# Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C [ID1055]

**Clinical & cost effectiveness**

1st Appraisal Committee meeting, 23 November 2017

Committee D

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# Preview: Key Issues

- The company's submission focused on the following populations:
  - DAA-experienced (all GTs and cirrhotic & non-cirrhotic combined)
    - GT subgroups were small and limits reliability of the data: no results by GT and cirrhotic status provided
  - DAA-naïve (cirrhotic and non-cirrhotic) for GT3 only (no analyses for GT1, 2, 4, 5 and 6 provided)
    - because the risk of progressing from NC to CC is highest in GT3
- Appropriate treatment duration for SOF/VEL/VOX for DAA-naïve GT3 CC
  - Marketing authorisation states 12 weeks and to consider 8 weeks
  - Only 8 weeks assessed in relevant clinical trials
- Does the committee accept assumptions as in previous Hep C appraisals?
  - Model structure, SVR rates, transition probabilities, utilities
- Re-infection and transmission included as an exploratory analysis for DAA-naïve GT3 population only
- Most plausible ICER based on the committee's preferred assumptions?
- Innovation – any uncaptured health-related benefits?
- Potential equality issues?

# Hepatitis C

- Blood borne (people who inject drugs major source ≈90%)
- Causes inflammation of liver
- Acute infection usually asymptomatic:
  - 75-85% develop chronic hepatitis C (CHC)
  - 10-20% CHC progress to cirrhosis
  - 1-4% per year hepatocellular carcinoma (HCC)
- 214,000 people with CHC in UK, estimated 160,000 in England (PHE, 2017)
- Six major genotypes (GT1-6)
  - GT1 and GT3 most common (approx. 90%)
  - GT3 (44% of Hep C population in England) associated with highest risk of disease progression (fibrosis, carcinoma) and death
- Aim of treatment is to cure the infection
  - Historically, treatment included pegylated-interferon plus ribavirin regimens
  - In recent times, direct-acting antivirals (DAAs) with better efficacy and improved safety profile have been recommended by NICE

# Sofosbuvir–velpatasvir–voxilaprevir
## (Gilead sciences)

| | |
|---|---|
| Marketing authorisation | For the treatment of chronic hepatitis C virus (HCV) infection in adults:<br>• All genotypes GT1-GT6<br>• Without cirrhosis and with compensated cirrhosis<br>• DAA naïve and DAA experienced*<br>**** Previous treatment includes: daclatasvir, dasabuvir, elbasvir, grazoprevir, ledipasvir, ombitasvir, paritaprevir, sofosbuvir, velpatasvir, and voxilaprevir*** |
| Mechanism of action | Fixed-dose combination of 3 drugs:<br>• sofosbuvir inhibits the non-structural protein 5B (NS5B);<br>• velpatasvir is an NS5A inhibitor;<br>• voxilaprevir is a second generation NS3/4A protease inhibitor |
| Administration | SOF/VEL/VOX (400 mg/100 mg/100 mg) film-coated tablet, taken orally, once daily:<br>• DAA-naïve without cirrhosis: 8 weeks duration<br>• DAA-naïve with compensated cirrhosis: 12 weeks & consider 8 for GT3<br>• DAA experienced patients: 12 weeks duration |
| Acquisition cost | 28 tablets: £14,942.33<br>• 8/12 weeks of treatment at list price: £29,884.66/£44,826.99<br>• The company have agreed a confidential pricing agreement with the Commercial Medicines Unit |

# Company's decision problem
(Source: Table 1 CS, page 11)

| | NICE scope | Company |
|---|---|---|
| **Pop.** | 1. **Treatment-experienced**<br>2. **Treatment-naïve** | 1. **DAA-experienced (all GT, NC/CC combined)**<br>2. **GT3 DAA-naïve NC**<br>3. **GT3 DAA-naïve CC**<br>• DAAs are 1st-line therapy<br>• No licensed treatment for DAA-experienced (GT subgroups small and limits reliability of the data)<br>• High unmet need for GT3 (44% of CHC) – highest risk of progressing from NC to CC |
| **Int.** | SOF/VEL/VOX | Treatment duration: 12 weeks for DAA experienced (1.)<br>8 weeks for DAA naïve (2. & 3.) |
| **Com.** | • BSC (GT1-6)<br>• SOF/DCV ± R (GT1, 3 or 4)<br>• **EBR/GZR (GT1 or 4)**<br>• **LDF/SOF (GT1 or 4)**<br>• **OBV/PTV/RTV + DCV ± R (GT1 or 4)**<br>• P + R (GT1-6)<br>• SOF + R ± P (GT1-6)<br>• SOF/VEL (GT1-6) | 1. **BSC** (GT1-6)<br>2. **SOF/VEL** (12 wks), **SOF + DCV + R** (12 weeks), **SOF + R** (24 wks), **P + R** (24 wks), **SOF + P + R** (12 weeks)<br>3. **P + R** (24 wks), **SOF + P + R** (12 wks), **SOF/VEL** (12 wks), **SOF + DCV** (12 wks)<br>• Excluded comparators not relevant to company's populations (DAA experienced and GT3 DAA-naïve) |
| **Out.** | SVR, resistance to treatment, mortality, AE, HRQL | Notes that resistance does not impact cost or QALYs |

