NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Daclatasvir for treating chronic hepatitis C

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using daclatasvir in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the Committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using daclatasvir in the NHS in England.

For further details, see the guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 19 August 2015

Third Appraisal Committee meeting: 3 September 2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Daclatasvir is recommended as an option for treating chronic hepatitis C in adults, as specified in table 1.

Table 1 Daclatasvir for treating chronic hepatitis C

HCV genotype, liver disease stage	Treatment	Duration (weeks)	Recommendation according to treatment history		
			Untreated	Treated	Interferon-ineligible or intolerant
1 or 4, without cirrhosis	Daclatasvir + sofosbuvir	12	Not recommended	Recommended only if the person has significant fibrosis (METAVIR fibrosis stage F3–F4)	Recommended only if the person has significant fibrosis (METAVIR fibrosis stage F3–F4)
1 or 4, with or without compensated cirrhosis	Daclatasvir + sofosbuvir (with or without ribavirin)	24	Not recommended	Not recommended	Not recommended
3, with or without compensated cirrhosis	Daclatasvir + sofosbuvir + ribavirin	24	Not recommended	Not recommended	Not recommended
4	Daclatasvir + peginterferon alfa + ribavirin	24	Not recommended	Not recommended	Not recommended
HCV; hepatitis C virus, IFN; interferon					

1.2 It is recommended that access to the drugs used to treat hepatitis C is managed through the specialised commissioning programme put in place by NHS England with prescribing decisions made by multidisciplinary teams/centres to ensure that treatment is prioritised for patients 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 with compensated cirrhosis and/or previous treatment: daclatasvir plus sofosbuvir and 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 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.

2.3 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). Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by Bristol-Myers Squibb and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical-effectiveness evidence

3.1 The company presented clinical data for daclatasvir from 4 trials – AI444-040, AI444-042, AI444-010 and ALLY-3 – which it identified from a systematic literature review and from company-held data (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

Study		AI444-040	AI444-010	AI444-042	ALLY-3
n		211	395	124	152
Location		Multicentre (US)	Multicentre (international; no UK sites)	Multicentre (international; 3 UK sites)	Multicentre (US and Puerto Rico)
Design		Randomised, open-label study	Double-blind RCT	Double-blind RCT	Open-label study
Genotypes included	**1**	✓ (n=167)	✓ (n=364)		
	2	✓ (n=26)			
	3	✓ (n=18)			✓ (n=152)
	4		✓ (n=31)	✓ (n=123)	
Treatment history		• Untreated (genotypes 1 , 2 and 3) • Treated[1] (genotype 1)	Untreated	Untreated	• Untreated • Treated
Cirrhotic disease?		×	✓	✓	✓
Intervention[2]		• DCV + SOF (n=121) • DCV + SOF + RBV (n=90)	• DCV **20 mg**[3] + PR (n=159) • DCV + PR (n=158)	DCV + PR (n=82)	DCV + SOF (n=152)
Comparator		–	Placebo + PR (n=78)	Placebo + PR (n=42)	–
Duration of treatment		12 or 24 weeks	Up to 48 weeks	Up to 48 weeks	12 weeks
Primary outcome(s)		SVR12	SVR24 and eRVR	SVR12	SVR12

[1]Previous treatment with boceprevir- or telaprevir-based therapy

[2]Unless otherwise stated, the dose of daclatasvir was 60 mg daily

[3]Unlicensed dose

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

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).

3.3 Daclatasvir received its marketing authorisation mainly on the basis of the AI444-040 trial, which included 10 treatment groups, but no placebo or active control group. AI444-040 compared 12 weeks' treatment (n=82) with 24 weeks' treatment (n=44) for previously untreated genotype 1 HCV. Furthermore, it compared daclatasvir plus sofosbuvir with (n=90) or without (n=121) ribavirin for previously untreated genotype 1, 2 or 3 HCV, and for previously treated genotype 1 HCV.

3.4 The key characteristics at baseline across the clinical trials were as follows:

- The proportion of people with cirrhosis was 7.3% in AI444-010, 10.5% in AI444-042 and 21.1% in ALLY-3. AI444-040 did not include anyone with cirrhosis, although the company stated that 13.5% of people with previously untreated HCV had METAVIR fibrosis stage F4, which is generally considered to be equivalent to cirrhosis, at the beginning of the trial.
- Most people (65.9%) in AI444-040 had a fibrosis stage of F2 or higher, whereas 78.3% of people in ALLY-3 had fibrosis stages of F0–F3. AI444-010 did not collect information on fibrosis stage at baseline, and AI444-042 did not report it for most people.
- AI444-040 and ALLY-3 included people with previously treated HCV. In AI444-040, 78.6% and 21.4% of those people had had telaprevir- or boceprevir-containing therapy respectively.

3.5 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).

3.6 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: not currently recommended; results were based on 12 weeks' treatment.
- Genotype 4 HCV
  - Daclatasvir plus peginterferon alfa and ribavirin (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

HCV genotype	Treatment history	Recommended treatment	Data source	SVR12 rate (%)		
				mITT (F0–F4)	Subgroups	
					F3–F4	F4
1	Previously untreated[1]	DCV+SOF	AI444-040	70/70 (100)	41/41 (100)	–
		DCV+SOF+RBV	AI444-040	54/56 (96)		–
	Previously treated	DCV+SOF	AI444-040	21/21 (100)	20/20 (100)	–
		DCV+SOF+RBV	AI444-040	19/20 (95)		–
3	Previously untreated	DCV+SOF	AI444-040	11/13 (85)[2]	–	–
			ALLY-3	91/101 (90)	28/36 (78)	11/19 (58)
		DCV+SOF+RBV	AI444-040	5/5 (100)[2]	5/5 (100)	–
	Previously treated	DCV+SOF	ALLY-3	44/51 (86)	15/21 (71)	9/13 (69)
		DCV+SOF+RBV	–			
4	Previously untreated	DCV+PR	AI444-010	12/12 (100)	–	–
			AI444-042	67/82 (82)[2]	–	7/9 (78)[2]
	Previously treated	DCV+PR	–			

[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

DCV, daclatasvir; HCV, hepatitis C virus; mITT, modified intention-to-treat; PR, peginterferon alfa plus ribavirin; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response

ERG comments

3.7 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.

3.8 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.

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

- People whose disease is difficult to treat, such as those co-infected with HIV, or who had, or were yet to have, a liver transplant.
- People who are dependent on alcohol.
- People who take drugs.

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.

3.10 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.

3.11 The ERG noted that the trials did not provide data for people who are ineligible for, or cannot tolerate, interferon (which is a subgroup in the scope). However, this group has different treatment options, and so may need to be considered separately.

3.12 The ERG highlighted that in ALLY-3, people with genotype 3 HCV had daclatasvir plus sofosbuvir for 12 weeks, although the recommended treatment for this genotype is 24 weeks and includes ribavirin. The ERG suggested that the recommended treatment may result in greater efficacy, particularly in people whose disease is difficult to treat.

Meta-analysis and benchmarking study

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

- peginterferon alfa and ribavirin (PR) for genotypes 1–4 HCV
- telaprevir plus PR for genotype 1 HCV
- boceprevir plus PR for genotype 1 HCV.

The primary end point was sustained virological response at 24 weeks (SVR24). 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. This was to validate the results of the uncontrolled trial and characterise the uncertainty in the data generated by it. Results were framed to show the minimum SVR24 rate needed for daclatasvir to show, with at least 95% probability, that it is better than standard of care (that is, the benchmark).

3.14 For genotype 1 HCV, the benchmarking study suggested that daclatasvir was superior to PR, telaprevir plus PR and boceprevir plus PR whether or not the person's HCV was previously treated. 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.

ERG comments

3.15 The ERG considered the benchmarking study to be appropriate given that the evidence for daclatasvir was from a non-randomised trial (AI444-040). It advised, however, that the results may be biased if the characteristics of people at baseline, or the method of carrying out the trials, differed between AI444-040 and the trials for the comparator treatments. Furthermore, it noted that the results were driven by the SVR24 rates

nearing 100% in AI444-040 and, given the small numbers of people in the trial, these results may not be robust. Overall, the ERG considered that the benchmarking study provided the most robust evidence that daclatasvir was superior to PR, boceprevir plus PR, and telaprevir plus PR for genotype 1 HCV.

Matching-adjusted indirect comparison

3.16 The company carried out a 'matching-adjusted indirect comparison' for some comparisons in the scope for which there was no direct evidence. Without a common comparator between trials, which is needed to carry out traditional indirect comparisons, a matching-adjusted indirect comparison can be used to match and adjust for differences in demographic characteristics at baseline across different study populations. The company presented 3 separate comparisons for genotypes 1 and 3 HCV. For each one, it used data for daclatasvir from AI444-040 or ALLY-3, and carried out a literature search to identify clinical trials for the comparator treatments. The end points compared were SVR rates (at 12 or 24 weeks, depending on which was reported in both the daclatasvir and comparator trials), the rate at which people stopped treatment because of an adverse event, and the rate at which specific adverse events occurred.

