 48 weeks; daclatasvir may only be taken for 24 weeks). The company has agreed a nationally available price reduction for daclatasvir with the Commercial Medicines Unit. The contract prices agreed through the framework are commercial in confidence.
3 The company's submission

The Appraisal Committee (section 7) considered evidence submitted by Bristol-Myers Squibb and a review of this submission by the Evidence Review Group (ERG; section 8).

Clinical effectiveness

Clinical trial data

3.1 The company presented clinical data for daclatasvir from 4 trials: AI444-040, AI444-042, AI444-010 and ALLY-3 (table 2). The focus of the company's submission was on treating chronic hepatitis C in people with significant fibrosis, which it defined as METAVIR fibrosis stage F3–F4 but with no cirrhosis, and in people with compensated cirrhosis (METAVIR fibrosis stage F4). The company indicated that this is an area of high unmet need because existing treatments have limited effectiveness and suboptimal safety profiles.

Table 2 Overview of clinical evidence for daclatasvir

<table>
<thead>
<tr>
<th>Study</th>
<th>AI444-040</th>
<th>AI444-010</th>
<th>AI444-042</th>
<th>ALLY-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>211</td>
<td>395</td>
<td>124</td>
<td>152</td>
</tr>
<tr>
<td>Location</td>
<td>Multicentre (US)</td>
<td>Multicentre (international; no UK sites)</td>
<td>Multicentre (international; 3 UK sites)</td>
<td>Multicentre (US and Puerto Rico)</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, open-label study</td>
<td>Double-blind RCT</td>
<td>Double-blind RCT</td>
<td>Open-label study</td>
</tr>
<tr>
<td>Genotypes of HCV included</td>
<td>1 (n=167), 2 (n=26), 3 (n=18)</td>
<td>1 (n=364), 4 (n=31)</td>
<td>4 (n=123)</td>
<td>3 (n=152)</td>
</tr>
<tr>
<td>Treatment history</td>
<td>● Untreated (genotypes 1, 2 and 3)</td>
<td>Untreated</td>
<td>Untreated</td>
<td>● Untreated ● Treated</td>
</tr>
<tr>
<td>Cirrhotic disease</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>Intervention</th>
<th>DCV + SOF (n=121)</th>
<th>DCV 20 mg(^3) + PR (n=159)</th>
<th>DCV + PR (n=158)</th>
<th>DCV + SOF (n=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>(-) Placebo + PR (n=78)</td>
<td>Placebo + PR (n=42)</td>
<td>(-)</td>
<td></td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>12 or 24 weeks</td>
<td>Up to 48 weeks</td>
<td>Up to 48 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Primary outcome(s)</td>
<td>SVR12</td>
<td>SVR24 and eRVR</td>
<td>SVR12</td>
<td>SVR12</td>
</tr>
</tbody>
</table>

**Abbreviations:** DCV, daclatasvir; eRVR, extended rapid virological response; PR, peginterferon alfa plus ribavirin; RBV, ribavirin; RCT, randomised controlled trial; SOF, sofosbuvir; SVR12/24, sustained virological response at follow-up week 12 or 24.

1. Previous treatment with boceprevir- or telaprevir-based therapy.
2. Unless otherwise stated, the dose of daclatasvir was 60 mg daily.
3. Unlicensed dose.

### 3.2 The following treatments were not studied in clinical trials, although they are recommended in the marketing authorisation for daclatasvir:

- Daclatasvir plus sofosbuvir for genotype 4 hepatitis C virus (HCV) in people without cirrhosis, and daclatasvir plus sofosbuvir with or without ribavirin for genotype 4 HCV in people with cirrhosis.

- Daclatasvir plus sofosbuvir and ribavirin for genotype 3 HCV (apart from a small number of people [n=5] in AI444-040).

- Daclatasvir plus peginterferon alfa and ribavirin (PR) for previously treated genotype 4 HCV.

### 3.3 All the included studies used sustained virological response (SVR) as the primary efficacy end point. This was defined as undetectable HCV RNA at a pre-specified time point (usually 12 weeks; SVR12) after treatment ends. None of the trials collected data on health-related quality of life. For all 4 trials, the primary analysis was based on a 'modified intention-to-treat' population (that is, all people who were randomised and had at least 1 dose of study treatment). In
addition, the company presented results with data imputation for AI444-040 and AI444-042 (in which it considered that people whose data were missing at follow-up week 12 had an SVR12 if their next recorded HCV RNA was below a certain threshold).

3.4 The marketing authorisation for daclatasvir recommends specific dosages and treatment durations based on genotype, cirrhosis status, treatment history and prognostic factors. The company presented results by genotype and treatment history for people with any fibrosis stage, and separately for 2 subgroups: people with significant fibrosis (fibrosis stage F3–F4 without cirrhosis) and those with compensated cirrhosis (fibrosis stage F4). Although fibrosis stage F4 is generally considered to be cirrhosis, the company clarified that fibrosis stage F3–F4 included people with fibrosis stage F3, as well as those with fibrosis stage F4 according to non-invasive tests (such as FibroTest or FibroScan), but in whom cirrhosis was not confirmed by liver biopsy. The marketing authorisation recommends different treatment durations by HCV genotype and patient population. The results presented by the company sometimes pooled these treatment durations as follows:

- **Genotype 1 HCV**
  - Daclatasvir plus sofosbuvir: 12 or 24 weeks' treatment is recommended; results were pooled across both treatment durations.
  - Daclatasvir plus sofosbuvir and ribavirin: 12 or 24 weeks' treatment is recommended; results were pooled across both treatment durations.

- **Genotype 3 HCV**
  - Daclatasvir plus sofosbuvir and ribavirin: 24 weeks' treatment is recommended; results were based on this treatment duration.
  - Daclatasvir plus sofosbuvir: results were based on 12 weeks' treatment.

- **Genotype 4 HCV**
  - Daclatasvir plus PR: 24 weeks of daclatasvir with 24–48 weeks of PR is recommended; results were based on this treatment duration.

Table 3 shows the clinical trial results in the modified intention-to-treat population and the 2 subgroups selected by the company. When data for the
modified intention-to-treat population were not reported in the company's submission, results with data imputation are presented instead.

### Table 3 Clinical trial results

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>Treatment history</th>
<th>Recommended treatment</th>
<th>Data source</th>
<th>SVR12 rate (%)</th>
<th>Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>mLTT (F0–F4)</td>
<td></td>
<td>People with significant fibrosis (fibrosis stage F3–F4) without cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Previously untreated¹</td>
<td>DCV+SOF</td>
<td>AI444-040</td>
<td>70/70 (100)</td>
<td>41/41 (100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCV+SOF+RBV</td>
<td>AI444-040</td>
<td>54/56 (96)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Previously treated</td>
<td>DCV+SOF</td>
<td>AI444-040</td>
<td>21/21 (100)</td>
<td>20/20 (100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCV+SOF+RBV</td>
<td>AI444-040</td>
<td>19/20 (95)</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Previously untreated</td>
<td>DCV+SOF</td>
<td>AI444-040</td>
<td>11/13 (85)²</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALLY-3</td>
<td>91/101 (90)</td>
<td>28/36 (78)</td>
<td>11/19 (58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCV+SOF+RBV</td>
<td>AI444-040</td>
<td>5/5 (100)²</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td></td>
<td>Previously treated</td>
<td>DCV+SOF</td>
<td>ALLY-3</td>
<td>44/51 (86)</td>
<td>15/21 (71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCV+SOF+RBV</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Previously untreated</td>
<td>DCV+PR</td>
<td>AI444-010</td>
<td>12/12 (100)</td>
<td>–</td>
</tr>
<tr>
<td>Previously treated</td>
<td>DCV+PR</td>
<td>67/82 (82)^2</td>
<td>7/9 (78)^2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>--------</td>
<td>-------------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DCV, daclatasvir; F0–F4, fibrosis stage; HCV, hepatitis C virus; mITT, modified intention-to-treat; PR, peginterferon alfa plus ribavirin; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response.

1 The SVR12 rate in people with previously untreated genotype 1 HCV who had 24 or 12 weeks of treatment was 100% and 97.6% respectively.

2 SVR rate with imputation.

**ERG comments**

3.5 The ERG stated that the company’s systematic review of clinical evidence was of a reasonable quality and used appropriate methods. It agreed that all the included trials were relevant to the decision problem. The ERG considered that the baseline demographics of people in the trials were broadly comparable to those of people with chronic hepatitis C in the UK.

3.6 AI444-040 and ALLY-3 did not have a control group. The ERG stated that this may have introduced bias because the observed effect could have been a placebo effect or confounded by an unknown variable. However, it indicated that SVR is an objective outcome measure, which reduces the risk of bias.

3.7 The ERG noted that the trials excluded the following groups in whom it considered the effectiveness of daclatasvir to be uncertain:

- People who are co-infected with HIV, or who have had, or are yet to have, a liver transplant.
- People who misuse alcohol or drugs or have been misusing them recently.

The company indicated that when daclatasvir received its marketing authorisation, no data were available for people co-infected with HIV or those who had, or were yet to have, a liver transplant. However, it noted that daclatasvir is not contraindicated in these people in the marketing authorisation.
3.8 The ERG stated that the results for people with previously treated HCV and those with compensated cirrhosis were based on small numbers of people, and so the reported SVR rates for these subgroups were uncertain. It acknowledged, however, that high rates of SVR were seen in the trials whether or not the disease was previously treated.

3.9 The ERG noted that the trial data for people who are ineligible for, or cannot tolerate, interferon were not used in the economic analyses.

**Meta-analysis and benchmarking study**

3.10 The company carried out a systematic review and a meta-analysis of clinical evidence for the following comparators:

- PR for genotypes 1–4 HCV
- telaprevir plus PR for genotype 1 HCV
- boceprevir plus PR for genotype 1 HCV.

The company used the results of the meta-analysis to inform a 'benchmarking' study; that is, a study to estimate the relative efficacy of an intervention (daclatasvir) studied in an uncontrolled trial (AI444-040) compared with standard of care. The benchmarking study suggested that daclatasvir plus sofosbuvir with or without ribavirin was superior to PR, telaprevir plus PR and boceprevir plus PR for genotype 1 HCV. Similarly, daclatasvir plus sofosbuvir and ribavirin was found to be superior to PR for genotype 3 HCV. For daclatasvir plus sofosbuvir without ribavirin, the evidence was limited, but suggested that daclatasvir plus sofosbuvir was likely to be superior to PR for genotype 3 HCV.

**Matching-adjusted indirect comparison**

3.11 The company carried out a 'matching-adjusted indirect comparison' for some comparisons in the scope for which there was no direct evidence. It presented 3 separate comparisons for genotypes 1 and 3 HCV and reported results for people with any fibrosis stage (F0–F4). Where the baseline characteristics were comparable, the company also provided results for those with fibrosis stage F3–F4. Overall, the matching-adjusted indirect comparison showed that SVR rates were higher for daclatasvir plus sofosbuvir with or without ribavirin, than for other treatments (sofosbuvir, simeprevir, telaprevir or boceprevir) in...
previously untreated genotype 1 HCV. For genotype 3 HCV, daclatasvir had higher SVR rates than PR, but no statistically significant differences in rates between daclatasvir plus sofosbuvir and sofosbuvir plus ribavirin were found.

Naive trial data

3.12 The company extracted naive trial data for all interventions and comparators in the scope. The company compiled all SVR rates based on the 'best available evidence', including those based on naive trial data. SVR rates were presented for significant fibrosis (F3–F4), compensated cirrhosis (F4) and any fibrosis stage (F0–F4).

ERG comments

3.13 The ERG stated that naive comparisons across trials with potentially different populations and methods provided weak evidence that was prone to bias. This was compounded by the assumptions that the company made when comparing SVR rates, some of which were clinically inappropriate (for example, in some comparisons, the company assumed that SVR rates were equal for people with or without cirrhosis and for previously untreated and previously treated HCV).

Adverse events

3.14 The company stated that in AI444-040 and ALLY-3, daclatasvir plus sofosbuvir with or without ribavirin was generally safe and well tolerated by all people. In AI444-042 and AI444-010 (daclatasvir plus PR compared with PR alone), the company indicated that the adverse events that occurred were those typically associated with PR, and that no adverse events specifically related to daclatasvir were identified. The matching-adjusted indirect comparison showed that daclatasvir-containing treatments generally had lower rates of adverse events than the comparator treatments.

ERG comments

3.15 The ERG stated that daclatasvir appeared well tolerated and safe.
Cost effectiveness

Model structure

3.16 The company's model incorporated a decision tree and a Markov model, which was based on published models that had been used in previous technology appraisals for boceprevir, telaprevir, and PR. The model evaluated 3 daclatasvir treatments for chronic hepatitis C:

- daclatasvir plus sofosbuvir for genotypes 1, 3 and 4 HCV
- daclatasvir plus sofosbuvir and ribavirin for genotype 3 HCV
- daclatasvir plus PR for genotype 4 HCV.

The company's model used a lifetime time horizon (80 years). The cycle length was 4 weeks in the decision tree and 1 year in the Markov model. Costs and health effects were discounted at an annual rate of 3.5%. The perspective of the analysis on costs was that of the NHS and personal social services.