**Key:** BSC, best supported care; CC, cirrhotic; DAA, direct-acting antivirals; DCV, daclatasvir; EBR/GZR, elbasvir-grazoprevir; GT, genotype; LDV, ledipasvir; NC, non-cirrhotic; OBV/PTV/RTV, ombitasvir/paritaprevir/ritonavir; P, pegylated-interferon; QALYs, quality-adjusted life years; R, ribavirin; SOF, sofosbuvir; VEL, velparasvir; vox, voxilaprevir; wks, weeks.

# ERG's critique of decision problem

- Population:
  - Narrower than scope: no results for DAA-naïve GT1, 2, 4, 5, 6
  - DAA experienced not presented by GT and cirrhotic status (NC/CC)
    - ERG considers company's approach to report results for a pan-genotype group for DAA-experienced patients to be appropriate
- Intervention:
  - MA: 12 weeks and consider 8 weeks for CC GT3 DAA-naïve
    - Company used 8 weeks based on clinical trials (12-weeks was not studied). However, clinicians may prefer to treat for 12 weeks
- Comparators:
  - SOF/VEL used off-label for DAA-experienced, but not included in company's model
  - DAA-naïve GT3 CC: SOF+DCV ± R (TA364) & SOF+R (TA330) only recommended for interferon-ineligible/intolerant
  - SOF+DCV+R for CC modelled for 12 wks in DAA-naïve GT3 CC patients, but recommended for 24 weeks (TA364)

# Patient Perspectives

- Submissions from: Haemophilia Society, Hepatitis C Trust
- Experiences and feelings of people with Hepatitis C:
  - “chronic fatigue, memory problems, get muddled and depressed”
  - “some people cannot work and find their social/emotional/sexual life significantly impaired... encounter stigma and even discrimination,”
  - “people who were infected through the NHS often feel extremely angry and bitter” because never adequately compensated
  - “significant uncertainty about when they will have access to interferon-free therapy and hence a cure because NHS England has introduced a cap on the number to be treated in 2017/18”
- SOF/VEL/VOX therapy:
  - “very high cure rates”...“works very well for people who have been unsuccessfully treated”
  - “of particular benefit to people with a bleeding disorder who were often infected with multiple genotypes via their NHS treatment”
  - “provides competition and drives the price down”

# Clinicians' perspectives

- Submissions from: RCP, British Society of Gastroenterology
- SOF/VEL/VOX would address unmet needs including:
  - "effective re-treatment options for all HCV genotypes treatment failures with previous DAA (particularly NS5A inhibitor) exposure"
  - "shorter treatment regimens - particularly special groups e.g. prison population"
- SOF/VEL/VOX:
  - "Serious adverse events have been rare in trials (2%) and similar to placebo"
  - "RBV-free pan-genotypic treatment with response rates similar in cirrhotic & non cirrhotic patients" – no need to genotype, so cheaper, easier treatment
- No new infrastructure or training required
- Patients are treated via regional Operational Delivery Network:
  - "NHS England stipulates which drug regimens may be used on patients"
  - Numbers of patients treated each month limited by the NHSE "run rate"
  - "Not ideal for many of the patient sub-groups who suffer from chronic HCV infection e.g. prisoners and people who inject drugs"

# NHS England comments

- Fixed duration therapy for all genotypes with durations modified by the degree of liver fibrosis: 8 weeks for all patients with mild disease
  - ‘immediate access’ to therapy without the need for genotyping
  - access for people struggling to engage in traditional care pathways
  - due to experienced teams working in multi-disciplinary networks, the benefits of this approach are marginal
- At present there is no licensed therapy for the very few patients who have failed to respond to currently available treatments
- NHS England fund hepatitis C treatments via a managed access programme which will fund a target of 12,500 patients in 2017/2018 – it is not envisaged that extra resource will be required for this technology appraisal
- The technology should be delivered by Operational Delivery Networks
- Current rules recommend stopping therapy if there is evidence of virological failure and we would recommend that these rules be applied to the new technology