3.17 The company reported results for people with any fibrosis stage (F0–F4) and, when the reported baseline characteristics allowed, also for those with fibrosis stage F3–F4. Results for people with any fibrosis stage are presented in table 4.

Table 4 Matching-adjusted indirect comparison results for people with any fibrosis stage (F0–F4)

Treatment history	Treatment	Before weighting			After weighting		
		SVR rate (%)	Difference (%)	95% CI	SVR rate (%)	Difference (%)	95% CI
MAIC 1: genotype 1 HCV							
Previously untreated	DCV+SOF±RBV	95.1	22***	17 to 27	91.5	19***	9 to 28
	TVR+PR	73.0			73.0		
	DCV+SOF±RBV	98.4	32***	27 to 37	98.9	32***	27 to 38
	BOC+PR	66.6			66.6		
	DCV+SOF±RBV	98.4	9**	5 to 13	98.0	9***	4 to 13
	SOF+PR	89.6			89.6		
	DCV+SOF±RBV	98.4	18***	14 to 22	99.2	19***	15 to 22
	SMV+PR	80.6			80.6		
MAIC 2: genotype 3 HCV							
Previously untreated	DCV+SOF±RBV	88.9	23*	8 to 38	89.1	23*	3 to 43
	PR	66.1			66.1		
MAIC 3: genotype 3 HCV							
Previously untreated and treated	DCV+SOF	89.6	4.4	−2 to 11	88.8	3	−8 to 15
	SOF+RBV	85.2			85.2		
Previously untreated	DCV+SOF	90.1	−4.2	−12 to 3	96.4	2	−3 to 8
	SOF+RBV	94.3			94.3		
	DCV+SOF	87.8	21***	13 to 30	95.6	29***	23 to 36
	PR	66.5			66.5		
Previously treated	DCV+SOF	88.4	9.8	−2 to 21	83.2	5	−14 to 23
	SOF+RBV	78.6			78.6		
*p<0.05; **p<0.01; ***p<0.001							
BOC, boceprevir; CI, confidence interval; DCV, daclatasvir; HCV, hepatitis C virus; MAIC, matching-adjusted indirect comparison; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR12/24, sustained virological response at follow-up week 12 or 24; TVR, telaprevir							

ERG comments

3.18 The ERG noted that the matching-adjusted indirect comparison may be biased, particularly if baseline characteristics differed significantly across trials. It explained that, although the company had aimed to adjust for some of the potential differences, whether or not the adjustment was

reliable depended on correctly selecting the factors that influence outcomes. The ERG considered that important characteristics may not have been adjusted for.

3.19 The ERG stated that only 1 person in AI444-040 and 17 people in ALLY-3 did not have an SVR12. It explained that adjusting the SVR rates in AI444-040 and ALLY-3 was sensitive to the baseline characteristics of these few people who did not have an SVR. For this reason, the ERG advised treating the results of the comparisons as unadjusted analyses. However, in the ERG's opinion, daclatasvir was unlikely to be inferior to other treatments for genotype 1 HCV. For genotype 3 HCV, however, the ERG stated that the data were limited, preventing firm conclusions to be drawn.

Naive trial data

3.20 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

3.21 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 had to make when comparing SVR rates, some of which the ERG considered 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). Because of this, the ERG did not consider that these comparisons provided robust evidence that daclatasvir was superior to other treatments, although it provided some weak evidence that it was at least not inferior to them.

Adverse effects of treatment

3.22 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.

3.23 The matching-adjusted indirect comparison showed that daclatasvir-containing treatments generally had lower rates of adverse events than the comparator treatments, with most comparisons showing statistically significant differences. After adjusting the baseline characteristics, no adverse event had a statistically significantly higher rate with the daclatasvir-containing treatment.

ERG comments

3.24 The ERG stated that daclatasvir appeared well tolerated and safe.

Cost-effectiveness evidence

Model structure

3.25 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.

3.26 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 3.44). 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

3.27 The ERG commented that the model structure was generally appropriate and similar to models used in previous hepatitis C appraisals. However, it noted that a key difference between this model and other models was 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 patient groups. Because of this, the ERG considered that relevant data may have been excluded.

3.28 The ERG noted that, in the company's model, 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

3.29 The company's base-case analysis comprised 2 subgroups; people with significant fibrosis (fibrosis stage F3–F4 without cirrhosis), 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 5). '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 a strikethrough in table 5).

Table 5 Intervention and comparator treatments modelled

	Treatment (treatment duration in weeks, treatment duration for PR in weeks [if applicable])		
	Previously untreated HCV	*Previously treated HCV*	*Interferon-ineligible or -intolerant*
Genotype 1 HCV			
Without cirrhosis (F3–F4)	**DCV+SOF (12)** SOF+PR (12, 12) SMV+PR (12, 24) TVR+PR (12, 24−48)	**DCV+SOF (12)** ~~SOF+PR (12, 12)~~	**DCV+SOF (12)** SOF+RBV (24) SMV+SOF (12)

	BOC+PR (32, 28−48) PR (48)		
With cirrhosis (F4)	**DCV+SOF (24)** SOF+PR (12, 12) SMV+PR (12, 24) TVR+PR (12, 48) BOC+PR (44, 48) PR (48)	**DCV+SOF (24)** ~~SOF+PR (12, 12)~~	**DCV+SOF (24)** SOF+RBV (24) SMV+SOF (12)
Genotype 3 HCV			
Without cirrhosis (F3–F4)	**DCV+SOF (12)** ~~SOF+PR (12, 12)~~ SOF+RBV (24) PR (24)	**DCV+SOF (12)** SOF+PR (12, 12) SOF+RBV (24) PR (48)	**DCV+SOF (12)** SOF+RBV (24)
With cirrhosis (F4)	**DCV+SOF+RBV (24)** ~~SOF+PR (12, 12)~~ SOF+RBV (24) PR (24)	**DCV+SOF+RBV (24)** SOF+PR (12, 12) SOF+RBV (24) PR (48)	**DCV+SOF+RBV (24)** SOF+RBV (24)
Genotype 4 HCV			
Without cirrhosis (F3–F4)	**DCV+SOF (12)** **DCV+PR (24, 24−48)** SOF+PR (12, 12) SMV+PR (12, 24) PR (48)	**DCV+SOF (12)** **DCV+PR (24, 24−48)** ~~SOF+PR (12, 12)~~ SMV+PR (12, 48) PR (48)	**DCV+SOF (12)** ~~SOF+RBV (24)~~ ~~SMV+SOF (12)~~
With cirrhosis (F4)	**DCV+SOF (24)** **DCV+PR (24, 24−48)** SOF+PR (12, 12) SMV+PR (12, 24) PR (48)	**DCV+SOF (24)** **DCV+PR (24, 24−48)** ~~SOF+PR (12, 12)~~ SMV+PR (12, 48) PR (48)	**DCV+SOF (24)** ~~SOF+RBV (24)~~ ~~SMV+SOF (12)~~

Strikethrough indicates that the company did not find data for these comparators.

BOC, boceprevir; DCV, daclatasvir; GT, genotype; HCV, hepatitis C virus; PR, peginterferon alpha plus ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

ERG comments

3.30 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.

3.31 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 3.29). The ERG did not consider this justification to be adequate because these comparators are expected to be used in clinical practice. This included:
  - **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.

3.32 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.

3.33 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.

3.34 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.

3.35 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

3.36 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).

3.37 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.

3.38 For genotype 3 HCV, daclatasvir plus sofosbuvir is currently recommended with ribavirin for 24 weeks. The company modelled this treatment for people with compensated cirrhosis. For those with significant fibrosis, the base-case analysis modelled 12 weeks' treatment without ribavirin using data from ALLY-3. However, the company presented a scenario analysis for this population in which it modelled daclatasvir plus sofosbuvir and ribavirin for 24 weeks (the recommended treatment for genotype 3 HCV) using data from AI444-040.

ERG comments

3.39 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 (F3–F4) 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 (F3–F4): 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 (F4): 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 (F4): the ERG noted that the SVR was based on 2 people, and so was unreliable.

Model transitions

3.40 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

3.41 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 (these were

explored by the ERG in sensitivity analyses to its base case; see section 3.54).

3.42 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.

3.43 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

3.44 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.

3.45 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

3.46 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.

3.47 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

3.48 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 3.43).
- 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 table 6.