3.17 The model included 5 states; chronic hepatitis C, decompensated cirrhosis, hepatocellular carcinoma, liver transplant and death, with the chronic hepatitis C state further split by fibrosis stage into 5 sub-states. The decision tree captured the first year in the model, including the treatment period. People entered the model at 50 years, with HCV defined by its fibrosis stage (F0, F1, F2, F3 or F4). After treatment, people remained in their baseline state for the rest of the first year, but health-related quality of life improved in those who had an SVR (see section 3.35). Treatment stopped in the model because of adverse events, or if a rapid response occurred (for response-guided treatments only; telaprevir plus PR for previously untreated genotype 1 HCV, boceprevir plus PR for previously untreated genotype 1 HCV, and daclatasvir plus PR for previously untreated genotype 4 HCV). After the first year, people moved to the Markov model. In those who had an SVR, the disease could not progress to decompensated cirrhosis or hepatocellular carcinoma. People who did not have an SVR transitioned through fibrosis stages F0 to F4. Once they reached fibrosis stage F4, their disease could progress to decompensated cirrhosis or hepatocellular carcinoma. From decompensated cirrhosis, people could remain in that state, develop hepatocellular carcinoma, have a liver transplant or die. Those who developed hepatocellular carcinoma could remain in that state, have
a liver transplant or die. After having a liver transplant, people could only move to the death state.

**ERG comments**

3.18 The ERG commented that the model structure was generally appropriate and similar to models used in previous hepatitis C appraisals. It noted that the health states were defined by METAVIR fibrosis stages. The ERG highlighted that the available data were not typically stratified by METAVIR fibrosis stage, and so the company had to extrapolate estimates across different groups. Because of this, the ERG considered that relevant data may have been excluded.

3.19 The ERG noted that, in the company's base-case assumptions, people who had an SVR could not develop decompensated cirrhosis or hepatocellular carcinoma. It stated that existing evidence suggests that disease progression can still occur in people who have an SVR, although at a lower rate than in those who do not.

**Populations, intervention and comparators**

3.20 The company's base-case analysis comprised 2 subgroups; people with significant fibrosis (fibrosis stage F3–F4), and those with compensated cirrhosis (fibrosis stage F4). Within each subgroup, the company considered 3 further groups: people with previously untreated HCV, people with previously treated HCV, and people who are ineligible for, or cannot tolerate, interferon. For each of the groups, the company modelled the appropriate intervention and comparator treatments recommended in their respective marketing authorisations (table 4). 'No treatment' was included as a comparator in all the analyses. Treatment duration in the model differed between people with or without cirrhosis, in line with the marketing authorisation. The company could not find data for some comparators, which it did not include in the cost-effectiveness analysis (these are shown with in square brackets in table 4).

**Table 4 Intervention and comparator treatments modelled**

<table>
<thead>
<tr>
<th>Treatment (treatment duration in weeks, treatment duration for PR in weeks, if applicable)</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Genotype</th>
<th>Previously untreated HCV</th>
<th>Previously treated HCV</th>
<th>Interferon-ineligible or -intolerant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1 HCV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Without cirrhosis (F3–F4)</strong></td>
<td><strong>With cirrhosis (F4)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DCV+SOF</td>
<td>(12)</td>
<td>DCV+SOF</td>
</tr>
<tr>
<td></td>
<td>[SOF+PR]</td>
<td>(12, 12)</td>
<td>[SOF+PR]</td>
</tr>
<tr>
<td></td>
<td>SOF+PR</td>
<td>(12, 24)</td>
<td>SOF+RBV</td>
</tr>
<tr>
<td></td>
<td>SMV+PR</td>
<td>(12, 24–48)</td>
<td>SMV+SOF</td>
</tr>
<tr>
<td></td>
<td>TVR+PR</td>
<td>(32, 28–48)</td>
<td>TVR+PR</td>
</tr>
<tr>
<td></td>
<td>BOC+PR</td>
<td>(48)</td>
<td>BOC+PR</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td></td>
<td>PR</td>
</tr>
<tr>
<td>Genotype 3 HCV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Without cirrhosis (F3–F4)</strong></td>
<td><strong>With cirrhosis (F4)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DCV+SOF+RBV</td>
<td>(24)</td>
<td>DCV+SOF+RBV</td>
</tr>
<tr>
<td></td>
<td>[SOF+PR]</td>
<td>(12, 12)</td>
<td>[SOF+PR]</td>
</tr>
<tr>
<td></td>
<td>SOF+RBV</td>
<td>(24)</td>
<td>SOF+RBV</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td></td>
<td>PR</td>
</tr>
<tr>
<td>Genotype 4 HCV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DCV+SOF+RBV</td>
<td>(24)</td>
<td>DCV+SOF+RBV</td>
</tr>
<tr>
<td></td>
<td>[SOF+PR]</td>
<td>(12, 12)</td>
<td>[SOF+PR]</td>
</tr>
<tr>
<td></td>
<td>SOF+RBV</td>
<td>(24)</td>
<td>SOF+RBV</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td></td>
<td>PR</td>
</tr>
</tbody>
</table>
### Abbreviations
- **BOC**: boceprevir
- **DCV**: F3 or F4, fibrosis stage; daclatasvir
- **GT**: genotype
- **HCV**: hepatitis C virus
- **PR**: peginterferon alfa plus ribavirin
- **RBV**: ribavirin
- **SMV**: simeprevir
- **SOF**: sofosbuvir
- **TVR**: telaprevir

Square brackets [ ] indicate that the company did not find data for these comparators.

### ERG comments

3.21 In the company's submission, significant fibrosis referred to fibrosis stage F3, as well as fibrosis stage F4 according to non-invasive tests (such as FibroTest or FibroScan), but cirrhosis was not confirmed by liver biopsy. The ERG stated that fibrosis stage F3–F4 could be simplified to include only people with fibrosis stage F3 because those with fibrosis stage F4 and unconfirmed cirrhosis represent a small group.

3.22 The ERG commented that the comparators considered by the company reflected those in the scope. However, it noted that, for certain subgroups, some relevant comparators were excluded and some irrelevant comparators were included.

- **Relevant comparators that were excluded**: the ERG noted that the company excluded comparators that were recently recommended by NICE (subject to publication at the time) because data were lacking (see section 3.20). The ERG did not consider this justification to be adequate because these comparators are expected to be used in clinical practice. This included:

<table>
<thead>
<tr>
<th>Without cirrhosis (F3–F4)</th>
<th>DCV+SOF</th>
<th>(12)</th>
<th>DCV+SOF</th>
<th>(12)</th>
<th>DCV+SOF</th>
<th>(12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCV+PR</td>
<td>(24, 24–48)</td>
<td>(12, 24, 48)</td>
<td>DCV+PR</td>
<td>[SOF+PR]</td>
<td>(12, 24)</td>
<td>SMV+PR</td>
</tr>
<tr>
<td>SOF+PR</td>
<td>(12, 12)</td>
<td>(48)</td>
<td>DCV+PR</td>
<td>[SOF+PR]</td>
<td>(12, 12)</td>
<td>SMV+PR</td>
</tr>
<tr>
<td>SMV+PR</td>
<td>(12, 24)</td>
<td>(48)</td>
<td>DCV+PR</td>
<td>[SOF+PR]</td>
<td>(12, 48)</td>
<td>SMV+PR</td>
</tr>
<tr>
<td>PR</td>
<td>(48)</td>
<td></td>
<td>DCV+PR</td>
<td>[SOF+PR]</td>
<td>(48)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>With cirrhosis (F4)</th>
<th>DCV+SOF</th>
<th>(24)</th>
<th>DCV+SOF</th>
<th>(24)</th>
<th>DCV+SOF</th>
<th>(24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCV+PR</td>
<td>(24, 24–48)</td>
<td>(12, 24)</td>
<td>DCV+PR</td>
<td>[SOF+PR]</td>
<td>(12, 12)</td>
<td>SMV+PR</td>
</tr>
<tr>
<td>SOF+PR</td>
<td>(12, 12)</td>
<td>(48)</td>
<td>DCV+PR</td>
<td>[SOF+PR]</td>
<td>(12, 48)</td>
<td>SMV+PR</td>
</tr>
<tr>
<td>SMV+PR</td>
<td>(12, 12)</td>
<td>(48)</td>
<td>DCV+PR</td>
<td>[SOF+PR]</td>
<td>(12, 48)</td>
<td>SMV+PR</td>
</tr>
<tr>
<td>PR</td>
<td>(48)</td>
<td></td>
<td>DCV+PR</td>
<td>[SOF+PR]</td>
<td>(48)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BOC, boceprevir; DCV, F3 or F4, fibrosis stage; daclatasvir; GT, genotype; HCV, hepatitis C virus; PR, peginterferon alfa plus ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

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- **Genotype 1:** sofosbuvir plus PR for previously treated HCV in people with or without cirrhosis.

- **Genotype 3:** sofosbuvir plus PR for previously untreated HCV in people with cirrhosis.

- **Genotype 4:**
  - Sofosbuvir plus PR for previously treated HCV in people with cirrhosis.
  - Simeprevir plus sofosbuvir for people with or without cirrhosis who are ineligible for, or cannot tolerate, interferon.

- **Irrelevant comparators that were included:** the ERG noted that some of the comparators the company included in its analysis were not recommended by NICE:
  - **Genotype 1:** sofosbuvir plus ribavirin for people with or without cirrhosis who are ineligible for, or cannot tolerate, interferon.
  - **Genotype 3:** sofosbuvir plus ribavirin (except for people with cirrhosis who are ineligible for, or cannot tolerate, interferon; subject to publication at the time).
  - **Genotype 4:** sofosbuvir plus PR for previously untreated HCV in people without cirrhosis.

3.23 Best supportive care (watchful waiting) was a comparator in the scope for all HCV genotypes. However, the company modelled a 'no treatment' option instead. The ERG considered that a 'watchful waiting' strategy, by which the disease is monitored and treated if needed, was a relevant comparator, particularly for people with less severe disease in whom treatment may start at a later stage when the disease progresses.

3.24 The ERG noted that the marketing authorisations for daclatasvir, sofosbuvir and simeprevir allow for more than 1 treatment duration, and that modelling only 1 treatment duration may underestimate or overestimate the cost of treatment:

- **Genotypes 1, 3 and 4:** 12 weeks' treatment with sofosbuvir plus PR is recommended. However, this can be extended to 24 weeks in people with certain characteristics associated with poor prognosis. In its base case, the company modelled 12 weeks' treatment.

- **Genotypes 1 and 4:**
- **People without cirrhosis:** 12 weeks' treatment with daclatasvir plus sofosbuvir is recommended and was modelled by the company. However, this can be extended to 24 weeks in people who had previous treatment including a NS3/4A protease inhibitor.

- **People with cirrhosis:** 24 weeks' treatment with daclatasvir plus sofosbuvir with or without ribavirin is recommended and was modelled by the company. However, this can be shortened to 12 weeks in previously untreated HCV in people with certain characteristics associated with good prognosis.

- **Genotype 4 (people with or without cirrhosis):** for simeprevir plus PR for previously treated HCV, simeprevir is recommended for 24 weeks, whereas PR is recommended for 24–48 weeks depending on the type of previous response. In its base case, the company modelled 48 weeks' treatment with PR.

3.25 The ERG commented that the company considered people with previously treated HCV as a single group. It stated that the type of response to previous treatment (no response, partial response, or relapse) predicts the SVR rate after subsequent treatment, and that collectively modelling all people with previously treated HCV was unlikely to reflect the heterogeneity within this group.

3.26 The ERG noted that people with previously treated genotype 1 HCV included only those whose disease had failed to respond to protease inhibitors (boceprevir or telaprevir). In response to a clarification request from the ERG, the company stated that established practice for treating genotype 1 HCV is protease inhibitor triple therapy with boceprevir or telaprevir, and that those in whom PR alone had failed would represent a much smaller group. However, the ERG’s clinical experts indicated that approximately half the treated population would have had PR rather than a protease inhibitor, and so the ERG considered that this assumption may be inappropriate.

**SVR rates**

3.27 All SVR rates applied in the base case were based on unadjusted comparisons of naive trial data. Data for daclatasvir in people who were ineligible for, or cannot tolerate, interferon were not available from clinical trials. Therefore, the company assumed that the efficacy of daclatasvir in this group was the same as in people whose HCV was previously untreated with the same genotype and fibrosis stage (F3–F4, or F4).
3.28 Although recommended in the marketing authorisation, some daclatasvir treatments were not studied in clinical trials, or were studied in small numbers of people:

- Daclatasvir plus sofosbuvir and ribavirin for genotype 3 HCV: the company obtained SVR rates from a small group in AI444-040 (n=5), who had previously untreated HCV without cirrhosis. It extrapolated the SVR12 rate in this group (100%) to people with previously untreated HCV with cirrhosis, and to people with previously treated HCV with or without cirrhosis.