# Clinical evidence

(Source: Table 8 CS, page 43)

| Study | POLARIS-1 (N=415) | POLARIS-4 (N=333) | POLARIS-2 (N=941) | POLARIS-3 (N=219) |
|---|---|---|---|---|
| Study design | Multicentre (108 sites), double-blind, placebo-controlled, Phase III RCT | Multicentre (101 sites), open-label, Phase III RCT | Multicentre (117 sites), open-label, Phase III RCT | Multicentre (84 sites), open-label, Phase III RCT |
| UK sites | 9 patients/ 6 sites | 12 patients/ 5 sites | 47 patients/ 8 sites | 15 patients/ 6 sites |
| Population | DAA-experienced<br>- previously treated with NS5A inhibitor (GT1-6) | DAA-experienced<br>- not previously treated with NS5A inhibitor (GT1-6) | DAA-naïve<br>- with & without cirrhosis (GT1,2,4-6),and<br>- GT3 without cirrhosis | DAA-naïve<br>- GT3 with cirrhosis |
| Intervention | SOF/VEL/VOX for 12 weeks | | SOF/VEL/VOX for 8 weeks | |
| Comparator | Placebo for 12 weeks | SOF/VEL for 12 weeks | | |
| SVR12 (primary outcome) | HCV RNA<LLOQ12 weeks after cessation of treatment, in full analysis set in the SOF/VEL/VOX population. The LLOQ was 15 IU/mL | | | |

Key: LLOQ, lower limit of quantification; N, number of participants; NS, non-structural protein; RNA, ribonucleic acid; SVR12, sustained virologic response at 12 months;

# SVR12 results: NS5A-experienced POLARIS 1

(Source: Table 12 CS Appendix)

| Subgroups | | SOF/VEL/VOX (12 weeks) | |
|---|---|---|---|
| | | n/N (%) | 95%CI |
| GT | All | **253/263 (96.2)** | **93.1, 98.2** |
| | GT1 | 146/150 (97.3) | [redacted] |
| | GT2 | 5/5 (100.0) | [redacted] |
| | GT3 | 74/78 (94.9) | [redacted] |
| | GT4 | 20/22 (90.9) | [redacted] |
| | GT5 | 1/1 (100.0) | [redacted] |
| | GT6 | 6/6 (100.0) | [redacted] |
| | unknown | 1/1 (100.0) | [redacted] |
| Cirrhosis | yes | 113/121 (93.4) | [redacted] |
| | no | 140/142 (98.6) | [redacted] |
| DAA-experienced 253/263 (96.2%) | NS5A ± other DAA | 252/262 (96.2) | [redacted] |
| | Others | 1/1 (100.0) | [redacted] |
| | NS5A & NS5B | 151/161 (93.8) | [redacted] |
| | NS5A & NS3 ± NS5B | 83/83 (100.0) | [redacted] |
| | NS5A ± Others | 18/18 (100.0) | [redacted] |

**Key:** CI, confidence intervals; DAA, direct-acting antivirals; NS, non-structural protein; SVR12, sustained virologic response at 12 months.

# SVR12 results: DAA-experienced (not NS5A) POLARIS 4

(Source: Table 13 CS Appendix)

| Subgroups | | SOF/VEL/VOX (12 weeks) | | SOF/VEL (12 weeks) | |
|---|---|---|---|---|---|
| | | n/N (%) | 95%CI | n/N (%) | 95%CI |
| GT | All | **178/182 (97.8)**[a] | [redacted][a] | 136/151 (90.1) | [redacted] |
| | GT1 | 76/78 (97.4) | [redacted] | 60/66 (90.9) | [redacted] |
| | GT2 | 31/31 (100.0) | [redacted] | 32/33 (97.0) | [redacted] |
| | GT3 | 51/54 (94.4) | [redacted] | 44/52 (84.6) | [redacted] |
| | GT4 | 19/19 (100.0) | [redacted] | NA | NA |
| | GT5 | 1/1 (100.0) | [redacted] | NA | NA |
| Cirrhosis | yes | 81/84 (96.4) | [redacted] | 59/69 (85.5) | [redacted] |
| | no | 96/98 (98.0) | [redacted] | 77/82 (93.9) | [redacted] |
| Prior treatment | DAA- naive | NA | NA | 1/1 (100.0) | [redacted] |
| | DAA- experienced | 177/182 (97.3) | [redacted] | 135/150 (90.0) | [redacted] |
| | NS5B only | 130/134 (97.0) | [redacted] | 99/109 (90.8) | [redacted] |
| | NS5B & NS3 | 45/46 (97.8) | [redacted] | 33/38 (86.8) | [redacted] |
| | others | 18/18 (100.0) | [redacted] | 3/3 (100.0) | [redacted] |

**Key**: CI, confidence intervals; DAA, direct-acting antivirals; NS, non-structural protein; SVR12, sustained virologic response at 12 months.
**Notes:** a, results updated with an achievement of SVR24 by 1 subject who had missed SVR12 assessment.