Table 6 Cost-effectiveness results for HCV with significant fibrosis and HCV with compensated cirrhosis (updated company base case)

		Significant fibrosis (F3–F4)		Compensated cirrhosis (F4)	
HCV genotype	**Treatment history**	**Treatment[1]**	**Incremental ICER[2] (£/QALY gained)**	**Treatment[1]**	**Incremental ICER[2] (£/QALY gained)**
1	Previously untreated HCV	PR	–	PR	–
		No treatment	Dominated	No treatment	Dominated
		SMV+PR	6945	SMV+PR	Extendedly dominated
		TVR+PR	Dominated	TVR+PR	Extendedly dominated
		SOF+PR	8692	SOF+PR	4964
		BOC+PR	Dominated	BOC+PR	Dominated
		DCV+SOF	25,454	DCV+SOF	61,484
	Previously treated HCV	No treatment	–	No treatment	–
		DCV+SOF	4587	DCV+SOF	12,443
		SOF+PR	No data	SOF+PR	No data
	Interferon-ineligible or -intolerant	No treatment	–	No treatment	–
		DCV+SOF	4587	SMV+SOF	2857
		SMV+SOF	Dominated	SOF+RBV	Dominated
		SOF+RBV	Dominated	DCV+SOF	151,547
3	Previously untreated HCV	PR	–	PR	–
		No treatment	Dominated	No treatment	Dominated
		DCV+SOF	Extendedly dominated	SOF+RBV	9957
		SOF+RBV	51,247	DCV+SOF+RBV	89,126
		SOF+PR	No data	SOF+PR	No data
	Previously treated HCV	PR	–	PR	–
		No treatment	Dominated	SOF+PR	6543
		SOF+PR	9043	No treatment	Dominated
		DCV+SOF	Dominated	SOF+RBV	Dominated
		SOF+RBV	439,757	DCV+SOF+RBV	72,662
	Interferon-ineligible or -intolerant	No treatment	–	No treatment	–
		DCV+SOF	7523	SOF+RBV	Extendedly dominated
		SOF+RBV	Dominated	DCV+SOF+RBV	11,781
4	Previously	PR	–	SMV+PR	–

		Significant fibrosis (F3–F4)		Compensated cirrhosis (F4)	
HCV genotype	**Treatment history**	**Treatment[1]**	**Incremental ICER[2] (£/QALY gained)**	**Treatment[1]**	**Incremental ICER[2] (£/QALY gained)**
	untreated HCV	SMV+PR	2016	PR	Dominated
		SOF+PR	3375	No treatment	Dominated
		No treatment	Dominated	DCV+PR	Dominated
		DCV+PR	Dominated	SOF+PR	Dominated
		DCV+SOF	868,019	DCV+SOF	80,548
	Previously treated	No treatment	–	No treatment	–
		PR	Extendedly dominated	PR	2557
		SMV+PR	Extendedly dominated	SMV+PR	Extendedly dominated
		DCV+PR	Extendedly dominated	DCV+PR	3481
		DCV+SOF	3750	DCV+SOF	41,522
		SOF+PR	No data	SOF+PR	No data
	Interferon-ineligible or -intolerant	No treatment	–	No treatment	–
		DCV+SOF	3750	DCV+SOF	12,443
		SMV+SOF	No data	SMV+SOF	No data
		SOF+RBV	No data	SOF+RBV	No data

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.

[1] Treatments are ranked by order of increasing total costs

[2] ICERs comparing the treatment with the cheaper alternative (preceding in the list of treatments) that is neither dominated nor extendedly dominated

BOC, boceprevir; DCV, daclatasvir; HCV, hepatitis C virus; PR, peginterferon alfa plus ribavirin; ICER, incremental cost-effectiveness ratio; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir

3.49 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 rate of SVR, 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

3.50 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 3.48).

3.51 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.

ERG exploratory analyses

3.52 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 3.31).

- Using alternative SVR rates for the following 3 treatments (see section 3.39).
  - **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 3.42).
- **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 3.28).
- **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 3.46).
- **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 3.46).

3.53 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 7 and 8. 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 7 Comparison of cost-effectiveness results from the ERG's and company's base cases: significant fibrosis (fibrosis stage F3–F4 without cirrhosis)

HCV genotype	Treatment history	Daclatasvir treatment	Incremental ICER (£/QALY gained)	
			Company's base case	*ERG's amended base case*
1	Previously untreated HCV	DCV+SOF	25,454 (versus SOF+PR)	19,739 (versus SOF+PR)
	Previously treated HCV		4587 (versus no treatment)	15,687 (versus SOF+PR)
	Interferon-ineligible or -intolerant		4587 (versus no treatment)	5906 (versus no treatment)
3	Previously untreated HCV	DCV+SOF	Extendedly dominated	254,711 (versus PR)
	Previously treated HCV		Dominated	Dominated
	Interferon-ineligible or -intolerant		7523 (versus no treatment)	9607 (versus no treatment)
4	Previously untreated HCV	DCV+PR	Dominated	Dominated
		DCV+SOF	868,019 (versus SOF+PR)	36,203 (versus SMV+PR)
	Previously treated HCV	DCV+PR	Extendedly dominated	Extendedly dominated
		DCV+SOF	3750 (versus no treatment)	5906 (versus no treatment)
	Interferon-ineligible or -intolerant	DCV+SOF	3750 (versus no treatment)	5906 (versus no treatment)

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

The above ICERs for genotype 3 HCV reflect treatment with daclatasvir plus sofosbuvir for 12 weeks, but daclatasvir has a marketing authorisation for genotype 3 HCV only in combination with sofosbuvir and ribavirin and taken for 24 weeks. In response to a request from NICE, the

ERG presented ICERs reflecting the marketing authorisation for genotype 3 HCV, which used alternative SVR rates for daclatasvir (100% from AI0444-040, instead of rates from ALLY-3). Daclatasvir plus sofosbuvir and ribavirin for 24 weeks had the following ICERs:

- £81,260 per QALY gained compared with PR for previously untreated people
- £102,939 per QALY gained compared with sofosbuvir plus PR for previously treated people
- £18,979 per QALY gained compared with no treatment for people who are ineligible for, or cannot tolerate, interferon.

Table 8 Comparison of cost-effectiveness results from the ERG's and company's base cases: compensated cirrhosis (fibrosis stage F4)

HCV genotype	Treatment history	Daclatasvir treatment	Incremental ICER (£/QALY gained)	
			Company's base case	*ERG's amended base case*
1	Previously untreated HCV	DCV+SOF	61,484 (versus SOF+PR)	118,636 (versus SOF+PR)
	Previously treated HCV		12,443 (versus no treatment)	105,972 (versus SOF+PR)
	Interferon-ineligible or -intolerant		151,547 (versus SMV+SOF)	311,193 (versus SMV+SOF)
3	Previously untreated HCV	DCV+SOF	89,126 (versus SOF+RBV)	139,045 (versus SOF+PR)
	Previously treated HCV		72,662 (versus SOF+PR)	143,489 (versus SOF+PR)
	Interferon-ineligible or -intolerant		11,781 (versus no treatment)	172,219 (versus SOF+RBV)
4	Previously untreated HCV	DCV+PR	Dominated	Dominated
		DCV+SOF	80,548 (versus SMV+PR)	150,076 (versus SMV+PR)
	Previously treated HCV	DCV+PR	3481 (versus PR)	52,459 (versus SOF+PR)
		DCV+SOF	41,522 (versus DCV+PR)	73,768 (versus DCV+PR)
	Interferon-ineligible or -intolerant	DCV+SOF	12,443 (versus no treatment)	190,379 (versus SMV+SOF)

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

Sensitivity analyses to the ERG's amended base case

3.54 The ERG carried out 5 scenario analyses to explore the uncertainty of its amended base case. For the results, see tables 9–12.

- **Scenario 1** – excluding 2 comparators:
  - **Scenario 1.1 (genotype 1)**: excluding simeprevir plus PR for previously untreated HCV because it is thought to have reduced effectiveness in people with genotype 1a HCV who have a genetic mutation called Q80K polymorphism.
  - **Scenario 1.2 (genotypes 1 and 4)**: Excluding simeprevir plus sofosbuvir, because it is will be a future NICE appraisal, for people with HCV with or without cirrhosis (F3–F4, or F4) who are ineligible for, or cannot tolerate, interferon.
- **Scenario 2** – using alternative treatment durations that are recommended in the marketing authorisation, for the following treatments:
  - **Scenario 2.1 (genotypes 1 and 4)**
    - Daclatasvir plus sofosbuvir for previously treated genotype 1 HCV in people without cirrhosis (F3–F4) – 24 weeks instead of 12 weeks.
    - Daclatasvir plus sofosbuvir for previously untreated genotype 1 or 4 HCV, in people with cirrhosis (F4) – 12 weeks instead of 24 weeks.
  - **Scenario 2.2 (genotype 4)**: simeprevir plus PR for previously treated HCV – 48 weeks instead of 24 weeks for the PR component.
  - **Scenario 2.3 (genotypes 1, 3 and 4)**: sofosbuvir plus PR for all relevant subgroups – 24 weeks instead of 12 weeks.
- **Scenario 3 (genotype 1)** – using an alternative rate for stopping treatment for previously untreated HCV in people without cirrhosis (F3–F4). The ERG noted that, unlike for other HCV

genotypes , the rate applied in the company's model for genotype 1 HCV related to discontinuation because of an adverse event and did not capture other reasons for stopping treatment.