- Daclatasvir plus sofosbuvir for genotype 4 HCV in people without cirrhosis: the company used the SVR12 rate for genotype 1 HCV in people without cirrhosis in AI444-040 (previously untreated: 100%; previously treated: 100%).

- Daclatasvir plus sofosbuvir with or without ribavirin for genotype 4 HCV in people with cirrhosis: for daclatasvir plus sofosbuvir without ribavirin, the company used the SVR12 rate for genotype 1 HCV in people without cirrhosis in AI444-040 (previously untreated: 100%; previously treated: 100%); daclatasvir plus sofosbuvir and ribavirin was not assessed.

- Daclatasvir plus PR for previously treated genotype 4 HCV: the company used the same SVR12 rates as observed in previously untreated genotype 4 HCV in AI444-042 for people without cirrhosis (81.2%) and people with cirrhosis (77.8%).

3.29 For genotype 3 HCV, the company modelled daclatasvir plus sofosbuvir for 24 weeks for people with compensated cirrhosis using data from AI444-040. For those with significant fibrosis, the base-case analysis modelled 12 weeks' treatment without ribavirin using data from ALLY-3.

**ERG comments**

3.30 The ERG noted that the company obtained the SVR rates from individual trial groups. It stated that this represented ‘naive’ indirect comparisons that were highly uncertain, and that this was compounded by generalising SVR rates across populations with different patient and disease characteristics. This was of particular concern for people with significant fibrosis because data were almost never reported specifically for this group. In general, the ERG considered that the company had selected appropriate SVR rates given the available evidence, but it was particularly concerned about the SVR rates applied for 3 treatments:
• Daclatasvir plus sofosbuvir for previously untreated, genotype 1 HCV in people who have significant fibrosis: the ERG stated that the source of the SVR rate was unclear and appeared to have been adjusted.

• Sofosbuvir plus ribavirin for people with genotype 3 HCV who are ineligible for, or cannot tolerate, interferon and who have compensated cirrhosis: the ERG indicated that the SVR rate did not reflect the recommended treatment duration (24 weeks), whereas an alternative SVR rate that did was available.

• Sofosbuvir plus PR for previously untreated genotype 4 HCV in people who have compensated cirrhosis: the ERG noted that the SVR rate was based on 2 people, and so was unreliable.

Model transitions

3.31 The company estimated the rates at which people transition between the different states in the model, using a study by Thein et al. (2008). This study allowed transition rates to be estimated for genotype 1 and non-genotype 1 HCV. For genotypes 3 and 4 HCV, the company used the transition rates for non-genotype 1. To estimate the transition rates for genotype 3 HCV, the company applied multipliers to the baseline transition rates for non-genotype 1 because genotype 3 HCV is typically associated with increased rates of disease progression.

ERG comments

3.32 The ERG commented that the data from Thein et al. were based on aggregate data and that the methods applied were not yet validated. Therefore it stated that these should be considered with caution. The ERG pointed out that individual UK patient data on disease progression were available and may be considered a more appropriate source.

3.33 The ERG stated that applying the transition rates for non-genotype 1 HCV to genotype 4 HCV was not appropriate. It noted that in the study by Thein et al. almost all people with non-genotype 1 HCV had either genotype 2 or 3 HCV. In addition, the ERG noted that existing evidence suggested that there is no difference between the transition probabilities for genotypes 1 and 4 HCV, and considered it more appropriate to apply the transition rates for genotype 1 HCV to genotype 4 HCV.
To estimate the transition rates for genotype 3 HCV, the company applied multipliers to the baseline transition rates for non-genotype 1 HCV in the study by Thein et al. The ERG stated that the multipliers represented the increased rate of transitions for genotype 3 HCV compared with genotype 1 HCV, and so the multipliers should be applied to the baseline transition rates for genotype 1 HCV.

Utility values and costs

The clinical trials for daclatasvir did not collect health-related quality of life data, so the company sourced utility values from the published literature. Based on a study by Wright et al. (2006), it assigned a utility value to each state and sub-state in the model. This study categorised chronic hepatitis C by disease severity rather than fibrosis stage, reporting a utility value of 0.77 for mild disease, 0.66 for moderate disease, and 0.55 for severe disease. Therefore, the company assumed that mild disease was fibrosis stage F0 or F1, moderate disease was fibrosis stage F2 or F3, and severe disease was fibrosis stage F4. Achieving SVR in a given state in the model increased the utility value for that state: from fibrosis stage F0 or F1, the utility value increased to 0.82 (an increase of 0.05), and from F2 or F3, it increased to 0.72 (an increase of 0.06). When SVR was achieved from fibrosis stage F4, the company assumed that the utility value was the same as that for achieving SVR from fibrosis stage F2 or F3 (0.72; an increase of 0.17). The company also applied utility decrements to reflect the decrease in health-related quality of life associated with adverse events.

The base-case analysis included treatment and monitoring costs, and those associated with the modelled health states. Drug acquisition costs were taken from the British national formulary. The company stated that monitoring is particularly important in managing chronic hepatitis C. It therefore applied monitoring costs in the model every 4 weeks, up to week 48 after treatment started, based on a published economic evaluation for chronic hepatitis C. These costs captured outpatient visits, physician and nurse time, blood and liver function tests, and the assessment of viral load. Health-state costs were sourced from the published literature. The company did not model the costs associated with adverse events in its base case because adverse events were inconsistently reported across clinical trials, and the cost of managing them generally has little
impact on cost effectiveness. However, it included them in a deterministic sensitivity analysis.

**ERG comments**

3.37 The ERG considered the company's approach to estimating health-related quality of life to be generally appropriate. However, it noted that people who had an SVR in fibrosis stage F4 showed a greater increase in utility (0.17) than those who achieved it from F0 or F1 (0.05), or F2 or F3 (0.06), and had the same absolute utility value. The ERG stated that this assumption did not reflect the available evidence, preferring to assume that SVR results in equal utility increments across the different fibrosis stages from which people may start treatment.

3.38 The ERG noted that the model included monitoring costs for a year after treatment ends, for people who had an SVR. The ERG's clinical experts stated that people with cirrhosis who had an SVR would continue to be monitored throughout their lifetime because of the risk of developing hepatocellular carcinoma. They advised that the monitoring typically consists of ultrasound scans of the liver every 6 months.

**Company's base-case results and sensitivity analysis**

3.39 The company initially presented results from its base case, deterministic and probabilistic sensitivity analyses, a threshold analysis and 3 scenario analyses. All results were based on pairwise comparisons (that is, comparing daclatasvir with each of its comparators individually). In response to a request for clarification from the ERG, the company updated its base-case model with the following changes:

- Applying a utility decrement for aging to capture the effect of age on health-related quality of life.
- Applying the transition rate multipliers for genotype 3 HCV to the transition rates estimated for genotype 1 HCV (see section 3.34).
- Including both daclatasvir plus sofosbuvir and daclatasvir plus PR within the same analyses for people with genotype 4 HCV (except for those who are ineligible for, or cannot tolerate, interferon in whom only daclatasvir plus sofosbuvir would be
appropriate).

The company presented the updated base-case results as a fully incremental analysis (that is, comparing all technologies simultaneously from the least costly to the most costly), as well as pairwise incremental cost-effectiveness ratios (ICERs). It also updated its probabilistic sensitivity analysis and threshold analysis, but presented pairwise ICERs only. An updated deterministic sensitivity analysis was not presented. The results of the updated base case are presented in tables 5 and 6.

3.40 The company's deterministic sensitivity analyses (which did not incorporate the changes in the updated model) suggested that the model was generally robust to changes in parameter values. The cost effectiveness of daclatasvir was most sensitive to the SVR rate, the duration of treatment, the time horizon of the model, and the discount rate for costs and quality-adjusted life-years (QALYs). In the company's updated probabilistic sensitivity analysis, most pairwise comparisons had either a high or low probability of being cost effective at a maximum acceptable ICER of £20,000 per QALY gained. The company's updated threshold analysis found that when daclatasvir was cost effective at a maximum acceptable ICER of £20,000 per QALY gained in a given pairwise comparison, the SVR rate had to be reduced significantly before the ICER exceeded £20,000 per QALY gained.

**ERG comments**

3.41 The ERG stated that the deterministic sensitivity analyses, probabilistic sensitivity analysis, and threshold analysis used pairwise rather than incremental ICERs, which the ERG considered inappropriate. Furthermore, it noted that the company presented the deterministic sensitivity analyses within the initial base case, without incorporating the changes requested by the ERG (see section 3.39).

3.42 The ERG commented that the company did not justify the choice of the alternative values used in the deterministic sensitivity analyses, and did not test potentially important inputs and assumptions. In addition, it stated that the company's probabilistic sensitivity analysis did not provide ICERs based on the probabilistic results (except for some graphical representations), nor did it assign distributions to baseline characteristics appropriately.
3.43 The ERG presented an amended base case with the following changes to the company’s model:

- **Genotypes 1, 3 and 4**: including the relevant comparators for which the company did not present cost-effectiveness results, and excluding the comparators that were included in the scope but subsequently not recommended by NICE (see section 3.22).

- Using alternative SVR rates for the following 3 treatments (see section 3.30).
  - **Genotype 1**: daclatasvir plus sofosbuvir for previously untreated HCV in people with significant fibrosis (F3–F4) – 100% instead of 95%.
  - **Genotype 3**: sofosbuvir plus ribavirin for people who are ineligible for, or cannot tolerate, interferon and who have compensated cirrhosis (F4) – 92.3% instead of 21.4%.
  - **Genotype 4**: sofosbuvir plus PR for previously untreated HCV in people with compensated cirrhosis (F4) – 79.6% instead of 50%.

- **Genotype 4**: Applying the transition rates for genotype 1 HCV estimated from the study by Thein et al. to genotype 4 HCV (see section 3.33).

- **Genotypes 1, 3 and 4**: Assuming a relatively small risk of disease progression to decompensated cirrhosis or hepatocellular carcinoma in people with compensated cirrhosis who had an SVR (see section 3.19).

- **Genotypes 1, 3 and 4**: Assuming equal utility increments for having an SVR in fibrosis stage F4 or in fibrosis stage F2 or F3 (0.05; see section 3.37).

- **Genotypes 1, 3 and 4**: Applying the cost of ultrasound scans of the liver every 6 months (monitoring costs) to people with compensated cirrhosis who had an SVR (see section 3.38).

3.44 A comparison of the results from the ERG's amended base case (that is, combining all the above-listed changes) and the company's base case is presented in tables 5 and 6. The ERG indicated that the difference between its results and the company's base-case results was mostly driven by amending the comparators and SVR rates.
### Table 5 Comparison of cost-effectiveness results from the ERG’s and company’s base cases: significant fibrosis (fibrosis stage F3–F4 without cirrhosis)

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>Treatment history</th>
<th>Daclatasvir treatment</th>
<th>Incremental ICER (£/QALY gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Company’s base case</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCV+SOF</td>
<td>25,454 (versus SOF+PR)</td>
</tr>
<tr>
<td>1</td>
<td>Previously untreated HCV</td>
<td></td>
<td>15,687 (versus SOF+PR)</td>
</tr>
<tr>
<td></td>
<td>Previously treated HCV</td>
<td>DCV+SOF</td>
<td>4587 (versus no treatment)</td>
</tr>
<tr>
<td></td>
<td>Interferon-ineligible or -intolerant</td>
<td></td>
<td>9607 (versus no treatment)</td>
</tr>
<tr>
<td>3</td>
<td>Previously untreated HCV</td>
<td>DCV+SOF</td>
<td>Extendedly dominated</td>
</tr>
<tr>
<td></td>
<td>Previously treated HCV</td>
<td></td>
<td>Dominate (by SOF+PR)</td>
</tr>
<tr>
<td></td>
<td>Interferon-ineligible or -intolerant</td>
<td></td>
<td>7523 (versus no treatment)</td>
</tr>
<tr>
<td>4</td>
<td>Previously untreated HCV</td>
<td>DCV+PR</td>
<td>Dominate (by SOF+PR)</td>
</tr>
<tr>
<td></td>
<td>DCV+SOF</td>
<td>868,019 (versus SOF+PR)</td>
<td>36,203 (versus SMV+PR)</td>
</tr>
<tr>
<td></td>
<td>Previously treated HCV</td>
<td>DCV+PR</td>
<td>Extendedly dominated</td>
</tr>
<tr>
<td></td>
<td>DCV+SOF</td>
<td></td>
<td>(by no treatment and DCV+SOF)</td>
</tr>
</tbody>
</table>

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### Table 6 Comparison of cost-effectiveness results from the ERG's and company's base cases: compensated cirrhosis (fibrosis stage F4)

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>Treatment history</th>
<th>Daclatasvir treatment</th>
<th>Incremental ICER (£/QALY gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Company's base case</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>ERG's amended base case</strong></td>
</tr>
<tr>
<td></td>
<td>Previously untreated HCV</td>
<td>DCV+SOF</td>
<td><strong>61,484</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>(versus SOF+PR)</strong></td>
</tr>
<tr>
<td>1</td>
<td>Previously treated HCV</td>
<td>DCV+SOF</td>
<td><strong>12,443</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>(versus no treatment)</strong></td>
</tr>
<tr>
<td>3</td>
<td>Interferon-ineligible or -intolerant</td>
<td>DCV+SOF</td>
<td><strong>151,547</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>(versus SMV+SOF)</strong></td>
</tr>
<tr>
<td>3</td>
<td>Previously untreated HCV</td>
<td>DCV+SOF</td>
<td><strong>89,126</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>(versus SOF+RBV)</strong></td>
</tr>
<tr>
<td>3</td>
<td>Previously treated HCV</td>
<td>DCV+SOF</td>
<td><strong>72,662</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>(versus SOF+PR)</strong></td>
</tr>
</tbody>
</table>

Abbreviations: DCV, daclatasvir; ERG, Evidence Review Group; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; PR, peginterferon alfa plus ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

Dominated, treatment gives fewer QALYs at greater cost than the comparator.