# SVR12 results: DAA-naive POLARIS 2 & 3

(Source: Table 14 & 20 CS Appendix)

| Trial | Subgroup | | SOF/VEL/VOX (8 weeks) | | SOF/VEL (12 weeks) | |
|---|---|---|---|---|---|---|
| | | | n/N (%) | 95%CI | n/N (%) | 95%CI |
| Polaris 2 | GT | All | **477/501 (95.2)**[a] | [redacted] | 432/440 (98.2) | [redacted] |
| | | GT1 | 217/233 (93.1) | [redacted] | 228/232 (98.3) | [redacted] |
| | | GT2 | 61/63 (96.8) | [redacted] | 53/53 (100.0) | [redacted] |
| | | GT3 | 91/92 (98.9) | [redacted] | 86/89 (96.6) | [redacted] |
| | | GT4 | 58/63 (92.1) | [redacted] | 56/57 (98.2) | [redacted] |
| | | GT5 | 17/18 (94.4) | [redacted] | NA | NA |
| | | GT6 | 30/30 (100.0) | [redacted] | 9/9 (100.0) | [redacted] |
| | | other | 2/2 (100.0) | [redacted] | NA | NA |
| | Cirrhosis | yes | 82/90 (91.1) | [redacted] | 83/84 (98.8) | [redacted] |
| | | no | 394/411 (95.9) | [redacted] | 349/356 (98.0) | [redacted] |
| | Previous treatment | Naive | 367/383 (95.8) | [redacted] | 332/340 (97.6) | [redacted] |
| | | Exp. | 109/118 (92.4) | [redacted] | 100/100 (100.0) | [redacted] |
| | | P+R | [redacted] | [redacted] | [redacted] | [redacted] |
| Polaris 3 - GT3 CC | Overall | | **106/110 (96.4)** | **91.0 to 99.0** | 105/109 (96.3) | [redacted] |
| | Previous treatment | Naive | 72/75 (96.0) | [redacted] | 76/77 (98.7) | [redacted] |
| | | Exp. | 34/35 (97.1) | [redacted] | 29/32 (90.6) | [redacted] |
| | | P+R | [redacted] | [redacted] | [redacted] | [redacted] |