- **Scenario 4** – using alternative SVR rates for the following treatments and populations:
  - **Genotype 1**: sofosbuvir plus PR for previously untreated HCV in people without cirrhosis (F3–F4).
  - **Genotype 3**:
    - Daclatasvir plus sofosbuvir and ribavirin for previously untreated HCV, in people with cirrhosis (F4).
    - Daclatasvir plus sofosbuvir and ribavirin for previously treated HCV, in people with cirrhosis (F4).
    - Daclatasvir plus sofosbuvir and ribavirin for people with cirrhosis (F4) who are ineligible for, or cannot tolerate, interferon.
    - Sofosbuvir plus ribavirin for people with cirrhosis (F4) who are ineligible for, or cannot tolerate, interferon.
  - **Genotype 4**:
    - Sofosbuvir plus PR for previously untreated HCV, in people with cirrhosis (F4).
- **Scenario 5 (genotypes 1, 3 and 4)** – using alternative transition probabilities to model the natural history of the disease, specifically:
  - **Scenario 5.1**: disease progression from fibrosis stage F3 to fibrosis stage F4 based on people who attended non-tertiary referral centres.
  - **Scenario 5.2**: disease progression from fibrosis stage F3 to fibrosis stage F4 based on people who attended tertiary referral centres.

- **Scenario 5.3**: disease progression from fibrosis stage F4 to decompensated cirrhosis and hepatocellular carcinoma.

Table 9 ICERs (£/QALY gained) from the ERG scenario analyses (genotype 1)

	Significant fibrosis (F3–F4)			Compensated cirrhosis (F4)		
	Previously untreated HCV	**Previously treated HCV**	**Interferon-ineligible / intolerant**	**Previously untreated HCV**	**Previously treated HCV**	**Interferon-ineligible / intolerant**
BC	**19,739 versus SOF+PR**	**15,687 versus SOF+PR**	**5906 versus NT**	**118,636 versus SOF+PR**	**105,972 versus SOF+PR**	**311,193 versus SMV+SOF**
1.1	19,739 versus SOF+PR	–	–	118,636 versus SOF+PR	–	–
1.2	–	–	5906 versus NT	–	–	25,349 versus NT
2.1	–	24 weeks: 81,733 versus SOF+PR	–	12 weeks: 24,074 versus SOF+PR	–	–
2.3	15,943 versus SMV+PR	5906 versus NT	–	59,390 versus SOF+PR	52,297 versus SOF+PR	–
3	19,838 versus SOF+PR	–	–	–	–	–
4	31,005 versus SOF+PR	–	–	–	–	–
5.1	28,542 versus SOF+PR	23,152 versus SOF+PR	10,196 versus NT	–	–	–
5.2	24,525 versus SOF+PR	19,736 versus NT	8199 versus NT	–	–	–
5.3	18,901 versus SOF+PR	15,091 versus SOF+PR	5901 versus NT	114,967 versus SOF+PR	102,821 versus SOF+PR	298,134 versus SMV+SOF

BC, base case (as amended by the ERG, see section 3.54); ERG, Evidence Review Group; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; PR, peginterferon and ribavirin; SMV, simeprevir; SOF, sofosbuvir; NT, no treatment

Table 10 ICERs (£/QALY gained) from the ERG scenario analyses (genotype 3)

	Significant fibrosis (F3–F4)			Compensated cirrhosis (F4)		
	Previously untreated HCV	**Previously treated HCV**	**Interferon-ineligible / intolerant**	**Previously untreated HCV**	**Previously treated HCV**	**Interferon-ineligible / intolerant**
BC	**254,711 versus PR**	**Dominated**	**9607 versus NT**	**139,045 versus SOF+PR**	**143,489 versus SOF+PR**	**172,219 versus SOF+RBV**
2.3	–	Extendedly dominated	–	68,893 versus SOF+PR	73,086 versus SOF+PR	–
4.	–	–	–	Dominated	Dominated	24,477 versus NT
5.1	317,490 versus PR	Dominated	14,354 versus NT	–	–	–
5.2	289,250 versus PR	Dominated	12,102 versus NT	–	–	–
5.3	238,497 versus PR	Dominated	9238 versus NT	133,822 versus SOF+PR	138,039 versus SOF+PR	165,620 versus SOF+RBV

BC, base case (as amended by the ERG, see section 3.54); ERG, Evidence Review Group; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; PR, peginterferon alpha and ribavirin; RBV, ribavirin; SOF, sofosbuvir; NT, no treatment

Table 2 ICERs (£/QALY gained) from the ERG scenario analyses (genotype 4, daclatasvir plus sofosbuvir)

	Significant fibrosis (F3–F4)			Compensated cirrhosis (F4)		
	Previously untreated HCV	**Previously treated HCV**	**Interferon-ineligible / intolerant**	**Previously untreated HCV**	**Previously treated HCV**	**Interferon-ineligible / intolerant**
BC	**36,203 versus SMV+PR**	**5906 versus NT**	**5906 versus NT**	**150,076 versus SMV+PR**	**73,768 versus DCV+PR**	**190,379 versus SMV+SOF**
1.2	–	–	5906 versus NT	–	–	25,349 versus NT
2.1	–	–	–	12 weeks: 45,695 versus	–	–

				SMV+PR		
2.2	–	5906 versus NT	–	–	73,768 versus DCV+PR	–
2.3	–	–	–	150,076 versus SMV+PR	73,768 versus DCV+PR	–
4	–	–	–	150,076 versus SMV+PR	–	–
5.1	50,174 versus SMV+PR	10,196 versus NT	10,196 versus NT	–	–	–
5.2	43,855 versus SMV+PR	8199 versus NT	8199 versus NT	–	–	–
5.3	34,413 versus SMV+PR	5901 versus NT	5901 versus NT	145,415 versus SMV+PR	72,177 versus DCV+PR	183,308 versus SMV+SOF
BC, base case (as amended by the ERG, see section 3.54); DCV, daclatasvir; ERG, Evidence Review Group; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; PR, peginterferon alpha and ribavirin; SMV, simeprevir; SOF, sofosbuvir; NT, no treatment						

Table 3 ICERs (£/QALY gained) from the ERG scenario analyses (genotype 4, daclatasvir plus PR)

	Significant fibrosis (F3–F4)		**Compensated cirrhosis (F4)**	
	Previously untreated HCV	**Previously treated HCV**	**Previously untreated HCV**	**Previously treated HCV**
BC	**Dominated**	**Extendedly dominated**	**Dominated**	**52,459 versus SOF+PR**
2.2	–	Extendedly dominated	–	52,459 versus SOF+PR
2.3	–	–	150,076 versus SMV+PR	8775 versus PR
4	–	–	Dominated	–

5.1	Dominated	Extendedly dominated	–	–
5.2	Dominated	Extendedly dominated	–	–
5.3	Dominated	Extendedly dominated	Dominated	50,837 versus SOF+PR
BC, base case (as amended by the ERG, see section 3.54); ERG, Evidence Review Group; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; PR, peginterferon alpha and ribavirin; SMV, simeprevir; SOF, sofosbuvir				

Company's additional evidence

3.55 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.
- NHS England Early Access Programme: daclatasvir plus sofosbuvir or ledipasvir–sofosbuvir.
- 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.

3.56 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 13. The NHS England Early Access Programme used a12-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 13 'Real-world' data for daclatasvir treatments

Source	Endpoint	SVR rate (%)					
		Genotype 1 HCV		Genotype 3 HCV		Genotype 4 HCV	
		DCV + SOF	DCV + SOF + RBV	DCV + SOF	DCV + SOF + RBV	DCV + SOF	DCV + SOF + RBV
NHS EAP	SVR4	4/5 (80)	40/45 (89)	5/7 (71)	92/113 (81)	Not reported	Not reported
EU CUP	SVR12	77/78 (99)	30/31 (97)	11/11 (100)	11/13 (85)	4/4 (100)	5/5 (100)
CUP, Compassionate Use Programme; DCV, daclatasvir; EAP; Early Access Programme; HCV, hepatitis C virus; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response.							

3.57 The company, citing the clinical guidelines of the European Association for the Study of the Liver, noted that treatment options for genotype 3 HCV are limited: ledipasvir–sofosbuvir is not recommended for this genotype, and sofosbuvir plus ribavirin is recommended only for people without cirrhosis. Because of this, it presented a cost-effectiveness analysis for genotype 3 HCV in people with cirrhosis who are ineligible for, or cannot tolerate, interferon, because these people have no further treatment options and a high unmet need. Using SVR rates observed in the 'real-world' setting, the company reported ICERs for daclatasvir plus sofosbuvir with or without ribavirin compared with no treatment ranging from £4152 per QALY gained (12 weeks' treatment) to 14,037 per QALY gained (24 weeks' treatment).

ERG critique of the company's additional evidence

3.58 The ERG stated that because people were not randomised to treatment groups, the treatment given was decided individually, which may have introduced selection bias. The ERG noted that the 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 considered daclatasvir to be clinically effective in people with decompensated cirrhosis. However, it stated that patient numbers remain limited to draw firm conclusions about the differences across genotypes or other subgroups.