Extendedly dominated, a combination of 2 of its comparators provides equal health at a reduced cost.
<table>
<thead>
<tr>
<th></th>
<th>Interferon-ineligible or -intolerant</th>
<th>Previously untreated HCV</th>
<th>Previously treated HCV</th>
<th>Interferon-ineligible or -intolerant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11,781 (versus no treatment)</td>
<td>DCV+PR</td>
<td>DCV+PR</td>
<td>DCV+SOF (versus no treatment)</td>
</tr>
<tr>
<td></td>
<td>172,219 (versus SOF+RBV)</td>
<td>Dominated (by SMV+PR)</td>
<td>Dominated (by SMV+PR)</td>
<td>12,443 (versus no treatment)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80,548 (versus SMV+PR)</td>
<td>150,076 (versus SMV+PR)</td>
<td>190,379 (versus SMV+SOF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3481 (versus PR)</td>
<td>52,459 (versus SOF+PR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>41,522 (versus DCV+PR)</td>
<td>73,768 (versus DCV+PR)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DCV, daclatasvir; ERG, Evidence Review Group; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; PR, peginterferon alfa plus ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

Dominated, treatment gives fewer QALYs at greater cost than the comparator. Extendedly dominated, a combination of 2 of its comparators provides equal health at a reduced cost.

Company's additional evidence

3.45 The company submitted 'real-world' evidence from worldwide compassionate use and early-access programmes that were set up to use new direct-acting antivirals. This included data from the following programmes:

- Temporary Authorization of Use: French compassionate use programme for daclatasvir.
- EU Compassionate Use Programme: daclatasvir plus sofosbuvir with or without ribavirin.
- French cohort ANRS CO22 HEPATHER: sofosbuvir-based regimens.
HCV-TARGET: sofosbuvir-based regimens (did not include daclatasvir treatments).

The programmes generally included people with more severe disease than in the original submission, including people with decompensated cirrhosis.

The company also presented data for genotype 3 HCV from a UK cohort of the EU Compassionate Use Programme for daclatasvir plus sofosbuvir with or without ribavirin.

Results from the French Temporary Authorization of Use are designated as commercial in confidence by the company and cannot be presented here, but results from the other programmes are presented in table 7. The NHS England Early Access Programme used a 12-week treatment duration in people with decompensated cirrhosis, whereas the EU Compassionate Use Programme used a 24-week treatment duration in people at risk of hepatic decompensation or death.

Table 7 Real-world data for daclatasvir treatments

<table>
<thead>
<tr>
<th>Source</th>
<th>End point</th>
<th>SVR rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Genotype 1 HCV</td>
<td>Genotype 3 HCV</td>
</tr>
<tr>
<td></td>
<td>DCV + SOF</td>
<td>DCV + SOF + RBV</td>
</tr>
<tr>
<td>NHS Early Access Programme</td>
<td>SVR4</td>
<td>4/5 (80)</td>
</tr>
<tr>
<td>EU Compassionate Use Programme</td>
<td>SVR12</td>
<td>77/78 (99)</td>
</tr>
<tr>
<td>UK cohort of EU Compassionate Use Programme</td>
<td>SVR12</td>
<td>97/120 (80.8)</td>
</tr>
</tbody>
</table>

Abbreviations: DCV, daclatasvir; HCV, hepatitis C virus; RBV, ribavirin; SOF, sofosbuvir; SVR4, sustained virological response at 4 weeks; SVR12, sustained virological response at 12 weeks.
For genotype 3, the company did not agree with the SVR rate used in the ERG's amended base case for the comparator sofosbuvir plus ribavirin (see section 3.43). Sofosbuvir plus ribavirin was a relevant comparator in only 1 group, specifically people with genotype 3 HCV and cirrhosis who cannot have interferon. The ERG had preferred an SVR rate of 92.3%, extrapolated from the SVR in people with previously untreated genotype 3 HCV with compensated cirrhosis from the VALENCE trial. The company presented SVR rates for sofosbuvir plus ribavirin from 5 trials and 1 'real-world' source. SVR rates for 24-week treatment with sofosbuvir plus ribavirin, as recommended in the marketing authorisation for genotype 3 HCV in people with cirrhosis, were available from 2 trials (VALENCE and BOSON) and 1 'real-world' source (HCV-TARGET). The SVR rates for people with compensated cirrhosis were 67.2% (VALENCE), 78.6% (BOSON) and 53.4% (HCV-TARGET).

The company submitted additional cost-effectiveness analyses using a reduced price for daclatasvir based on contract pricing arrangements between the company and the Commercial Medicines Unit. The contract price reflected the relevant price paid by the NHS for daclatasvir (and is considered commercial in confidence). As per the updated marketing authorisation (see section 2.1), the company incorporated treatment duration of 12 weeks with daclatasvir plus sofosbuvir for people with genotype 3 HCV with significant fibrosis (without cirrhosis). The company stated that in these new cost-effectiveness analyses it used 'the Committee's preferred assumptions' as follows:

- People with significant fibrosis without cirrhosis distributed across F3 and F4 states.
- Progression from SVR F4: transition rates of 0.002 to decompensated cirrhosis and 0.004 to hepatocellular carcinoma (as implemented in the ERG's amended base-case, see section 3.43).
- Updated comparators and appropriate SVR rates.
- The same effect on utility associated with SVR from F4 and in people with significant fibrosis without cirrhosis.
- An annual cost of £127 associated with the SVR-F4 state from the second year.
- The same transition probabilities applied to genotype 1 and genotype 4 HCV.
3.49 The company presented the results of its updated analyses as commercial in confidence because they allow the contract prices to be calculated. The resulting ICERs fell within the ranges presented in tables 8 and 9.

3.50 For people with genotype 3 HCV and cirrhosis who were ineligible for or cannot tolerate interferon, the company explored the effect of alternative SVR rates for the comparator (sofosbuvir plus ribavirin) in a scenario analysis. The alternative SVR rates were taken from the VALENCE trial, and were 92.3% (people with previously untreated HCV and cirrhosis) and 62.7% (all people with cirrhosis).

3.51 The company also included a scenario in which it used SVR rates for daclatasvir plus sofosbuvir and ribavirin and the comparator (sofosbuvir plus ribavirin) taken from a 'real-world' data source (French Temporary Authorization of Use).

3.52 As with the company's additional cost-effectiveness analyses, the results of these scenario analyses were presented as commercial in confidence and therefore are not reported here.

**ERG critique of the company's additional evidence**

3.53 The ERG stated that SVR rates from 'real-world' use were broadly consistent with the trial results in the original submission, although the rates for genotype 3 HCV were higher than those observed for people with cirrhosis in ALLY-3. The ERG agreed that the real-world data indicated daclatasvir plus sofosbuvir with or without ribavirin is an effective treatment for genotype 3 HCV, including in people with advanced liver disease. However, the ERG highlighted that the real-word evidence included in the submission was based on relatively small numbers of people, spread across 2 different treatment regimens (daclatasvir plus sofosbuvir with or without ribavirin), 2 different durations of treatment (12 weeks and 24 weeks), various treatment histories and varying degrees of liver disease.

3.54 The ERG could not confirm if the evidence presented by the company for a lower efficacy of sofosbuvir plus ribavirin in treating genotype 3 HCV with cirrhosis was exhaustive or whether more relevant, population-specific estimates were available. Taking the results at face value, the ERG agreed that an SVR rate of 92.3% (taken from people with previously untreated HCV and
cirrhosis from the VALENCE trial) was likely an overestimate. The ERG suggested instead that the SVR rates from all people with cirrhosis in VALENCE (67.2%) or BOSON (78.2%) were more reasonable estimates for people who were ineligible for or who cannot tolerate interferon. Noting the wide range of SVR rates reported in the literature, the ERG postulated that the difference in SVR rate between daclatasvir plus sofosbuvir and sofosbuvir plus ribavirin would fall between 8% and 30%.

3.55 The ERG could not replicate the company's revised results. It did not agree with the company's approach of distributing people with significant fibrosis across the F3 and F4 states at baseline. It noted that the company's revised model did not distinguish between F4 without cirrhosis and F4 with cirrhosis, and so people considered as F4 without cirrhosis started in the 'cirrhotic state'. The ERG also highlighted that the company had included the following comparators which are not recommended in NICE technology appraisal guidance on sofosbuvir for treating chronic hepatitis C:

- sofosbuvir plus ribavirin (for people with genotype 1 HCV with significant fibrosis and compensated cirrhosis, who cannot have interferon)
- sofosbuvir plus PR (for people with previously untreated genotype 4 HCV with significant fibrosis).

3.56 The ERG also detected that in the revised model, the company had changed the SVR rate associated with PR for previously untreated genotype 3 HCV to 49%, taken from a study labelled as 'Shiffman'. The ERG could not confirm whether this revised SVR rate was sourced from the right population, but commented that PR is an effective treatment for previously untreated genotype 3 HCV and 49% appeared to be very low. The ERG preferred the SVR rate of 79% from FISSION used in the company's base case and its own amended base case.

3.57 The ERG re-ran the analyses using the same parameters as in its amended base case, but applying the reduced contract price of daclatasvir. The ICERs are commercial in confidence because they allow the confidential contract prices to be calculated. The resulting ICERs fell within the ranges presented in tables 8 and 9.

3.58 For people with genotype 3 HCV and cirrhosis who cannot have interferon, the ERG conducted a threshold analysis to establish the minimum difference in SVR
rates at which the ICER for daclatasvir plus sofosbuvir compared with sofosbuvir plus ribavirin would be below £20,000 per QALY gained. The analysis demonstrated that for the ICER to be less than £20,000 per QALY gained, the difference should be at least 9%.

Table 8 Cost-effectiveness results from the company’s revised analyses and ERG’s correction: significant fibrosis without cirrhosis

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>Treatment history</th>
<th>Daclatasvir treatment</th>
<th>Range for incremental ICER (£/QALY gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Company’s revised analyses</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>ERG’s correction</strong></td>
</tr>
<tr>
<td>1</td>
<td>Previously untreated HCV</td>
<td>DCV+SOF</td>
<td>&lt;20,000 (versus SMV+PR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;20,000 (versus PR)</td>
</tr>
<tr>
<td>2</td>
<td>Previously treated HCV</td>
<td>DCV+SOF</td>
<td>&lt;20,000 (versus no treatment)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;20,000 (versus no treatment)</td>
</tr>
<tr>
<td>3</td>
<td>Interferon-ineligible or -intolerant</td>
<td>DCV+SOF</td>
<td>20,000 to 30,000 (versus PR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;50,000 (versus PR)</td>
</tr>
<tr>
<td>4</td>
<td>Previously untreated HCV</td>
<td>DCV+PR</td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCV+SOF</td>
<td>&gt;50,000 (versus SOF+PR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20,000 to 30,000 (versus DCV+PR)</td>
</tr>
<tr>
<td></td>
<td>Previously treated HCV</td>
<td>DCV+PR</td>
<td>Referent</td>
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<td></td>
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<td></td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCV+SOF</td>
<td>20,000 to 30,000 (versus DCV+PR )</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20,000 to 30,000 (versus DCV+PR )</td>
</tr>
</tbody>
</table>
Interferon-ineligible or -intolerant DCV+SOF <20,000 (versus no treatment) <20,000 (versus no treatment)

Abbreviations: DCV, daclatasvir; ERG, Evidence Review Group; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; PR, peginterferon alfa plus ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; referent, least costly treatment in the incremental analysis; SMV, simeprevir; SOF, sofosbuvir.

Dominated, treatment gives fewer QALYs at greater cost than the comparator.