# ERG: critique of the trial evidence

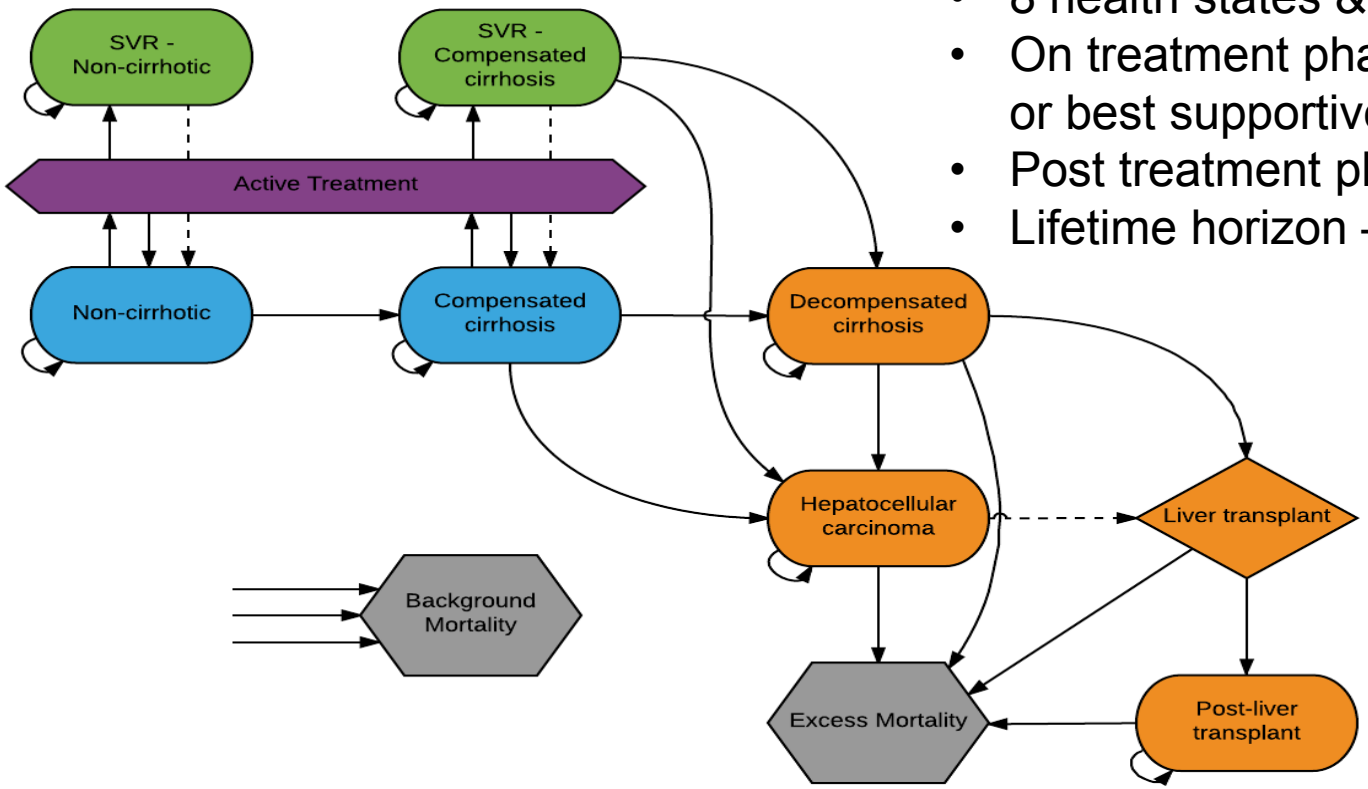
- POLARIS trials are of reasonable methodological quality
- Only POLARIS-3 randomised all participants
- POLARIS-1, 3 and 4: trial arms not compared with each other. Individual arms compared against a predefined SVR12 (85% for POLARIS-1 & -4, and 83% for POLARIS-3).
- POLARIS-2 was a non-inferiority trial comparing SOF/VEL/VOX 8 weeks with SOF/VEL 12 weeks
  - only GT3 subgroup included so not sufficiently powered
  - did not demonstrate non-inferiority, but GT3 patients with SOF/VEL/VOX had SVR12 of 98.9% and 96.6% with SOF/VEL
- POLARIS-4, -2 and -3 were open label trials, so there is scope for bias
- Company explored the possibility of a network meta-analysis for the DAA-naïve HCV GT3 patient group but this was not feasible
- ERG agrees with the interpretation of clinical and safety evidence

# Company's model

(Source: Figure 2 CS, page 128)

**Markov model**

- 8 health states & death
- On treatment phase (active therapy or best supportive care)
- Post treatment phase (orange)
- Lifetime horizon – 100 years




- Excess mortality: disease-specific (decompensated cirrhosis, liver transplant & HCC)
- Backroad mortality: mortality rate of the general population
- Dashed arrows represent transitions only investigated in sensitivity analysis

**Key:** HCC, hepatocellular carcinoma; SVR, sustained virologic response.

# ERG: critique of company's model

- Structure is similar to previous NICE technology appraisals:
  - LDV/SOF (TA363), SOF+R (TA330) and SOF/VEL (TA430)
- Includes a scenario attempting to address re-treatment due to re-infection or treatment failure
- Does not account for mortality risk or disease progression for patients in active treatment phase (NC; also raised in TA430)
- Mortality assumption: treatment-related and background mortality is related to treatment duration and leads to counter-intuitive results:
  - QALYs for SOF/VEL are greater than SOF/VEL/VOX, but SVR rates are lower for SOF/VEL than SOF/VEL/VOX
  - it would be more appropriate for mortality to start at the same time

**Key:** CC, compensated cirrhosis; LDV, ledipasvir; NC, non-cirrhotic; QALYs, quality-adjusted life years R, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velparasvir; VOX, voxilaprevir.