3.59 The ERG stated that the company's model was not designed to reflect the different prognosis of people with decompensated cirrhosis; as a result, the company modelled treatment for this population in the F4 state of the model. The ERG highlighted the uncertainty around this, and stated that the effect on the ICERs was not predictable. For the analysis for people with genotype 3 HCV who are ineligible for, or cannot tolerate, interferon, the ERG noted that the data used reflected both previously untreated and previously treated subgroups. It also questioned why the company used a 12-week treatment duration for daclatasvir plus sofosbuvir when the licence recommends 24 weeks' treatment for genotype 3 HCV with compensated cirrhosis. The ERG noted that, although recommended by NICE, the company excluded sofosbuvir plus ribavirin as a comparator because the clinical guidelines of the European Association for the Study of the Liver do not recommend it for this population.

3.60 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 discussed the clinical management of chronic hepatitis C in adults. It recognised that treatment decisions and response to treatment are influenced by hepatitis C virus (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 Committee recognised 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. Without treatment people risk further

disease progression, for example, to compensated 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.

4.2 The Committee discussed whether the technologies in the 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 in combination with 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 in combination with 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 for treating chronic hepatitis C (given sofosbuvir plus ribavirin is not recommended for people with genotype 1 or 4 HCV) and on simeprevir for treating chronic hepatitis C. The Committee acknowledged that the marketing authorisation for daclatasvir offers people with genotype 1 or 4 HCV the option to have shortened courses of treatment, without peginterferon alfa, thereby avoiding the adverse effects associated with interferon-based therapy. The Committee was also aware that

the oral combination of simeprevir plus sofosbuvir has not yet been appraised by NICE. Therefore it could not be considered as established practice. The Committee concluded that sofosbuvir in combination with ribavirin, with or without peginterferon alfa, and simeprevir in combination with peginterferon alfa and ribavirin, as recommended in NICE guidance, were relevant comparators for daclatasvir plus sofosbuvir.

4.3 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.

4.4 The Committee noted that the marketing authorisation for daclatasvir recommends 2 treatment combinations for genotype 4 HCV: daclatasvir plus sofosbuvir and daclatasvir plus 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. The Committee concluded that, in clinical practice, daclatasvir plus sofosbuvir would be predominantly used for genotype 4 HCV.

Clinical effectiveness

4.5 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 severe disease, 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.

4.6 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 heard from the clinical experts that in ALLY-3, which evaluated 12 weeks' treatment with daclatasvir plus sofosbuvir for genotype 3

HCV with or without cirrhosis, people had treatment for a shorter duration than recommended in the marketing authorisation (12 instead of 24 weeks) and without ribavirin. This was likely to have underestimated the efficacy of daclatasvir plus sofosbuvir in people with cirrhosis in ALLY-3. The Committee agreed that the data from ALLY-3 could not reliably inform the effectiveness of daclatasvir plus sofosbuvir and ribavirin for genotype 3 HCV in people with cirrhosis. It was aware that the data underpinning the treatment for this population were available from only 5 people in AI444-040. 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, and so was uncertain.

4.7 The Committee discussed the SVR rates for daclatasvir and its comparators. It understood that the company compiled the SVR rates from individual arms in trials groups without doing formal comparisons. The Committee considered this to be a limitation of the data that reduced the validity of the SVR rates and introduced considerable uncertainty. 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.

4.8 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 daclatasvir 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.

4.9 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 3.55 and 3.56). The Committee was aware that the marketing authorisation for daclatasvir 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 daclatasvir was clinically effective in people with decompensated cirrhosis. The company considered that the trial results in the original submission 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 daclatasvir was largely in line with the evidence from clinical trials. The Committee noted, however, that the SVR rates for genotype 3 HCV from 'real-world' use were higher than those observed in people with cirrhosis in ALLY-3. They were also higher than the rates observed in other trials including people with decompensated cirrhosis who had 12 weeks of daclatasvir plus sofosbuvir and ribavirin (ALLY-1). The Committee reiterated its previous conclusion (see section 4.6) that daclatasvir was clinically

effective in treating chronic hepatitis C, although some uncertainty remained for genotype 3 HCV.

Cost effectiveness

4.10 The Committee discussed the appropriate population for the consideration of daclatasvir'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 having 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 daclatasvir 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 concluded that it would focus its considerations on people with significant fibrosis without cirrhosis (fibrosis stage F3–F4) and those with compensated cirrhosis (fibrosis stage F4).

4.11 The Committee noted the ERG's comment that the company considered the population of people with previously treated HCV as a single group without stratifying it by the type of response to previous treatment (that is, no response, partial response or relapse). It heard from the clinical experts that the type of previous response would not influence the SVR rate with daclatasvir. The Committee concluded that the population with previously treated HCV could be treated as a single group.

4.12 The Committee discussed the transition probabilities in the company's model. It noted the ERG's concern that in the 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 disease progression in people with cirrhosis who had SVR. The Committee concluded that it would be plausible to assume in the model a reduced risk of disease progression for people with cirrhosis who had an SVR compared with those who did not have an SVR.

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 included the comparators that are recommended in NICE technology appraisal guidance, for which the company could not find data, and excluded those that are not. The Committee agreed that the comparators recommended by NICE are expected to be used in clinical practice, and so should be included in the analysis. It also agreed that the comparators that are not recommended by NICE should be excluded because they do not represent established clinical practice. The Committee noted that simeprevir plus sofosbuvir was included as a comparator in both the company's base case and the ERG's amended base case, although the ERG excluded it in a scenario analysis. The Committee was aware that simeprevir plus sofosbuvir has not been appraised by NICE for people with HCV who are ineligible for, or cannot tolerate, interferon. Because of this, it agreed that simeprevir plus sofosbuvir would not be considered, at present, to represent established clinical practice, and should not be included as a comparator. The Committee concluded that the comparators included by the ERG were appropriate, but that simeprevir plus sofosbuvir should not be included as a comparator for people with HCV who are ineligible for, or cannot tolerate, interferon.

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 noted that the ERG had used alternative SVR rates in its amended base case for 3 treatments:

- **Daclatasvir plus sofosbuvir for previously untreated genotype 1 HCV with significant fibrosis:** the ERG used 100% instead of 95%. The Committee concluded that the difference in SVR rates was small and unlikely to affect cost effectiveness.
- **Sofosbuvir plus ribavirin for genotype 3 HCV in people with compensated cirrhosis who are ineligible for, or cannot tolerate, interferon:** the ERG used an SVR rate of 92.3% compared with a rate of 21.4% used by the company. The Committee noted the significant 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 previously untreated people with compensated cirrhosis in the VALENCE trial who had 24 weeks' treatment. It considered that extrapolating this SVR rate to people who are ineligible for, or cannot tolerate, interferon was appropriate because the clinical data for daclatasvir plus sofosbuvir in people who are ineligible for, or cannot tolerate, interferon was extrapolated from people with previously untreated HCV. The Committee agreed that although both rates were uncertain, the SVR rate used by the company (21.4%) did not reflect the recommended treatment duration for sofosbuvir plus ribavirin and was too low. Therefore, it concluded that the alternative rate used by the ERG (92.3%) was more likely to be a valid estimate for this population.

- **Sofosbuvir plus PR for previously untreated, genotype 4 HCV in people with compensated cirrhosis:** the ERG used 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.

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 (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. 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, others may have long-term health effects. The Committee considered that assuming the same utility value after SVR for people with or without cirrhosis was highly uncertain. It was aware that equal utility increments for having an SVR were used in previous technology appraisals for hepatitis C. Without further evidence, the Committee concluded that the effect of SVR on health-related quality of life in the model should be assumed to be the same whether or not the person has cirrhosis.

4.17 The Committee considered the costs included in the model. It noted that the company applied monitoring costs to people who had an SVR for 1 year after treatment ends. However, the ERG assumed in its amended base case that people with cirrhosis who had an SVR would continue to be monitored throughout their lifetime. The Committee recalled its conclusion that it would be plausible to assume a risk of disease progression for people with cirrhosis who had an SVR, although it would be lower than for those who did not have an SVR (see section 4.12). Because of this, the Committee considered that it would be appropriate to apply ongoing monitoring costs for all people with cirrhosis. The clinical experts also confirmed that in clinical practice, people with cirrhosis would be monitored every 6 months. The Committee concluded that extending monitoring beyond 1 year for people with cirrhosis who had an SVR was appropriate.

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. Because of this, the Committee concluded that it should be cautious about considering the cost effectiveness of daclatasvir based on the presented incremental cost-effectiveness ratios (ICERs).

4.19 The Committee discussed what would be the best source of evidence on the cost effectiveness of daclatasvir. It agreed that the ERG's amended base case (see section 3.52) provided the best evidence because it reflected the Committee's preferred analysis more closely than the company's base case. The Committee noted that the difference between the ICERs estimated by the ERG and those estimated by the company was driven mainly by amending the comparators and SVR rates. The Committee agreed that the comparators included by the ERG were appropriate, but that simeprevir plus sofosbuvir should not be included as a comparator for people with HCV who are ineligible for, or cannot tolerate, interferon (see section 4.13). It also agreed that the alternative SVR rates used by the ERG for daclatasvir plus sofosbuvir, sofosbuvir plus ribavirin, and sofosbuvir plus PR were generally appropriate (see section 4.15). However, the Committee recognised that all the ICERs presented were uncertain, mainly because the evidence

base used to inform the SVR rates in the model was weak. It agreed that the high uncertainty in the SVR rates should be taken into account in its decision-making, by considering the effect of alternative SVR rates on the ICERs. The Committee concluded that it would need to be persuaded that the ICERs were sufficiently robust to plausible changes in parameter values, especially SVR rates, before recommending daclatasvir.