Table 9 Cost-effectiveness results from the company’s revised analyses and ERG’s correction: compensated cirrhosis

<table>
<thead>
<tr>
<th>HCV genotype</th>
<th>Treatment history</th>
<th>Daclatasvir treatment</th>
<th>Range for incremental ICER (£/QALY gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Company’s revised analyses ERG’s correction</td>
</tr>
<tr>
<td>1</td>
<td>Previously untreated HCV</td>
<td>DCV+SOF</td>
<td>&gt;50,000 (versus SOF+PR)</td>
</tr>
<tr>
<td></td>
<td>Previously treated HCV</td>
<td></td>
<td>40,000 to 50,000 (versus SOF+PR)</td>
</tr>
<tr>
<td></td>
<td>Interferon-ineligible or -intolerant</td>
<td></td>
<td>&lt;20,000 (versus no treatment)</td>
</tr>
<tr>
<td>3</td>
<td>Previously untreated HCV</td>
<td>DCV+SOF</td>
<td>&gt;50,000 (versus SOF+PR)</td>
</tr>
<tr>
<td></td>
<td>Previously treated HCV</td>
<td></td>
<td>&gt;50,000 (versus SOF+PR)</td>
</tr>
<tr>
<td></td>
<td>Interferon-ineligible or -intolerant</td>
<td></td>
<td>&lt;20,000 (versus no treatment)</td>
</tr>
<tr>
<td>4</td>
<td>Previously untreated HCV</td>
<td>DCV+PR</td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td>DCV+SOF</td>
<td></td>
<td>&gt;50,000 (versus DCV+PR)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Previously treated HCV</th>
<th>DCV+PR</th>
<th>Referent</th>
<th>Referent</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCV+SOF</td>
<td>&gt;50,000 (versus DCV+PR)</td>
<td>&gt;50,000 (versus DCV+PR)</td>
<td></td>
</tr>
<tr>
<td>Interferon-ineligible or -intolerant</td>
<td>DCV+SOF</td>
<td>&lt;20,000 (versus no treatment)</td>
<td>&lt;20,000 (versus no treatment)</td>
</tr>
</tbody>
</table>

DCV, daclatasvir; ERG, Evidence Review Group; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; PR, peginterferon alfa plus ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; referent, least costly treatment in the incremental analysis; SMV, simeprevir; SOF, sofosbuvir.

3.59 Full details of all the evidence are in the committee papers.
4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of daclatasvir, having considered evidence on the nature of chronic hepatitis C and the value placed on the benefits of daclatasvir by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee heard from the clinical and patient experts about the nature of chronic hepatitis C. The patient expert stated that some people with chronic hepatitis C do not have any symptoms, but others may have chronic fatigue, mood swings and symptoms of sexual dysfunction. The severity of symptoms does not depend on the stage of fibrosis. The clinical and patient experts also commented that the psychological effect of having chronic hepatitis C can impair people's social life and ability to work, and that people can have anxiety about transmitting the virus. There is also stigma about having chronic hepatitis C because it is associated with drug use. The Committee heard from the patient expert that people who have chronic hepatitis C are a disadvantaged population. The patient expert anticipated that the availability of clinically effective treatment options of short treatment duration, such as daclatasvir, will encourage more people to seek diagnosis and treatment. It would also allow access to treatment for people who have found it difficult to access treatment before, such as people in prison, people who use injectable drugs and migrant populations. The Committee recognised the effect of chronic hepatitis C on the lives of people with the virus. It concluded that treatments that give very high levels of sustained virological response (which is considered equivalent to a cure), and so help reduce the rate of hepatitis C virus (HCV) transmission and the stigma associated with having chronic hepatitis C, are of major importance.

4.2 The Committee discussed the clinical management of chronic hepatitis C in adults. It heard from the clinical experts that treatment decisions and response to treatment are influenced by HCV genotype, level of liver damage, comorbidities and treatment history. The Committee was aware that daclatasvir plus sofosbuvir has a marketing authorisation for adults with genotype 1, 3 or 4 HCV, and that daclatasvir plus peginterferon alfa and ribavirin (PR) has a marketing authorisation for adults with genotype 4 HCV. For people with genotype 1 HCV, the Committee noted that boceprevir plus peginterferon alfa and ribavirin or telaprevir plus peginterferon alfa and ribavirin (see NICE's technology appraisal guidance on boceprevir for...
the treatment of genotype 1 chronic hepatitis C and telaprevir for the treatment of genotype 1 chronic hepatitis C) are commonly used, and that for people with genotype 1, 3 or 4 HCV, peginterferon alfa plus ribavirin is also used in clinical practice (see NICE’s technology appraisal guidance on peginterferon alfa and ribavirin for the treatment of chronic hepatitis C, peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C and interferon alfa and ribavirin for the treatment of chronic hepatitis C). The clinical experts highlighted that some people with chronic hepatitis C would choose not to have treatment with peginterferon alfa plus ribavirin because it can be associated with severe side effects, such as fatigue, neuropsychological effects and flu-like symptoms. The Committee heard from the clinical and patient experts that interferon-based treatment may cause chronic side effects (such as insulin-dependent diabetes). It may therefore pose another barrier to people starting and completing treatment. Without treatment people risk further disease progression, for example, to cirrhosis. The Committee recognised the importance of having further treatment options available for people with chronic hepatitis C, and that an interferon-free treatment, such as daclatasvir plus sofosbuvir, would provide a valuable treatment option.

4.3 The Committee discussed whether the technologies in the NICE scope that had recently been granted a marketing authorisation for treating adults with chronic hepatitis C were established clinical practice in England. The Committee was aware that:

- For people with genotype 1 or 4 chronic hepatitis C, whose disease has or has not been previously treated, NICE’s technology appraisal guidance on simeprevir for treating chronic hepatitis C recommends simeprevir plus peginterferon alfa and ribavirin as an option.

- For people with genotypes 1 to 6 chronic hepatitis C, whose disease has or has not been previously treated, NICE’s technology appraisal guidance on sofosbuvir for treating chronic hepatitis C recommends sofosbuvir plus ribavirin, with or without peginterferon alfa, as an option for some people.

The patient expert commented that all current treatment options for people with genotype 1 or 4 HCV involve injecting interferon weekly, including those recommended in NICE’s technology appraisal guidance on sofosbuvir (given sofosbuvir plus ribavirin is not recommended for people with genotype 1 or 4 HCV) and on simeprevir. The Committee acknowledged that the marketing authorisation for
Daclatasvir offers people the option to have shortened courses of treatment, without peginterferon alfa, thereby avoiding the adverse events associated with interferon-based therapy. The Committee was also aware that the oral combination of simeprevir plus sofosbuvir has not been appraised by NICE. Therefore it could not be considered as established practice. The Committee concluded that sofosbuvir plus ribavirin, with or without peginterferon alfa, and simeprevir plus peginterferon alfa and ribavirin, as recommended in NICE guidance, were relevant comparators for daclatasvir plus sofosbuvir.

4.4 The Committee noted that for genotype 1 or 4 HCV, the marketing authorisation for daclatasvir recommends alternative treatment durations with daclatasvir plus sofosbuvir (12 or 24 weeks) depending on whether or not the HCV was previously treated and the prognostic factors (see section 2.1). The Committee heard from the clinical experts that prolonging treatment would not necessarily improve effectiveness, and that a 12-week treatment would lead to a sustained virological response (SVR) in most people, including those with compensated cirrhosis. It understood that in clinical practice, only a very small proportion of people would be expected to have treatment for 24 weeks. The Committee was aware that, in AI444-040, the sustained virological response at 12 weeks (SVR12) in people with previously untreated genotype 1 HCV who had 24 or 12 weeks of treatment was similar at 100% and 97.6% respectively. The Committee concluded that, given the preference for shorter durations of treatment, most people would have daclatasvir plus sofosbuvir for 12 weeks.

4.5 The Committee noted that the marketing authorisation for daclatasvir recommends 2 treatment combinations for genotype 4 HCV: daclatasvir plus sofosbuvir and daclatasvir plus peginterferon alfa and ribavirin (PR). It heard from the clinical experts that both treatments had shown clinical activity for genotype 4 HCV. However, in clinical practice, daclatasvir plus sofosbuvir was likely to be the preferred choice because most people would rather avoid interferon-containing treatments, take an oral treatment and have shorter durations of treatment.

Clinical effectiveness

4.6 The Committee discussed the quality of the clinical trial evidence for daclatasvir. It was aware that neither AI444-040 nor ALLY-3 had a control group, but acknowledged that the rapidly evolving treatment landscape for chronic hepatitis C meant that trials with such a design were to be expected.
The Committee noted the Evidence Review Group's (ERG's) comment that the trials provided few data for people with previously treated HCV and those with compensated cirrhosis, which can both be associated with different treatment decisions and response to treatment. In addition, the trials did not provide any data for people who are ineligible for, or cannot tolerate, interferon. The Committee was aware that the company focused on subgroups of people with significant fibrosis, including those with compensated cirrhosis, and would have liked sufficiently large datasets to have informed these subgroups. Overall, the Committee concluded that the trials were of good quality, although the evidence base underpinning some subgroups was weak.

4.7 The Committee considered the efficacy of daclatasvir in the clinical trials. It noted that daclatasvir, either with sofosbuvir or PR, was associated with high SVR rates, which neared 100% in some trials. These were maintained in people whose disease is difficult to treat, such as people with previously treated HCV or cirrhosis, although results were based on small numbers of people. The Committee concluded that, overall, daclatasvir was clinically effective in treating chronic hepatitis C, but that the size of the effect could not be robustly determined in certain subgroups.

4.8 The Committee discussed the SVR rates for daclatasvir and its comparators. It understood that the company compiled the SVR rates from individual arms in trial groups without doing formal comparisons. The Committee considered this to be a limitation that reduced the validity of these comparisons. Furthermore, the available trial data did not always match the characteristics of the subgroup for which the data were extracted. This meant that the company had to extrapolate estimates across subgroups with different patient and disease characteristics, which further increased the uncertainty in the presented data. The Committee concluded that, for most comparisons, the SVR rates were numerically higher for daclatasvir than its comparators, but it could not robustly determine the size of the incremental benefit of daclatasvir from the compiled SVR rates.

4.9 The Committee discussed the subgroups of people co-infected with HIV, and those who had, or were yet to have, a liver transplant. It noted that there were no specific recommendations for either of these subgroups in the marketing authorisation for daclatasvir, and that the company had not presented clinical evidence for them. The Committee heard from the clinical experts that
dalatasvir would be expected to be an effective treatment in both of these subgroups. However, without any clinical trial evidence, the Committee could not make specific recommendations for people co-infected with HIV, or those who had, or were yet to have, a liver transplant.

4.10 The Committee discussed the ‘real-world’ evidence presented by the company, noting that this related mostly to people with decompensated cirrhosis, a population not included in the company’s original submission and not considered previously (see sections 3.45 and 3.46). The Committee was aware that the marketing authorisation for dalatavir does not make specific recommendations for people with decompensated cirrhosis. Although the company acknowledged that this population is not presently covered by the marketing authorisation, it stated that the data showed that dalatavir was clinically effective in people with decompensated cirrhosis. The company considered that the trial results could be considered robust because they were consistent with the ‘real-world’ data for people whose disease is harder to treat. The Committee was clear that it was not required to make recommendations for people with decompensated cirrhosis, but agreed that the clinical experience with dalatavir was largely in line with the evidence from clinical trials.

**Cost effectiveness**

4.11 The Committee discussed the appropriate population for the consideration of dalatavir’s cost effectiveness. It noted that the company presented subgroup analyses by METAVIR fibrosis stage (F0–F4, F0–F2, F3–F4 and F4), and focused its base case on fibrosis stages F3–F4 (significant fibrosis without cirrhosis) and fibrosis stage F4 (compensated cirrhosis) because this is an area of high unmet need with existing treatments that have only limited effectiveness and suboptimal safety profiles. By contrast, the ERG presented the same subgroups, but described them as ‘fibrosis stage F3’ and ‘fibrosis stage F4’. The Committee was aware that the marketing authorisation for dalatavir defined subgroups ‘without cirrhosis’ or ‘with compensated cirrhosis’. The Committee heard from the clinical experts that the METAVIR fibrosis stage was developed for liver biopsy. It also heard that non-invasive tests of fibrosis (such as FibroTest or FibroScan) are now well established in clinical practice, and can also be used to determine the METAVIR fibrosis stage. However, their use varied across the country depending on availability and expertise. The clinical experts explained that the differences in the descriptions used by the ERG and the company
reflected that non-invasive tests are less accurate than biopsy. Therefore, a non-invasive test could falsely indicate that a person without cirrhosis has fibrosis stage F4 (which is equivalent to cirrhosis), but the liver biopsy would show no cirrhosis. The clinical experts considered that treatment should start whether or not cirrhosis is confirmed by biopsy because without treatment, fibrosis stage F3 will eventually progress to the F4 stage. The Committee accepted the case put forward by the company to focus on people with severe disease. It noted that the ERG simplified fibrosis stage F3–F4 to F3, but understood that a person could have fibrosis stage F4 using non-invasive tests but no cirrhosis on liver biopsy. Because of this, the Committee agreed that the subgroup with significant fibrosis could represent people with fibrosis stage F3–F4, but that the key feature of this subgroup would be the absence of cirrhosis. The Committee noted that in its revised analyses, the company distributed people without cirrhosis across both F3 and F4 stages at baseline. The Committee understood that the model did not distinguish between F4 without cirrhosis and F4 with cirrhosis (see section 3.55). It agreed that given the structure of the model, people with significant fibrosis without cirrhosis at baseline could only be presented by the F3 state of the model.