# Model inputs

**SVR rates**

- SOF/VEL/VOX – derived from POLARIS trials according to population
- Comparators – respective clinical trials (as per previous appraisals)

**Transition probabilities**

- Same sources as per TA430 (including, Kanwal et al. 2014, Cardoso et al. 2010, Fattovich et al. 1997)

**Utilities**

- Health states – Wright et al. 2006,
- SVR utility increment – Vera-Llonch et al. 2013
- Utility decrement associated with treatment: all DAA regimen (0%), ribavirin regimen (-2.5%), peginterferon regimen (-4.7%)

**Resource use and cost**

- Includes costs associated with treatment, monitoring and adverse events (including management cost)
- Mainly based on TA430, updated to 2015/2016 costs

# ERG: critique of clinical inputs

- Use of SVR rates from individual trials were accepted in TA430
  - DAA naive GT3 CC: combined TN & TE rates for SOF+R (66.3%),
  - But rate for SOF + PR for TN only (CC 91.3% & NC 95.8%), thus combined TN & TE rates for SOF + PR more appropriate: CC 87.9% & NC 95.1%
- TPs: same as TA430, but old sources (already raised in HTAs), full review is due
  - Current mortality rates for liver transplant decreased to 16% in year 1 and 5.2% in subsequent years (vs. CS: 21% and 5.7% respectively)
  - Committee in TA430 also considered Fattovich et al. 1997 for the TPs where Cardoso et al. are used
- Search for utility values inadequate (severe health states not included)
- TA430 FAD: *committee prefers utility values collected from the clinical trials of the intervention under evaluation to those estimated from other sources*
  - POLARIS trials collected HRQL (SF-36,CLDQ-HCV, FACIT-F, WPAI)
- Baseline utilities: 83:17 split for NC mild & moderate disease
  - 50:50 better reflection (expert clinical advice & used by Hartwell et al. 2011)

# ERG: critique of resource use and costs

- Health states costs
  - ERG suggests follow-up for NC patients with SVR should be 1 year, (not 2 years as in company's model)
  - Cost based on 50:50 split for NC moderate and mild disease more appropriate (not 83:17)
- Treatment cost
  - Base case: SOF/VEL/VOX for 8 weeks for DAA-naïve GT3 CC patients (exploratory analysis used 12 weeks)
  - Clinicians may prefer to treat some patients for longer. ERG explored scenarios where clinicians were able to "choose" treatment duration (75% 8 wks & 25% 12 wks, 50% 8 wks & 50% 12 wks, and 25% 8 wks & 75% 12 wks ratios)
- Methods used to estimate costs are reasonable, but data, in general, are out of date and should be reviewed for future appraisals

# Company's Results (list prices)

(Source: Tables 64 - 66 CS)

- DAA-experienced (all GTs, NC and CC combined)
  - Pairwise analysis
  - SOF/VEL/VOX (12 weeks) vs. no treatment = **£8,153 per QALY gained**
- DAA-naïve (GT3 non-cirrhotic)
  - Fully incremental
  - SOF/VEL/VOX (8 weeks) vs. PR (24 weeks) = **£16,654 per QALY gained**
- DAA-naïve (GT3 cirrhotic)
  - Fully incremental
  - SOF/VEL/VOX (8 weeks) vs. PR (24 weeks) = **£4,088 per QALY gained**

***Results using discounted prices for intervention and comparators presented in a confidential appendix***

# Company's sensitivity analyses

(Source: Figures 6 - 8 CS)

- Key drivers: treatment TPs from NC with SVR to NC (re-infection), discount rate applied for costs and outcomes, treatment costs
- However, only re-infection was considered in DSAs (not disease transmission)
  - a separate dynamic transmission exploratory analysis considered both

- **DAA-experienced**: in all analyses ICER < £20,000
- **DAA-naïve GT3 NC**: SOF/VEL/VOX dominates SOF/VEL except for changes to the cost of SOF/VEL and SVR rates of SOF/VEL/VOX & SOF/VEL
- **DAA-naïve GT3 CC**: SOF/VEL/VOX remains less costly than SOF/VEL but has similar QALYs except for changes to the SVR rates of SOF/VEL/VOX & SOF/VEL