Genotype 1 with significant fibrosis

4.20 The Committee noted that in the ERG's amended base case, daclatasvir plus sofosbuvir was associated with the following ICERs:

- **People with previously untreated HCV (12 weeks' treatment):** £19,700 per quality-adjusted life-year (QALY) gained compared with sofosbuvir plus PR, which became £31,000 per QALY gained when a slightly higher SVR rate for sofosbuvir plus PR was used (86.5% instead of 81%).
- **People with previously treated HCV (12 weeks' treatment):** £15,700 per QALY gained compared with sofosbuvir plus PR, and all scenarios presented by the ERG for this treatment duration resulted in ICERs under £25,000 per QALY gained.
- **People with previously treated HCV (24 weeks' treatment):** £81,700 per QALY gained compared with sofosbuvir plus PR.
- **People who are ineligible for, or cannot tolerate, interferon (12 weeks' treatment):** £5,900 per QALY gained compared with no treatment, and all scenarios presented by the ERG resulted in ICERs under £20,000 per QALY gained. When simeprevir plus sofosbuvir was excluded as a comparator, the ICER for daclatasvir remained £5900 per QALY gained compared with no treatment.

The Committee agreed that daclatasvir plus sofosbuvir could be considered a cost-effective use of NHS resources for genotype 1 HCV with significant fibrosis only when used for 12 weeks in people with previously treated HCV, or in those who are ineligible for, or cannot tolerate, interferon. The Committee also agreed that daclatasvir plus sofosbuvir could not be considered a cost-effective use of NHS resources when used for 12 weeks for people with previously untreated genotype 1 HCV or for 24 weeks for treating genotype 1 HCV in people with significant fibrosis.

Genotype 1 with compensated cirrhosis

4.21 The Committee noted that in the ERG's amended base case, daclatasvir plus sofosbuvir was associated with the following ICERs:

- **People with previously untreated HCV (24 weeks' treatment):** £118,600 per QALY gained compared with sofosbuvir plus PR, and remained over £50,000 per QALY gained across all of the ERG's scenario analyses for this treatment duration.
- **People with previously untreated HCV (12 weeks' treatment):** £24,100 per QALY gained compared with sofosbuvir plus PR.
- **People with previously treated HCV (24 weeks' treatment):** £106,000 per QALY gained compared with sofosbuvir plus PR, and remained over £50,000 per QALY gained across all of the ERG's scenario analyses.
- **People who are ineligible for, or cannot tolerate, interferon (24 weeks' treatment):** £311,200 per QALY gained compared with simeprevir plus sofosbuvir, and £25,300 per QALY compared with no treatment when simeprevir plus sofosbuvir was excluded from the analysis.

The Committee agreed that daclatasvir plus sofosbuvir could not be considered a cost-effective use of NHS resources for treating genotype 1 HCV in people with cirrhosis.

Genotype 3 with significant fibrosis

4.22 The Committee was aware that the ICERs originally presented for genotype 3 HCV with significant fibrosis included 12 weeks' treatment with daclatasvir plus sofosbuvir, whereas the only recommended treatment regimen for genotype 3 HCV in the marketing authorisation is daclatasvir plus sofosbuvir and ribavirin for 24 weeks. The Committee noted that the ERG later presented ICERs using the recommended treatment regimen for genotype 3 HCV (see table 7). Daclatasvir plus sofosbuvir and ribavirin for 24 weeks was associated with ICERs of £81,300 per QALY gained compared with PR for previously untreated HCV, £102,900 per QALY gained compared with sofosbuvir plus PR for previously treated HCV, and £18,900 per QALY gained compared with no treatment for people who are ineligible for, or cannot tolerate, interferon. The Committee noted that the SVR rate used for daclatasvir in this analysis was 100% (for all 3 groups), based on only 5 people in AI4440-040 who had 24 weeks' treatment with daclatasvir plus sofosbuvir and ribavirin for genotype 3 HCV. Furthermore, the 5 people had previously untreated disease and the SVR rate was extrapolated to people with previously treated disease, and people who are ineligible for, or cannot tolerate, interferon. The Committee agreed that the SVR rate used for daclatasvir was highly uncertain and unreliable for this population, concluding that daclatasvir plus sofosbuvir and ribavirin for 24 weeks could not be considered a cost-effective use of NHS resources for genotype 3 HCV with significant fibrosis.

Genotype 3 with compensated cirrhosis

4.23 For genotype 3 HCV in people with compensated cirrhosis, the Committee noted that the ERG modelled the recommended treatment regimen (that is, daclatasvir plus sofosbuvir and ribavirin for 24 weeks). In the ERG's amended base case, daclatasvir plus sofosbuvir and ribavirin was associated with the following ICERs:

- **People with previously untreated HCV (24 weeks' treatment):** £139,000 per QALY gained compared with sofosbuvir plus PR. Daclatasvir plus sofosbuvir and ribavirin was either dominated (that is, was both less effective and more costly) or associated with ICERs over £50,000 per QALY gained across the ERG's scenario analyses.
- **People with previously treated HCV (24 weeks' treatment):** £143,500 per QALY gained compared with sofosbuvir plus PR. Daclatasvir plus sofosbuvir and ribavirin was either dominated or associated with ICERs over £50,000 per QALY gained across the ERG's scenario analyses.
- **People who are ineligible for, or cannot tolerate, interferon (24 weeks' treatment):** £172,200 per QALY gained compared with sofosbuvir plus ribavirin, which remained over £20,000 per QALY across the ERG's scenario analyses.

The Committee agreed that daclatasvir plus sofosbuvir and ribavirin could not be considered a cost-effective use of NHS resources for genotype 3 HCV in people with compensated cirrhosis.

4.24 The Committee noted that the company presented a cost-effectiveness analysis for people with genotype 3 HCV who are ineligible for, or cannot tolerate, interferon using SVR rates for HCV in people with decompensated cirrhosis seen in clinical practice (see section 3.57). In this, the ICER for daclatasvir plus sofosbuvir with or without ribavirin compared with no treatment was £14,000

per QALY gained when 24 weeks' treatment was used. The Committee was aware that the company's model was not set up to estimate cost effectiveness in people with decompensated cirrhosis, and that modelling treatment for this population in the F4 state would not reflect the natural history of HCV in people with decompensated cirrhosis. The Committee noted the company's suggestion that because daclatasvir was cost effective using SVR rates from people with decompensated cirrhosis, it would also be cost effective in people with less severe disease in whom higher SVR rates would be expected. The Committee discussed whether the company's analysis could be used to inform the cost effectiveness of daclatasvir for HCV in people with compensated cirrhosis. It noted that sofosbuvir plus ribavirin, which is a relevant comparator for this population and recommended by NICE, had not been included in the analysis. In addition, the ICERs produced did not reflect the ERG's amended base case (see section 3.52). Given the limitations in the analysis and the need to make decisions on a consistent basis using the same model, the Committee concluded that the company's additional evidence was not suitable to make recommendations for genotype 3 HCV in people with compensated cirrhosis who are ineligible for, or cannot tolerate, interferon.

Genotype 4 with significant fibrosis

4.25 The Committee noted that in the ERG's amended base case, daclatasvir plus sofosbuvir was associated with the following ICERs:

- **People with previously untreated HCV (12 weeks' treatment):** £36,200 per QALY gained compared with simeprevir plus PR, and remained over £30,000 per QALY gained across all of the ERG's scenario analyses.

- **People with previously treated HCV (12 weeks' treatment):** £5900 per QALY gained compared with no treatment, and all scenarios presented by the ERG resulted in ICERs under £20,000 per QALY gained.
- **People with previously treated HCV (24 weeks' treatment):** no results presented.
- **People who are ineligible for, or cannot tolerate, interferon (12 weeks' treatment):** £5900 per QALY gained compared with no treatment, and all scenarios presented by the ERG resulted in ICERs under £20,000 per QALY gained. When simeprevir plus sofosbuvir was excluded as a comparator, the ICER for daclatasvir remained at £5900 per QALY gained compared with no treatment.

The Committee agreed that daclatasvir plus sofosbuvir could be considered a cost-effective use of NHS resources for genotype 4 HCV with significant fibrosis only when used for 12 weeks in people with previously treated HCV, or in those who are ineligible for, or cannot tolerate, interferon. It also agreed that daclatasvir plus sofosbuvir could not be considered a cost-effective use of NHS resources when used for 12 weeks in people with previously untreated genotype 4 HCV or for 24 weeks for genotype 4 HCV in people with significant fibrosis. Without an ICER for daclatasvir plus sofosbuvir for 24 weeks in people with previously treated HCV, the Committee could not recommend this treatment duration for this subgroup.