4.12 The Committee discussed the transition probabilities in the company’s model. It noted the ERG’s concern that in the original model, disease progression to decompensated cirrhosis or hepatocellular carcinoma could not occur in people with cirrhosis who had SVR. The Committee heard from the clinical experts that, although emerging evidence suggests that fibrosis could regress after SVR, people would continue to be at risk of developing hepatocellular carcinoma. The clinical experts considered that having an SVR is likely to reduce, but not eliminate, the risk of hepatocellular carcinoma, but they stated that it was difficult to determine the extent of this reduction because the evidence was insufficient. The Committee appreciated that the existing evidence did not allow the natural history of the disease to be accurately modelled. It was aware that models for chronic hepatitis C used in previous technology appraisals allowed for disease progression in people with cirrhosis who had an SVR. The Committee appreciated that in the revised analyses, the company modelled a risk of disease progression for people with cirrhosis who had an SVR, and considered this appropriate.

4.13 The Committee discussed the comparators included in the economic model, noting that the company and the ERG had used different comparators. It was
aware that the ERG only included the comparators that were recommended by NICE and excluded those that were not recommended (see section 3.43). The Committee noted the ERG’s comment that in the revised analyses, the company had included some inappropriate comparators in certain subgroups (for example, sofosbuvir plus peginterferon alfa and ribavirin in people with previously untreated genotype 4 HCV without cirrhosis; see section 3.55). The Committee agreed that the treatments not recommended by NICE should not be considered as comparators for daclatasvir-containing regimens, and concluded that the comparators included in the ERG’s correction of the company’s revised analyses were appropriate.

4.14 The Committee noted that ‘best supportive care (watchful waiting)’ was included as a comparator in the final scope, and that the company represented this in the model with a ‘no treatment’ option. The Committee discussed whether best supportive care was a relevant comparator for daclatasvir-based therapy. It heard from the clinical experts that best supportive care, which may include watchful waiting, may be considered an appropriate option for some people. However, the clinical experts stated that this option would be likely to become a less common choice because with effective direct-acting antivirals, it would be possible to treat people easily, with relatively short durations of treatment. The Committee agreed that best supportive care had been used before the interferon-free, direct-acting antivirals were available. However, its use is likely to decline as the newer treatments become established in clinical practice. The Committee concluded that, at present, best supportive care (watchful waiting) was still an appropriate comparator in some populations.

4.15 The Committee discussed the SVR rates used in the model, noting that these were based on ‘naive’ comparisons of individual trial groups. It discussed in detail the modelled SVR rates for the following regimens:

- **Daclatasvir plus sofosbuvir for previously untreated genotype 1 HCV with significant fibrosis:** the ERG explored using 100% instead of 95% (see section 3.43). The Committee concluded that the difference in SVR rates was small and unlikely to affect its decision.

- **Daclatasvir plus PR for previously treated genotype 4 HCV:** the Committee noted that SVR rates for previously treated genotype 4 HCV were extrapolated from SVR rates observed in previously untreated genotype 4 HCV. It discussed whether assuming that daclatasvir plus PR is equally effective in previously treated and previously untreated
HCV was reasonable. The Committee was aware that interferon-based regimens are usually less effective in previously treated disease than in untreated disease. The Committee concluded that it would take into account the impact of potentially lower SVR rates while considering cost effectiveness of treatments for previously treated genotype 4 HCV (see sections 4.25 and 4.26).

- **Sofosbuvir plus ribavirin for genotype 3 HCV in people with compensated cirrhosis who are ineligible for, or cannot tolerate, interferon:** the ERG preferred an SVR rate of 92.3% for its amended base case compared with 21.4% in the company’s base case. The Committee noted the substantial difference between these SVR rates. It understood that the SVR rate used by the company (21.4%) was obtained from the relevant population in the POSITRON trial, but reflected a 12-week treatment duration, whereas the recommended duration for this treatment is 24 weeks. The ERG obtained the alternative SVR rate (92.3%) from people with previously untreated HCV and compensated cirrhosis in the VALENCE trial who had 24 weeks’ treatment. The Committee took into account consultation comments that the efficacy of sofosbuvir plus ribavirin for difficult-to-treat populations (such as people with cirrhosis who cannot have interferon) is clinically not well established. The Committee considered alternative estimates of SVR rates presented by the company (see section 3.50) and concluded that 92.3%, as explored by the ERG, was likely an overestimate for this population. The Committee heard from the ERG that given the available evidence, the SVR rates from people with genotype 3 HCV and cirrhosis who had a 24 weeks’ treatment with sofosbuvir plus ribavirin in BOSON (78.6%) or VALENCE (67.2%) were reasonable estimates for this group. The Committee was satisfied that the company had used the SVR rate from BOSON in its revised analyses.

- **Sofosbuvir plus PR for previously untreated, genotype 4 HCV in people with compensated cirrhosis:** the ERG explored an SVR rate of 79.6% compared with a rate of 50% used by the company. The SVR rate used by company was based on 2 people with genotype 4 or 5 HCV. The ERG’s alternative SVR rate was based on a wider population including people with genotype 1, 4, 5 or 6 HCV. The Committee concluded that the company’s SVR rate based on 2 people was unreliable, and that the ERG’s rate was more appropriate.

- **Sofosbuvir plus PR for previously untreated, genotype 3 HCV in people with significant fibrosis:** the Committee was aware that both the company’s base case and the ERG’s amended analyses used an SVR rate of 71%, taken from FISSION. The Committee noted that the company had used an SVR rate of 49% in its revised analyses without transparently stating it or providing any justification. The Committee agreed with the
ERG that PR in people with previously untreated, genotype 3 HCV is considered effective; the SVR rate of 49% was very low and would bias the results in favour of daclatasvir plus sofosbuvir. The Committee was aware that in the model this new SVR rate of 49% was referenced to ‘Shiffman’. The Committee agreed that it was not appropriate to make changes to the model’s parameters which it previously considered appropriate without providing an explicit justification. The Committee disregarded the new SVR rate introduced in the model and agreed that an SVR rate of 71% was the most reasonable estimate for this group.

4.16 The Committee discussed the utility values in the model, specifically the utility increments applied for having an SVR. It noted that the company assumed that the utility increased in people who had an SVR, and that this increase was greater when an SVR occurred in fibrosis stage F4, that is, people with cirrhosis (0.17) than when it occurred in fibrosis stage F0 or F1 (0.05), or F2 or F3 (0.06). The Committee noted that the ERG considered this to be uncertain and inconsistent with existing evidence. The Committee recalled that, in the previous and other ongoing technology appraisals for chronic hepatitis C, it accepted a constant utility benefit for having SVR across the different fibrosis stages. The Committee discussed whether people with cirrhosis (represented by stage F4 in the model) are expected to get more benefit from having an SVR than people without cirrhosis (represented by stage F3 in the model). It heard from the clinical experts that it is difficult to measure the extent to which health-related quality of life improves after SVR in people with cirrhosis compared with those without cirrhosis. The Committee understood that peoples’ quality of life after having an SVR varies, and that whereas some people with cirrhosis may benefit to an extent that they feel completely cured (that is, without cirrhosis), others may have long-term effects of cirrhosis that would continue to affect their health-related quality of life. The Committee considered that assuming the same health-related quality of life after SVR for people with or without cirrhosis was not justifiable. The Committee was satisfied that, in accordance with previous technology appraisals for chronic hepatitis C, the company used equal utility increments for having an SVR for people with significant fibrosis and for people with compensated cirrhosis in the revised analyses.

4.17 The Committee considered the costs included in the model. It noted that the list price of daclatasvir was used in the base-case analysis, whereas the company used confidential contract prices in its revised analysis. The Committee understood that the contract price was the relevant price the NHS pays for
daclatasvir. The Committee noted that NICE's guide to the methods of technology appraisal indicates a preference for using nationally available price reductions in the reference-case analysis to reflect the price relevant to the NHS. It understood that analyses based on price reductions for the NHS would only be considered if the reduced price is transparent and consistently available across the NHS, and if the period for which the specified price is available is guaranteed. The Committee noted from the evidence submitted by the company that the contract price was nationally available in England. It was also satisfied that the contract frameworks were transparent because they can easily be accessed by NHS organisations through the Commercial Medicines Unit. The Committee understood that the contract price was fixed for the duration specified in the framework agreement, after which it will be reviewed annually, and the price was likely to be the maximum the NHS would pay. The Committee concluded that the contract price was the most relevant price to the NHS and therefore the appropriate price on which to base its decision. It also concluded that its recommendations using the contract price are conditional on the price not rising above that considered in this appraisal, otherwise, the guidance will need to be considered for review.

4.18 The Committee discussed the robustness of the cost-effectiveness estimates for daclatasvir. It was aware that the estimates of SVR rates used to populate the model were highly uncertain. This was because the rates were based on individual trial groups with no formal comparisons between the different technologies. Furthermore, the SVR rates were not always specific to the subgroups modelled, and assumptions had to be made to extrapolate the data across subgroups with different characteristics that could potentially influence SVR rates. The Committee acknowledged that the evidence had been synthesised in the best possible way given the nature of the available data. However, it was concerned about the robustness and the plausibility of the inputs to the economic modelling, and agreed that the uncertainty in the modelled SVR rates meant that the cost-effectiveness estimates were also uncertain. The Committee therefore concluded that the ICERs presented were uncertain and agreed that the uncertainty should be taken into account in its decision-making.
Recommendations

4.19 The Committee was aware that for people without cirrhosis, the marketing authorisation does not restrict use of daclatasvir-based regimens only to those with significant fibrosis. The Committee understood that the company had positioned daclatasvir for treating severe disease (F3–F4) because of the suboptimal efficacy and safety of existing treatments for chronic hepatitis C in the advanced stages of liver fibrosis (see section 4.11). Given that the economic analyses presented by the company focused only on the population with significant fibrosis with or without compensated cirrhosis, the Committee agreed that it would make recommendations only for these subgroups.

4.20 The Committee discussed the ICERs estimated by the company in the revised analyses. The Committee noted that the company presented the cost effectiveness of daclatasvir plus sofosbuvir regimens in 18 subgroups defined by genotypes (genotype 1, 3 or 4 HCV), treatment history or whether people were ineligible for or cannot tolerate interferon (previously untreated, previously treated and interferon ineligible or intolerant), and the presence of cirrhosis (significant fibrosis or compensated cirrhosis). The Committee also discussed the cost effectiveness of daclatasvir plus PR in 4 subgroups of genotype 4 HCV, based on treatment history (previously untreated and previously treated) and presence of cirrhosis. The Committee's discussions on the cost effectiveness of daclatasvir containing regimens in different subgroups are presented in sections 4.21 to 4.27. The Committee was aware that the ERG could not exactly replicate the company's results and presented slightly different results. The Committee was reassured that the results of the ERG's correction were generally comparable to the company's revised analyses (see tables 8 and 9), except for 3 subgroups (see sections 4.23, 4.24 and 4.25).

Genotype 1 with significant fibrosis

4.21 The Committee noted that in both the company's revised analyses and the ERG's correction, the ICER for daclatasvir plus sofosbuvir was below £20,000 per quality-adjusted life year (QALY) gained in all 3 subgroups (people with previously untreated HCV, people with previously treated HCV and people who cannot have interferon). The Committee agreed that daclatasvir plus sofosbuvir could be considered a cost-effective use of NHS resources for genotype 1 HCV with significant fibrosis.
Genotype 1 with compensated cirrhosis

4.22 The Committee noted that in both the company's revised analyses and the ERG's correction, the ICER for daclatasvir plus sofosbuvir was above £40,000 per QALY gained for people with previously treated or untreated HCV. For people who cannot have interferon, both analyses found the ICER to be below £20,000 per QALY gained. The Committee agreed that daclatasvir plus sofosbuvir is a cost-effective use of NHS resources for treating genotype 1 HCV in people with cirrhosis, only if they cannot have interferon.

Genotype 3 with significant fibrosis

4.23 The Committee was aware that the revised ICERs presented for genotype 3 HCV with significant fibrosis included 12 weeks' treatment with daclatasvir plus sofosbuvir, which was in accordance with updated marketing authorisation. The Committee noted the substantial difference in the ICERs estimated in the company's revised analyses and the ERG's correction for people with previously untreated HCV. The Committee understood that this was because the company had used a more favourable SVR rate for the comparator in the model (see section 4.15). The Committee preferred the ERG's correction as a more reliable estimate but noted that both estimates were higher than £20,000 per QALY gained. It also noted that for people with previously treated HCV, daclatasvir plus sofosbuvir was dominated by (that is, was more costly and less effective than) sofosbuvir plus PR. For people who cannot have interferon, the ICER was below £20,000 per QALY gained for both the company's revised analyses and the ERG's correction. The Committee agreed that daclatasvir plus sofosbuvir is a cost-effective use of NHS resources for treating genotype 3 HCV in people with significant fibrosis, only if they cannot have interferon.