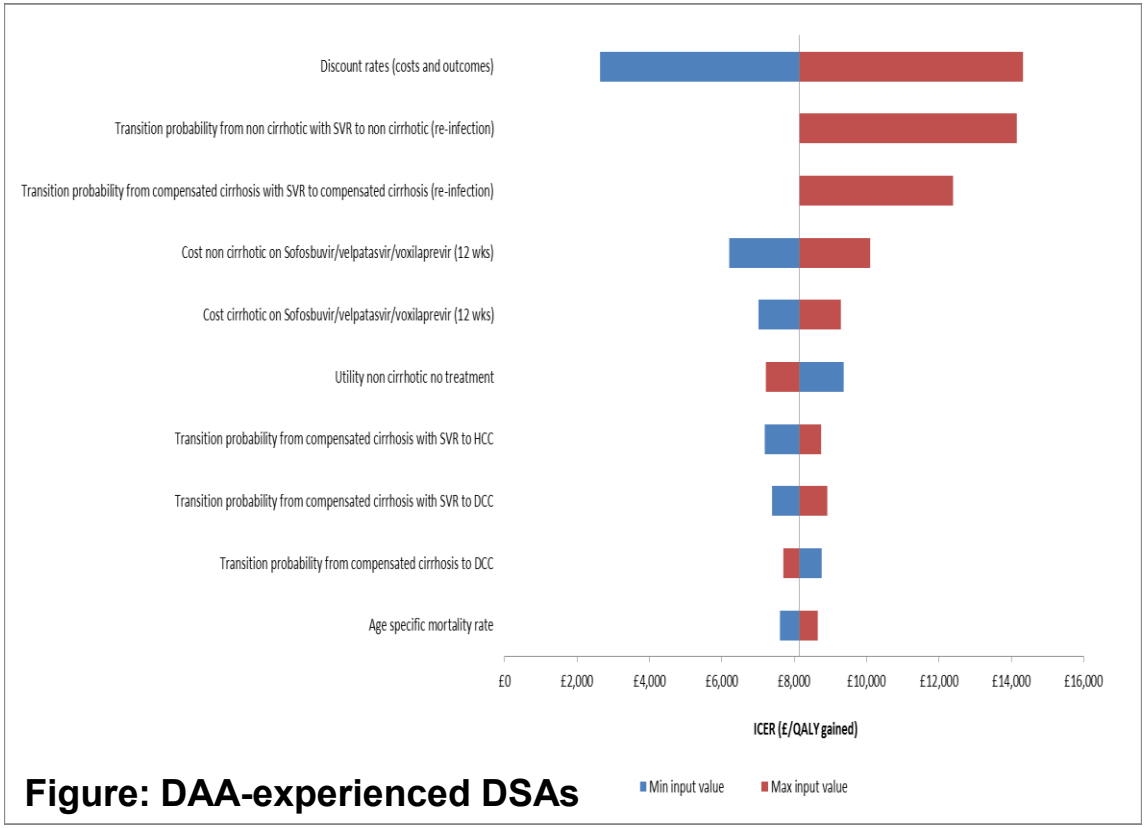



**Figure: DAA-experienced DSAs**

**Key:** CC, compensated cirrhosis; DAA, direct-acting antivirals; DCC, decompensated cirrhosis; DSA, deterministic analyses; GT, genotype; ICER, incremental cost-effectiveness ratio; NC, non-cirrhotic; QALYs, quality-adjusted life years; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR, sustained virologic response; TP transition probability.

# Company's scenario analyses

(Source: Tables 76 - 82 CS)

- DAA-experienced:
  - Using POLARIS-4 SVR rates for SOF/VEL/VOX instead of POLARIS 1
  - Using POLARIS-1 NC/CC ratio (58.6:41.4) instead of 66.3:36.7 ratio
  - Using TPs for GT3 and GT1 only instead of using blended transition probability from all genotypes

  **Results similar to base-case results**
- DAA-naïve GT3 NC:
  - Using SVR rates for SOF/VEL from ASTRAL-3 instead of POLARIS 3

  **Results similar to base-case results**
- DAA-naïve GT3 CC:
  - Using SVR rates for SOF/VEL from ASTRAL-3 instead of POLARIS 3
    - **Results similar to base-case results**
  - Using 12 weeks duration for SOF/VEL/VOX instead of 8 weeks: SOF/VEL/VOX becomes more expensive than SOF/VEL with the same incremental QALYs)
    - **ICER increased to £3,394,377**

# Company's exploratory analysis: Dynamic transmission modelling

(Source: Table 84, CS page 188)

- Conducted for GT3 DAA-naïve only to explore impact of onward transmission and re-infection
  - (not for DAA-experienced as impact is minimal)
- Assumed only people who inject drugs (PWID) can transmit disease or become infected (and re-infected)
- SOF/VEL/VOX (8 weeks) vs. PR (24 weeks) = **£11,489 per QALY**

**ERG comment**

- Dynamic transition scenario reinforces the results of the base case
- But it makes simplifying assumptions and conducted for GT3 DAA-naïve only
  - no results for CC vs NC in the DAA-naïve GT3 population, it is unclear how results in company's submission were calculated