4.26 The Committee noted that in the ERG's amended base case, daclatasvir plus PR was dominated for previously untreated HCV and extendedly dominated (that is, a combination of 2 of its comparators provides equal health at a reduced cost) for previously treated HCV, and remained so across all of the ERG's scenario analyses. The Committee agreed that daclatasvir plus PR could not

be considered a cost-effective use of NHS resources for treating genotype 4 HCV in people with significant fibrosis.

Genotype 4 with compensated cirrhosis

4.27 The Committee noted that in the ERG's amended base case, daclatasvir plus sofosbuvir was associated with the following ICERs:

- **People with previously untreated HCV (24 weeks' treatment):** £150,000 per QALY gained compared with simeprevir plus PR, and remained over £50,000 per QALY gained across all of the ERG's scenario analyses for this treatment duration.
- **People with previously untreated HCV (12 weeks' treatment):** £45,700 per QALY gained compared with simeprevir plus PR.
- **People with previously treated HCV (24 weeks' treatment):** £73,800 per QALY gained compared with daclatasvir plus PR, and remained over £50,000 per QALY gained across all of the ERG's scenario analyses.
- **People who are ineligible for, or cannot tolerate, interferon (24 weeks' treatment):** £190,400 per QALY gained compared with simeprevir plus sofosbuvir, and £25,300 per QALY compared with no treatment when simeprevir plus sofosbuvir was excluded from the analysis.

The Committee agreed that daclatasvir plus sofosbuvir could not be considered a cost-effective use of NHS resources for treating genotype 4 HCV in people with cirrhosis.

4.28 The Committee noted that in the ERG's amended base case, daclatasvir plus PR was dominated in people with previously untreated HCV, and remained so across all of the ERG's scenario

analyses, except when the duration of sofosbuvir plus PR was extended to 24 weeks, where the ICER was £150,100 per QALY gained compared with simeprevir plus PR. In people with previously treated HCV, the ICER was £52,500 per QALY gained compared with sofosbuvir plus PR in the ERG's amended base case. In all scenario analyses the ICER was over £50,000 per QALY gained, except when the duration of sofosbuvir plus PR was extended to 24 weeks, where the ICER was £8800 per QALY gained compared with PR. The Committee agreed that daclatasvir plus PR could not be considered a cost-effective use of NHS resources for treating genotype 4 HCV in people with cirrhosis.

Conclusion

4.29 Based on the considerations in sections 4.20 to 4.28, the Committee concluded:

- For treating genotype 1 or 4 HCV, daclatasvir plus sofosbuvir for 12 weeks is recommended as an option in adults, only if the person has significant fibrosis without cirrhosis and:
  - has had previous treatment for chronic hepatitis C or
  - is ineligible for, or cannot tolerate, interferon.
- For treating genotype 1 or 4 HCV, daclatasvir plus sofosbuvir (with or without ribavirin) for 24 weeks is not recommended in adults.
- For treating genotype 3 HCV, daclatasvir plus sofosbuvir in combination with ribavirin for 24 weeks is not recommended in adults with compensated cirrhosis or who have had previous treatment.
- For treating genotype 4 HCV, daclatasvir for 24 weeks plus PR for 24–48 weeks is not recommended in adults.

NHS England

4.30 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)
- 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 were 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. With this in mind, people with chronic hepatitis C may accept prioritising treatment for those with more severe disease (including some people without cirrhosis), potentially determined by multidisciplinary teams.

4.31 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 NHS England's estimates were significantly overestimated. 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 onwards transmission. The Committee further understood that NHS England is exploring other ways of managing the financial impact of use of these new drugs, such as tendering, and that some argue that the rebate provided by companies as part of the 2014 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 one of the key of objectives 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'.

4.32 The Committee recognised that the Guide to 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 preliminary recommendations. The Committee emphasised that, if the uncertainties were accounted for in the modelling of the cost effectiveness (for example, incremental QALYs gained from achieving SVR12, the costs and benefits associated with treatment of reinfection, and savings from prevention of onward transmission), the ICERs for the recommended regimens were likely to remain below the lower threshold of £20,000 per QALY gained.

4.33 The Committee understood that, given the rapid sequential assessment of direct antiviral drug combinations now licensed for the treatment of 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 patients, clinicians and the NHS. The Committee agreed that further work by NICE to support this should be initiated sooner rather than later.

Pharmaceutical Price Regulation Scheme

4.34 The Committee considered whether it should take into account the consequences of 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 for the consideration of the cost effectiveness of daclatasvir.

Equality issues

4.35 The Committee noted the potential equalities issue raised that there is ethnic variation in the genotype profile of chronic hepatitis C and that ethnic group influences treatment response. The company stated that there should be consideration of the ethical issues relating to the availability of treatment options for the HCV genotypes known to be more prevalent in different ethnic groups. The Committee was aware that minority ethnic groups are more highly represented in the genotype 4 HCV population than in

the genotype 1 or 3 populations. Because the Committee made its recommendations based on the cost-effectiveness data and on the treatment regimens specified in the marketing authorisation, and the recommendations for daclatasvir plus sofosbuvir were the same for genotypes 1 and 4 HCV, it did not consider that its recommendations constituted an equality issue.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Daclatasvir for treating chronic hepatitis C	Section
Key conclusion		
The Committee was aware that the estimates of sustained virological response (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, and this uncertainty was reflected in the cost-effectiveness estimates. The Committee concluded that it would need to be persuaded that the incremental cost-effectiveness ratios (ICERs) were sufficiently robust to plausible changes in parameter values, especially SVR rates, before recommending daclatasvir. **Genotype 1 with significant fibrosis** The Committee concluded that daclatasvir plus sofosbuvir could be considered a cost-effective use of NHS resources for genotype 1 hepatitis C virus (HCV) with significant fibrosis only when used for 12 weeks in people with previously treated HCV, or in those who are ineligible for, or cannot tolerate, interferon. The Committee concluded that daclatasvir plus sofosbuvir could not be considered a cost-effective use of NHS resources when used for 12 weeks for people with previously untreated genotype 1 HCV or for 24 weeks for treating		4.18–4.23, 4.25–4.28

genotype 1 HCV in people with significant fibrosis.

Genotype 1 with compensated cirrhosis

The Committee concluded that daclatasvir plus sofosbuvir could not be considered a cost-effective use of NHS resources for treating genotype 1 HCV in people with cirrhosis.

Genotype 3 with significant fibrosis

The Committee agreed that the SVR rate used for daclatasvir was highly uncertain and unreliable for this population, concluding that daclatasvir plus sofosbuvir and ribavirin for 24 weeks could not be considered a cost-effective use of NHS resources for genotype 3 HCV with significant fibrosis.

Genotype 3 with compensated cirrhosis

The Committee concluded that daclatasvir plus sofosbuvir and ribavirin could not be considered a cost-effective use of NHS resources for genotype 3 HCV in people with compensated cirrhosis.

Genotype 4 with significant fibrosis

The Committee concluded that daclatasvir plus sofosbuvir could be considered a cost-effective use of NHS resources for genotype 4 HCV with significant fibrosis only when used for 12 weeks in people with previously treated HCV, or in those who are ineligible for, or cannot tolerate, interferon. It also concluded that daclatasvir plus sofosbuvir could not be considered a cost-effective use of NHS resources when used for 12 weeks for people with previously untreated genotype 4 HCV or for 24 weeks for treating genotype 4 HCV in people with significant fibrosis. Without an ICER for daclatasvir plus sofosbuvir for 24 weeks in people with previously treated HCV, the Committee concluded that it could not recommend

this treatment duration for this subgroup. The Committee concluded that daclatasvir plus PR could not be considered a cost-effective use of NHS resources for treating genotype 4 HCV in people with significant fibrosis. **Genotype 4 with compensated cirrhosis** The Committee concluded that daclatasvir plus sofosbuvir and daclatasvir plus PR could not be considered a cost-effective use of NHS resources for treating genotype 4 HCV in people with cirrhosis.	
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) and 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 Committee 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. It 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.	4.1, 4.2
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee acknowledged that the marketing authorisation for daclatasvir plus sofosbuvir offers people the option to have shortened courses of treatment, without peginterferon alfa, thereby avoiding the adverse effects associated with interferon-based therapy. The Committee recognised that an interferon-free treatment, such as daclatasvir plus sofosbuvir, would provide a valuable treatment option.	4.1, 4.2
What is the position of the treatment in the pathway of care for the condition?	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.	4.3, 4.4

Adverse reactions	The Committee acknowledged that the marketing authorisation for daclatasvir offers people with genotype 1 or 4 HCV the option to have treatment without peginterferon alfa thereby avoiding the adverse effects associated with interferon-based therapy.	4.2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	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 sustained virological response (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.	4.5, 4.7, 4.8