Genotype 3 with compensated cirrhosis

4.24 For genotype 3 HCV in people with compensated cirrhosis, the Committee noted that both the company's analyses and the ERG's correction produced ICERs for daclatasvir plus sofosbuvir that were higher than £50,000 per QALY gained for both previously treated and untreated HCV. For people who cannot have interferon, the company's revised ICER was substantially less than the ERG's correction. The Committee understood that this was because the company and the ERG had used different SVR rates for the comparator regimen
sofosbuvir plus ribavirin. The Committee reiterated its conclusion that the SVR rate for sofosbuvir plus ribavirin used by the company (78.6%) was more reasonable than that used by the ERG (92.3%; see section 4.15). The Committee also noted the wide range of SVR rates in the literature (see section 3.47) and the ERG's suggestion that the difference in SVR rate between daclatasvir plus sofosbuvir and sofosbuvir plus ribavirin would fall somewhere between 8% and 30% (see section 3.54). The Committee was reassured by the ERG's threshold analysis, which demonstrated that the ICER for daclatasvir plus sofosbuvir compared with sofosbuvir plus ribavirin would be below £20,000 per QALY gained if the difference between the regimens' SVR rates was at least 9% (see section 3.58). The Committee concluded that the difference in the SVR rates between daclatasvir plus sofosbuvir and sofosbuvir plus ribavirin is likely to be more than 9%. Therefore, daclatasvir plus sofosbuvir could be considered a cost-effective use of NHS resources for genotype 3 HCV in people with compensated cirrhosis, only if they cannot have interferon.

Genotype 4 with significant fibrosis

4.25 For people with previously untreated HCV, the Committee noted the substantial difference in the estimated ICER for daclatasvir plus sofosbuvir by the company and the ERG. The Committee agreed that the ERG's estimate was more reasonable because the company included sofosbuvir plus PR as a comparator, which is not recommended by NICE for this group (see section 3.55). However, the Committee noted that in both the company's revised analyses and the ERG's correction, the ICER for daclatasvir plus sofosbuvir remained between £20,000 and £30,000 per QALY gained for both previously untreated and previously treated HCV. The Committee was aware that it had made preliminary recommendations for daclatasvir plus sofosbuvir in people with previously treated HCV. The Committee discussed the factors that increased the ICERs of daclatasvir plus sofosbuvir from an acceptable range in the ERG's amended base case to more than £20,000 per QALY gained in the ERG's correction of the revised analyses. The Committee understood that after using the contract price for daclatasvir in the modelling, daclatasvir plus PR became the reference intervention (least costly) and was more effective than all comparators except daclatasvir plus sofosbuvir. The Committee recalled that the effectiveness of daclatasvir plus PR was overestimated for previously treated HCV (see
section 4.15) and a lower SVR rate would increase the incremental benefit for daclatasvir plus sofosbuvir compared with daclatasvir plus PR, which would lead to a decrease in the estimated ICER. The Committee agreed that assuming a slightly lower SVR rate for daclatasvir plus PR would bring the ICER for daclatasvir plus sofosbuvir for previously treated HCV below £20,000 per QALY gained. It also agreed that the extent to which the SVR rate for daclatasvir plus PR for previously treated HCV needed to be decreased was much lower than the difference between the SVR rates for previously treated and previously untreated HCV it had seen for other interferon-based regimens. For people who cannot have interferon, the ICER was below £20,000 per QALY gained for both analyses. The Committee agreed that daclatasvir plus sofosbuvir is a cost-effective use of NHS resources for treating genotype 4 HCV in people with previously treated HCV and in people who cannot have interferon.

Genotype 4 with compensated cirrhosis

The Committee noted that in both the company’s revised analyses and the ERG’s correction, the ICER for daclatasvir plus sofosbuvir was above £50,000 per QALY gained for both previously untreated and previously treated HCV. The Committee was aware that the SVR rate used for daclatasvir plus PR in previously treated HCV was overestimated (see section 4.15), but agreed that a plausible slightly lower SVR rate would not bring the ICERs for daclatasvir plus sofosbuvir below £20,000 per QALY gained. For people who cannot have interferon, the ICER was below £20,000 per QALY gained for both analyses. The Committee agreed that daclatasvir plus sofosbuvir is a cost-effective use of NHS resources for treating genotype 4 HCV in people with cirrhosis, only if they cannot have interferon.

Daclatasvir plus PR for genotype 4 HCV

For genotype 4 HCV, the Committee noted that in both the company’s revised analyses and the ERG’s correction, daclatasvir plus PR was the least costly of and generally more effective than the active comparators across all 4 relevant subgroups (previously untreated or treated, with significant fibrosis or compensated cirrhosis). The Committee also noted that no other comparator included in the incremental analyses could be considered cost effective at a maximum acceptable ICER of £20,00 per QALY gained. The Committee was aware that daclatasvir plus PR is not recommended in the clinical guidelines.
(consensus guideline of the national societies and EASL [European Association for the Study of the Liver] guideline that had been previously presented to the Committee) and with the availability of other more effective, interferon-free regimens, interferon-containing regimens are not preferred by clinicians. However, the Committee agreed that daclatasvir plus PR is a cost-effective use of NHS resources for treating genotype 4 HCV in people who can have interferon-based treatment and that the regimen should be available as a treatment option.

**Innovation**

4.28 The Committee discussed whether daclatasvir could be considered innovative, and whether the company's economic analysis had captured all changes in health-related quality of life. The Committee agreed that compared with current treatment, daclatasvir plus sofosbuvir offers oral, shortened, interferon-free treatment, which is particularly important to people, and a major development in the clinical management of chronic hepatitis C. The Committee therefore acknowledged that daclatasvir is a valuable new therapy for treating chronic hepatitis C. The Committee agreed that there were other benefits for people with chronic hepatitis C (for example, possible regression of fibrosis) and wider benefits to society (for example, reduced transmission of HCV, improved earning capacity) that were not captured in the QALY calculation and that, if taken into account, were likely to decrease the ICERs. However, the Committee noted that it had taken these potential benefits into account when considering the cost effectiveness of daclatasvir and concluded that its recommendations for each population remained unchanged.

**NHS England**

4.29 The Committee discussed NHS England's submission relating to:

- the implementation of 3 oral treatments for hepatitis C in the NHS (ledipasvir–sofosbuvir, daclatasvir and ombitasvir–paritaprevir–ritonavir with or without dasabuvir)

- NICE's general duties 'to have regard to the broad balance between benefits and costs of the provision of health services or of social care in England and the degree of need of persons for health services or social care in England'.
The Committee understood that NHS England considered these new oral treatments to be excellent options, but was concerned about the increase in investment and capacity needed for their implementation. The Committee heard from the patient expert that people with chronic hepatitis C appreciated the capacity constraints placed on the NHS in delivering treatment for every eligible person. The Committee recalled that treatment decisions are influenced by clinical characteristics including HCV genotype, level of liver damage, comorbidities and treatment history (see section 4.2). With these factors in mind, people with chronic hepatitis C may accept treatment being prioritised for those with the highest unmet clinical need (including some people without cirrhosis), potentially determined by multidisciplinary teams.

4.30 The Committee heard from NHS England that up to 20,000 people could access treatment each year if NICE recommended these treatments for people with chronic hepatitis C (including people without cirrhosis). However, the Committee understood from the responses to the NHS England submission that this estimate was too high. The Committee heard from the clinical experts that a more realistic estimate for the number of people accessing treatment in England was likely to be between 7000 and 10,000 each year. The Committee was aware that NHS England considered that treating 7000 people with these new oral treatments each year would not be affordable within the current NHS budget. The Committee acknowledged that there would be significant impact on the total budget for specialised services associated with making these drugs available in the NHS. However, the Committee noted the responses from consultees on NHS England’s submission that the estimates presented by NHS England were not robust, and that they omitted potential savings from reducing transmission of HCV. The Committee further understood that NHS England is exploring other ways of managing the financial impact of using these new drugs, such as tendering, and that it could be argued that the rebate provided by companies as part of the 2014 Pharmaceutical Price Regulation Scheme (PPRS) payment mechanism could be considered as a way of managing the budgetary impact of access to these treatments. The Committee understood, in this context, that an important objective of PPRS is to ‘improve access to innovative medicines commensurate with the outcomes they offer patients by ensuring that medicines approved by NICE are available widely in the NHS’.

4.31 The Committee recognised that NICE’s guide to the methods of technology appraisal indicates that there needs to be increasing certainty of the cost effectiveness of a technology as the NHS budget impact of its adoption increases. However, the Committee noted that the ICERs were generally below
£20,000 per QALY gained for daclatasvir for the populations for whom it is recommended in NICE’s recommendations. The Committee emphasised that, if the uncertainties were accounted for in the modelling of the cost effectiveness (for example, incremental QALYs gained from an SVR12, the costs and benefits associated with treatment of reinfection, and savings from preventing transmission of HCV), the ICERs for the recommended regimens were likely to remain below £20,000 per QALY gained.

4.32 The Committee understood that, given the rapid sequential assessment of direct-acting antiviral drug combinations now licensed for treating hepatitis C, it will be worthwhile exploring whether there are combinations or sequences of treatments (for example, by genotype, treatment experience or cirrhosis status) that could be of particular value to people with chronic hepatitis C, clinicians and the NHS. The Committee agreed that further work by NICE to support this should be started as soon as possible.

4.33 The Committee discussed comments received from NHS England on the appraisal consultation document, which proposed that an 'only in research' recommendation should be considered for people with untreated genotype 1 HCV without cirrhosis. The Committee understood from NHS England that a clinical trial, STOP-HCV-1, will assess SVR rates in people with untreated genotype 1 HCV without cirrhosis who have direct-acting antiviral drugs, including daclatasvir, for shorter durations than stipulated in the marketing authorisation. The Committee was aware that the final protocol has not been agreed and STOP-HCV-1 has not started. It considered that the clinical effectiveness evidence available for daclatasvir for this population was more robust than the evidence available for other populations considered in this technology appraisal and that the ICER was below £20,000 per QALY gained. The Committee further agreed that its recommendation would not stop people from taking part in the proposed STOP-HCV-1 trial, particularly because it is advised that the treatment of chronic hepatitis C will be managed through established operational delivery networks in the NHS. The Committee concluded that an 'only in research' recommendation was not appropriate for daclatasvir in people with untreated genotype 1 HCV without cirrhosis.
Pharmaceutical Price Regulation Scheme

4.34 The Committee considered whether it should take into account the consequences of the PPRS 2014, and in particular the PPRS payment mechanism, when appraising daclatasvir. The Committee noted NICE's position statement about this, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal of daclatasvir. It therefore concluded that the PPRS payment mechanism was irrelevant in considering the cost effectiveness of daclatasvir.

Equality issues

4.35 The Committee noted the potential equality issue raised by consultees that minority ethnic groups and people with HIV co-infection are more highly represented in the genotype 4 HCV population than in the genotype 1 HCV population. The Committee also noted the consultation comment from the Haemophilia Society that any delay in access to treatment would have a significant adverse impact on people with haemophilia and other bleeding disorders. The Committee was satisfied that it had sufficiently considered the evidence available for people with genotype 4 HCV, which was limited. With no data available for daclatasvir plus sofosbuvir for genotype 4 HCV, the Committee had attempted to bridge this evidence gap by accepting the same SVR rates for genotype 1 HCV for the genotype 4 HCV population. The Committee noted that no clinical evidence or cost-effectiveness analysis had been presented specifically for people with haemophilia and HCV. The Committee also noted the consultation comment that genotype 3 HCV is more prevalent in people of South Asian or Pakistani family origin than other genotypes of HCV. Another consultee stated that there is evidence supporting increased rates of steatosis, hepatocellular carcinoma, cirrhosis/decompensation and death in those infected with genotype 3 HCV compared to other genotypes. The Committee understood that the consultees presented no data to support their comments. It noted that the data it had seen, during the appraisal of ledipasvir–sofosbuvir for treating chronic hepatitis C, suggested that a small proportion of people with genotype 3 HCV were of Asian family origin and from other minority ethnic groups. It also noted that the proportion
of people with this protected characteristic was not disproportionately higher in
genotype 3 HCV compared with other genotypes (such as genotype 4 HCV). The
Committee also acknowledged that the economic analysis had accounted for
different rates of disease progression for each genotype. Based on the
cost-effectiveness data it had made recommendations in line with the treatment
duration and regimen stated in the marketing authorisation for each
genotype population. Therefore, the Committee agreed that its
recommendations were fair and did not constitute an equality issue.

Summary of Appraisal Committee's key conclusions

<table>
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<th>TA364</th>
<th>Appraisal title: Daclatasvir for treating chronic hepatitis C</th>
<th>Section</th>
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<tr>
<td>Key conclusion</td>
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</table>
The Committee concluded that daclatasvir was clinically effective in treating chronic hepatitis C (HCV), but that the size of the effect could not be robustly determined in certain subgroups.

The Committee recognised that all the incremental cost-effectiveness ratios (ICERs) presented were uncertain, mainly because the evidence base used to inform the sustained virological response (SVR) rates in the model was weak. It agreed that the uncertainty in the results should be taken into account in its decision-making.

**Daclatasvir plus sofosbuvir**

The Committee concluded that daclatasvir plus sofosbuvir could be considered a cost-effective use of NHS resources for treating: 

**Genotype 1 with significant fibrosis**
- in all 3 subgroups (people with previously untreated HCV, people with previously treated HCV and people who cannot have interferon).