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. The Committee noted that the company presented subgroup analyses by METAVIR fibrosis stage, focusing on fibrosis stages F3–F4 and F4, which the ERG simply described as 'F3' and 'F4'. The Committee heard that non-invasive tests of fibrosis (such as FibroTest or FibroScan) are now well established in clinical practice, and can be used to determine the METAVIR fibrosis stage. However, their use varied across the country depending on availability and expertise.	4.9, 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 patients. The Committee agreed that the data from ALLY 3 could not reliably inform the effectiveness of daclatasvir plus sofosbuvir and ribavirin for genotype 3 HCV in people with cirrhosis. It also noted that the SVR rates for genotype 3 HCV from 'real-world' use were higher than those observed in people with cirrhosis in ALLY-3. The Committee considered the lack of formal comparisons in the company's complied SVR rates to be a limitation in the data that reduced the validity of the SVR rates and introduced considerable uncertainty.	4.5, 4.6, 4.7, 4.9
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.	4.5

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.	4.6, 4.7
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee agreed that the ERG's amended base case provided the best evidence because it reflected the Committee's preferred analysis more closely than the company's base case. However, it recognised that all the ICERs presented were uncertain, mainly because the evidence base used to inform the SVR rates in the model was weak.	4.19
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that in the company's model, disease progression could not occur in people with cirrhosis who had SVR. The clinical experts considered that having an SVR is likely to reduce the risk of hepatocellular carcinoma, but that the extent of this reduction was difficult to determine because the evidence was insufficient. The Committee appreciated that the existing	4.12, 4.18

	evidence did not allow the natural history of the disease to be accurately modelled. 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. Because of this, the Committee concluded that it should be cautious about considering the cost effectiveness of daclatasvir based on the presented ICERs.	
Incorporation of health-related quality-of-life benefits and utility values 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?	The Committee noted that the company assumed that the utility increased in people who had an SVR, and that this increase was greater when SVR occurred in fibrosis stage F4 than when it occurred in fibrosis stage F0–F3. The ERG considered this to be uncertain and inconsistent with existing evidence. The Committee heard 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, and that people's quality of life after SVR varies. Without further evidence, the Committee concluded that the effect of SVR on health-related quality of life should be assumed to be the same whether or not the person has	4.16

<table>
<tr><td></td><td>cirrhosis.</td><td></td></tr>
<tr><td>Are there specific groups of people for whom the technology is particularly cost effective?</td><td>Please refer to the key conclusions above.</td><td></td></tr>
<tr><td>What are the key drivers of cost effectiveness?</td><td>The Committee noted that the difference between the ICERs estimated by the ERG and those estimated by the company was driven mainly by amending the comparators and SVR rates.</td><td>4.19</td></tr>
<tr><td>Most likely cost-effectiveness estimate (given as an ICER)</td><td>
<table>
<tr><th>HCV genotype and cirrhosis status</th><th>Treatment history</th><th>ICER (£/QALY)</th></tr>
<tr><td colspan="3">Daclatasvir plus sofosbuvir with or without ribavirin</td></tr>
<tr><td rowspan="4">Genotype 1 with significant fibrosis
(12 weeks' treatment unless otherwise stated)</td><td rowspan="2">Previously untreated HCV</td><td>19,700</td></tr>
<tr><td>15,700</td></tr>
<tr><td rowspan="2">Previously treated HCV</td><td>81,700
(24 weeks)</td></tr>
<tr><td>Interferon-ineligible / intolerant</td><td>5,900</td></tr>
<tr><td rowspan="4">Genotype 1 with compensated cirrhosis
(24 weeks' treatment unless otherwise stated)</td><td rowspan="2">Previously untreated HCV</td><td>118,600</td></tr>
<tr><td>24,100
(12 weeks)</td></tr>
<tr><td>Previously treated HCV</td><td>106,000</td></tr>
<tr><td>Interferon-ineligible / intolerant</td><td>25,300</td></tr>
<tr><td>Genotype 3 with</td><td>Previously</td><td>81,300</td></tr>
</table>
</td><td>4.20–4.23, 4.25–4.28</td></tr>
</table>

	significant fibrosis (24 weeks' treatment)	untreated HCV	
		Previously treated HCV	102,900
		Interferon-ineligible / intolerant	18,900
	Genotype 3 with compensated cirrhosis (24 weeks' treatment)	Previously untreated HCV	139,000
		Previously treated HCV	143,500
		Interferon-ineligible / intolerant	172,200
	Genotype 4 with significant fibrosis (12 weeks' treatment unless otherwise stated)	Previously untreated HCV	36,200
		Previously treated HCV	5900
			No ICERs presented for 24 week's treatment
		Interferon-ineligible / intolerant	5900
	Genotype 4 with compensated cirrhosis (24 weeks' treatment unless otherwise stated)	Previously untreated HCV	150,000
			45,700 (12 weeks)
		Previously treated HCV	73,800
		Interferon-ineligible / intolerant	25,300
	Daclatasvir plus PR		
	Genotype 4 with significant fibrosis (24–48 weeks' treatment)	Previously untreated HCV	Dominated
		Previously treated HCV	Extendedly dominated
	Genotype 4 with compensated	Previously untreated	Dominated

	cirrhosis (24–48 weeks' treatment)	HCV		
		Previously treated HCV	52,500	
	HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year			
Additional factors taken into account				
Patient access schemes (PPRS)	Not applicable			
End-of-life considerations	Not applicable			

Equalities considerations and social value judgements	During the scoping process, it was noted that there is ethnic variation in the genotype profile of chronic hepatitis C and that ethnic group influences treatment response. The company stated that there should be consideration of the ethical issues relating to the availability of treatment options for the HCV genotypes known to be more prevalent in different ethnic groups. The Committee was aware that minority ethnic groups are more highly represented in the genotype 4 HCV population than in the genotype 1 or 3 populations. Because the Committee made its recommendations based on the cost-effectiveness data and on the treatment regimens specified in the marketing authorisation, and the recommendations for daclatasvir plus sofosbuvir were the same for genotypes 1 and 4 HCV, it did not consider that its recommendations constituted 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 patient 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 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Simeprevir for treating genotype 1 or 4 chronic hepatitis C. NICE technology appraisal guidance 331 (2015).
- Sofosbuvir for treating chronic hepatitis C. NICE technology appraisal guidance 330 (2015).
- Needle and syringe programmes. NICE public health guidance 52 (2014).
- Boceprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal guidance 253 (2012).
- Telaprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal guidance 252 (2012).
- Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. NICE technology appraisal guidance 200 (2010).
- Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. NICE technology appraisal guidance 106 (2006).
- Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C. NICE technology appraisal guidance 75 (2004).

Under development

- Ledipasvir–sofosbuvir for treating chronic hepatitis C. NICE technology appraisal. NICE technology appraisal. Publication date to be confirmed.
- Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C. NICE technology appraisal. Publication date to be confirmed.
- Hepatitis C: diagnosis and management of hepatitis C. NICE clinical guideline. Publication date to be confirmed.

7 Proposed date for review of guidance

7.1 It is proposed that all technology appraisal guidance recently developed by NICE for Hepatitis C will be considered for incorporation and contextualisation in the clinical guideline Hepatitis

C: diagnosis and management of hepatitis C, the development of which will restarted in the next couple of months.

Gary McVeigh
Chair, Appraisal Committee
July 2015

8 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

Ms Tracey Cole

Lay Member

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon

Professor of Health Economics, University of Sheffield

Susan Dutton

Senior Medical Statistician, Oxford Clinical Trials Research Unit

Dr Alexander Dyker

Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

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

Mr Warren Linley

Senior Research Fellow, Centre for Health Economics and Medicines Evaluation, Bangor University

Dr Malcolm Oswald

Lay Member

Professor Femi Oyebode

Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr Mohit Sharma

Consultant in Public Health, Public Health England

Dr Murray Smith

Associate Professor in Social Research in Medicines and Health, University of Nottingham

Guideline representatives

The following individuals, representing the Guideline Development Group responsible for developing NICE's clinical 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

Technical Lead(s)

Melinda Goodall and Raisa Sidhu

Technical Adviser

Kate Moore

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by CRD York:

- Woods B, Llewellyn A, Faria R, Simmonds M, Lomas J, Harden M, Woolacott N, Griffin S. Daclatasvir for treating chronic hepatitis C. A Single Technology Appraisal. CRD and CHE Technology Assessment Group, 2014.

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 are 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 BMS– clinical expert
- Dr Ranjababu Kulasegaram, Consultant Physician, nominated by British HIV Association and British Association for Sexual Health and HIV – clinical expert
- Dr Charles Millson, Consultant Hepatologist, nominated by British Society of Gastroenterology – clinical expert
- Dr Terence Wong, Consultant Gastroenterologist and Hepatologist, nominated by British Society of Gastroenterology - clinical expert
- Charles Gore, CEO, nominated by The Hepatitis C Trust – patient expert

- Richard Hall, nominated by Liver 4 Life – patient expert
- Robert James, nominated by British HIV Association and British Association for Sexual Health and HIV British HIV Association and British Association for Sexual Health and HIV – patient expert
- Raquel Peck, nominated 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 and providing a written statement to the Committee. They are 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