**Genotype 1 with compensated cirrhosis**
- only in people who cannot have interferon.

**Genotype 3 with significant fibrosis or with compensated cirrhosis**
- only in people who cannot have interferon.

**Genotype 4 with significant fibrosis**
- in people with previously treated HCV and in people who cannot have interferon.

**Genotype 4 with compensated cirrhosis**
- only in people who cannot have interferon.

**Daclatasvir plus peginterferon alfa and ribavirin**

The Committee agreed that daclatasvir plus PR is a cost-effective use of NHS resources for treating genotype 4 HCV in people who can have interferon-based treatment.

**Current practice**
Clinical need of patients, including the availability of alternative treatments

For people with genotype 1 HCV, the Committee noted that boceprevir plus peginterferon alfa and ribavirin (PR) or telaprevir plus PR are commonly used, and that for people with genotypes 1, 3 and 4 HCV, PR is also used in clinical practice.

The clinical experts noted that some people with chronic hepatitis C would choose not to have treatment with PR because it can be associated with severe side effects. The Committee recognised the importance of having further treatment options available for people with chronic hepatitis C.

The Committee concluded that sofosbuvir plus ribavirin, with or without peginterferon alfa, and simeprevir plus PR, as recommended in NICE guidance, were relevant comparators for daclatasvir plus sofosbuvir. However, it did not consider simeprevir plus sofosbuvir as established practice because this treatment has not been appraised by NICE.

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<th>The technology</th>
<th>Proposed benefits of the technology</th>
<th>4.2, 4.3</th>
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<tr>
<td>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</td>
<td>The Committee recognised that an interferon-free treatment, such as daclatasvir plus sofosbuvir, would provide a valuable treatment option. The Committee agreed that there were other benefits for people with chronic hepatitis C (for example, possible regression of fibrosis) and wider benefits to society (for example, reduced transmission of HCV, improved earning capacity).</td>
<td>4.2, 4.28</td>
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<tr>
<td>What is the position of the treatment in the pathway of care for the condition?</td>
<td>The Committee noted that for genotype 1 or 4 HCV, the marketing authorisation for daclatasvir recommends alternative treatment durations with daclatasvir plus sofosbuvir (12 or 24 weeks). The Committee understood that in clinical practice, only a very small proportion of people would be expected to have treatment for 24 weeks. The Committee noted that 2 daclatasvir treatments are licensed for genotype 4 HCV; daclatasvir plus sofosbuvir and daclatasvir plus PR. It heard that in clinical practice, daclatasvir plus sofosbuvir was likely to be the preferred choice because most people would rather avoid interferon-containing treatments, take an oral treatment and have shorter durations of treatment.</td>
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<td>Adverse reactions</td>
<td>The clinical experts highlighted that some people with chronic hepatitis C would choose not to have treatment with peginterferon alfa plus ribavirin because it can be associated with severe side effects and that an interferon-free treatment, such as daclatasvir plus sofosbuvir, would provide a valuable treatment option.</td>
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<td>Evidence for clinical effectiveness</td>
<td>The Committee concluded that the clinical trials for daclatasvir were of good quality, although few data were available for some subgroups. The Committee understood that the company compiled SVR rates from individual trial groups without doing formal comparisons. No clinical evidence was presented for people co-infected with HIV, or those who had, or were yet to have, a liver transplant. The Committee noted the company's assertion that the trial results could be considered robust because they were consistent with the 'real-world' data and agreed that the clinical experience with daclatasvir was largely in line with the evidence from clinical trials.</td>
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**4.4, 4.5**

4.2

4.6, 4.8, 4.9, 4.10
<p>| Relevance to general clinical practice in the NHS | The Committee agreed that the clinical experience with daclatasvir was largely in line with the evidence from clinical trials. | 4.10 |
| Uncertainties generated by the evidence | The Committee concluded that the evidence base underpinning some subgroups was weak, being based on small numbers of people. The Committee considered the lack of formal comparisons in the company’s compiled SVR rates to be a limitation in the data that reduced the validity of the comparisons and introduced considerable uncertainty. | 4.6–4.8 |
| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | The Committee noted that daclatasvir-based therapy was associated with high SVR rates, which were maintained in people whose disease is difficult to treat, although results were based on small subgroups. | 4.7 |
| Estimate of the size of the clinical effectiveness including strength of supporting evidence | The Committee noted that daclatasvir, either with sofosbuvir or PR, was associated with high SVR rates that neared 100% in some trials. The Committee concluded that in the company’s compiled SVR rates, daclatasvir generally had numerically higher SVR rates than most of its comparators. However, it could not determine the size of the incremental benefit of daclatasvir from these data. | 4.7, 4.8 |
| Evidence for cost effectiveness | The Committee acknowledged that the evidence had been synthesised in the best possible way given the nature of the available data. However, it was concerned about the robustness and the plausibility of the inputs to the economic modelling, and agreed that the uncertainty in the modelled SVR rates meant that the cost-effectiveness estimates were also uncertain. | 4.18 |</p>
<table>
<thead>
<tr>
<th>Uncertainties around and plausibility of assumptions and inputs in the economic model</th>
<th>The Committee was concerned about the robustness and the plausibility of the inputs to the economic modelling because the estimates of SVR rates were based on individual trial groups with no formal comparisons between the different technologies, and were not always specific to the subgroups modelled.</th>
<th>4.18</th>
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<tr>
<td>Incorporation of health-related quality-of-life benefits and utility values</td>
<td>The Committee was satisfied that, in accordance with previous technology appraisals for chronic hepatitis C, the company used equal utility increments for having an SVR for people with significant fibrosis and people with compensated cirrhosis in the revised analyses. The Committee agreed that compared with current treatment, daclatasvir plus sofosbuvir offers oral, shortened, interferon-free treatment, which is particularly important to people, and a major development in the clinical management of chronic hepatitis C. The Committee agreed that there were other benefits for people with chronic hepatitis C (for example, possible regression of fibrosis) and wider benefits to society (for example, reduced transmission of HCV, improved earning capacity) that were not captured in the quality-adjusted life year (QALY) calculation.</td>
<td>4.16, 4.28</td>
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<tr>
<td>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</td>
<td>Please refer to the key conclusions above.</td>
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<tr>
<td>Are there specific groups of people for whom the technology is particularly cost effective?</td>
<td>The Committee noted that the substantial differences between the ICERs estimated by the ERG and the company in 3 subgroups were driven mainly because of different comparators and different SVR rates for the comparators underpinning these analyses.</td>
<td>4.23–4.25</td>
</tr>
<tr>
<td><strong>Most likely cost-effectiveness estimate (given as an ICER)</strong></td>
<td>The company presented the results of its updated analyses as commercial in confidence because it could not allow the contract price of daclatasvir to be publicly calculated. For the ranges within which most plausible ICERs would fall, see ERG’s correction in tables 8 and 9 for all subgroups except for one. For genotype 3 HCV with compensated cirrhosis in people who cannot have interferon, the ICER presented in the company’s revised analyses was considered closer to the most plausible ICER.</td>
<td>4.21–4.27</td>
</tr>
</tbody>
</table>

| **Additional factors taken into account** | | |
| **Patient access schemes (PPRS)** | The company has agreed a nationally available price reduction for daclatasvir with the Commercial Medicines Unit. | 2.4 |
| **End-of-life considerations** | Not applicable | |
| **Equalities considerations and social value judgements** | The Committee noted the potential equality issue that minority ethnic groups and people with HIV co-infection are more highly represented in the genotype 4 HCV population than in the genotype 1 HCV population. The Committee was satisfied that it had sufficiently considered the evidence available for people with genotype 4 HCV, which was limited and had attempted to bridge this evidence gap by accepting the same SVR rates for the genotype 1 HCV for the genotype 4 HCV population. The Committee noted the consultation comments that genotype 3 HCV is more prevalent in people of South Asian or Pakistani family origin. However, it noted that the proportion of people with this protected characteristic was not disproportionately higher in genotype 3 HCV compared with other genotypes of HCV. Therefore, the Committee agreed that its recommendations were fair and did not constitute an equality issue. | 4.35 |
5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a person has chronic hepatitis C and the doctor responsible for their care thinks that daclatasvir is the right treatment, it should be available for use, in line with NICE’s recommendations.

5.4 The contract prices used for decision-making in this appraisal are the relevant prices the NHS pays for daclatasvir. These prices are based on contract pricing arrangements between the company and the Commercial Medicines Unit. The contract prices are commercial in confidence. Any enquiries from NHS organisations about the contract prices used in this appraisal should be directed to the Commercial Medicines Unit.
6 Review of guidance

6.1 All technology appraisal guidance recently developed by NICE for chronic hepatitis C will be considered for incorporation and contextualisation in the clinical guideline on hepatitis C.

Andrew Dillon
Chief Executive
November 2015
7 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Gary McVeigh (Chair)
Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Lindsay Smith (Vice Chair)
General Practitioner, West Coker Surgery, Somerset

Dr Aomesh Bhatt
Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser

Dr Andrew Black
General Practitioner, Mortimer Medical Practice, Herefordshire

Professor David Bowen
Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Matthew Bradley
Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline
Dr Ian Campbell
Honorary Consultant Physician, Llandough Hospital, Cardiff

Dr Ian Davidson
Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon
Professor of Health Economics, University of Sheffield

Mrs Susan Dutton
Senior Medical Statistician, Oxford Clinical Trials Research Unit

Dr Alexander Dyker
Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Mrs Gillian Ells
Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Professor Paula Ghaneh
Professor and Honorary Consultant Surgeon, University of Liverpool

Dr Susan Griffin
Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh
Professor in Nursing, Manchester Metropolitan University

Professor John Henderson
Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children

Professor John Hutton
Professor of Health Economics, University of York

Dr Tim Kinnaird
Lead Interventional Cardiologist, University Hospital of Wales, Cardiff
Guideline representatives

The following individuals, representing the Guideline Committee responsible for developing NICE's guideline related to this topic, were invited to attend the meeting to observe and to contribute as advisers to the Committee.

Professor Matthew Hickman
Professor of Public Health and Epidemiology, University of Bristol

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ahmed Elsada and Anwar Jilani
Technical Leads

Melinda Goodall, Raisa Sidhu and Nwamaka Umeweni
Technical Advisers

Kate Moore
Project Manager
8 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the Centre for Reviews and Dissemination York:


B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Bristol-Myers Squibb Pharmaceuticals

II. Professional/expert and patient/carer groups:

- Addaction
- Haemophilia Society
- Hepatitis C Trust
- Liver4Life
- British Association for Sexual Health and HIV
- British Association for the Study of the Liver
- British HIV Association
- British Society of Gastroenterology
- Royal College of Pathologists
- Royal College of Physicians
• UK Clinical Pharmacy Association

III. Other consultees:

• Department of Health
• NHS England
• Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

• Department of Health, Social Services and Public Safety for Northern Ireland
• Healthcare Improvement Scotland
• Gilead Sciences
• Janssen
• Merck Sharp & Dohme
• Roche Products

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on daclatasvir for treating chronic hepatitis C by attending the initial Committee discussion and providing a written statement to the Committee. They were also invited to comment on the ACD.

• Professor Matthew Cramp, Consultant Hepatologist, nominated by Gilead Sciences – clinical expert
• Professor Geoff Dusheiko, Emeritus Professor of Medicine, nominated by Bristol-Myers Squibb – clinical expert
• Dr Helen Harris, Clinical Scientist and Research Associate, nominated by Public Health England – clinical expert
• Dr Ranjababu Kulasegaram, Consultant Physician, nominated by the British HIV Association and British Association for Sexual Health and HIV – clinical expert
• Dr Charles Millson, Consultant Hepatologist, nominated by the British Society of Gastroenterology – clinical expert
• Dr Terence Wong, Consultant Gastroenterologist and Hepatologist, nominated by the British Society of Gastroenterology – clinical expert

• Mr Charles Gore, CEO, nominated by The Hepatitis C Trust – patient expert

• Mr Richard Hall, Co-Founder of Liver4Life, nominated by Liver 4 Life – patient expert

• Robert James, nominated by the British HIV Association and British Association for Sexual Health and HIV – patient expert

• Ms Raquel Peck, nominated by the Hepatitis C Trust – patient expert

D. The following individuals were nominated as NHS commissioning experts by NHS England. They gave their expert/NHS commissioning personal view on daclatasvir for treating chronic hepatitis C by attending the initial Committee discussion. They were also invited to comment on the ACD.

• James Palmer, Clinical Director, Specialised Commissioning selected by NHS England – NHS commissioning expert

• Ursula Peaple, Interim Internal Medicine National Programme Manager, selected by NHS England – NHS commissioning expert

• Malcolm Qualie, Pharmacy Lead, Specialised Services selected by NHS England – NHS commissioning expert

E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

• Bristol-Myers Squibb Pharmaceuticals
About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS.

This guidance was developed using the NICE single technology appraisal process.

We have produced information for the public explaining this guidance. Information about the evidence it is based on is also available.

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

Your responsibility
This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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