# ERG: exploratory analyses

| # | Change | Justification |
|---|---|---|
| **1** | Follow-up for non-cirrhotic patients with SVR should be for 1 year only | Clinical advice to the ERG |
| **2** | SVR for SOF+P+R changed to 95.1% for DAA naive NC patients and 87.9% for CC patients | DAA estimates include both TN and TE (not DAA) patients |
| **3** | TP from liver transplant to death in year 1 is 16% and 5.2 % in subsequent years | More recent mortality estimates |
| **4** | Proportion of mild and moderate patients for non-cirrhotic patients is 50:50 | Clinical advice to the ERG |
| 5 | Using transition probabilities from Fattovich et al. 1997 | requested by TA430 NICE committee |
| 6 | Different proportions of patients receiving SOF/VEL/VOX for 8 and 12 weeks for DAA-naïve GT3 cirrhotic patients | MA allows treatment with 8 or 12 weeks |
| **1-4** | **Scenarios 1-4 combined** | **ERG base-case** |

**Key:** DAA, direct-acting antivirals; MA, marketing authorisation; P, pegylated interferon; R ribavirin; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR, sustained virologic response; TE, treatment experienced, TN, treatment naïve; TP, transition probabilities.

# ERG: exploratory analyses results

(Source: Tables 49 - 65 ERG report)

- ERG base case (scenarios #1-4 combined)
  - did not change the conclusions on cost-effectiveness:
    - SOF/VEL/VOX (12 wks) for DAA-experienced, and
    - SOF/VEL/VOX (8 wks) for DAA-naïve GT3 NC and CC patients remained cost-effective
- Using TPs from Fattovich et al. 1997 (#5)
  - had a minimal impact, results are similar to company's base case
- Changing proportions (0, 25 75, & 100%) of DAA-naïve GT3 CC patients treated with 8 and 12 weeks (# 6)
  - had a significant impact:
    - SOF/VEL/VOX is less expensive than SOF/VEL when treatment is for 8 weeks and remains cost saving until 75% of patients are treated for 12 weeks:
      - 75% 12 weeks: SOF/VEL dominates
      - 100% 12 weeks: ICER of £3,394,377

# Company: Innovation

- EMA adopted an accelerated regulatory process granted to those medicines of major public health interest
- SOF/VEL/VOX fulfils a number of criteria identified by the Kennedy Report as constituting innovation
- DAA-experienced
  - Currently no licensed and reimbursed pharmacologic treatment option for this group
  - SOF/VEL/VOX is the only pan-genotypic single tablet regime available (regardless of cirrhosis status)
  - SOF/VEL/VOX addresses a substantial current unmet need
- DAA-naïve GT3
  - GT3 represents a large (44%) and difficult to treat group
  - Patients have typically worse virologic response to DAA therapy
  - SOF/VEL/VOX demonstrated high cure rates in NC and CC patients
  - Short duration treatment (8 weeks)

# Equalities

- During the scoping process, it was noted that chronic hepatitis C disproportionately affects certain populations such as certain immigrant populations, prison populations, and drug users, in terms of accessing the healthcare system and having access to innovative new treatments.
- The appraisal committee have previously discussed these issues in previous hepatitis C appraisals, and concluded that its recommendations were fair regarding these groups of people.

**Clinical expert:**

- *Nothing specific – however technology would not be recommended for those with severe renal impairment (eGFR<30) (as it contains sofosbuvir which is contra-indicated in such patients) or those with decompensated liver disease (as it contains an NS3/4 protease inhibitor which as a class are contra-indicated in such patients even though there is no specific data for voxilaprevir in this scenario)*

**Haemophilia society**

- *Due to the nature of the infection route for people with bleeding disorders (via NHS treatment) with potentially multiple genotypes, we believe people with a bleeding disorder should be seen as priority for this treatment*

**Key:** eGFR, estimated glomerular filtration rate; NS, non-structural protein

# Preview: Key Issues

- The company's submission focused on the following populations:
  - DAA-experienced (all GTs and cirrhotic & non-cirrhotic combined)
    - GT subgroups were small and limits reliability of the data: no results by GT and cirrhotic status provided
  - DAA-naïve (cirrhotic and non-cirrhotic) for GT3 only (no analyses for GT1, 2, 4, 5 and 6 provided)
    - because the risk of progressing from NC to CC is highest in GT3
- Appropriate treatment duration for SOF/VEL/VOX for DAA-naïve GT3 CC
  - Marketing authorisation states 12 weeks and to consider 8 weeks
  - Only 8 weeks assessed in relevant clinical trials
- Does the committee accept assumptions as in previous Hep C appraisals?
  - Model structure, SVR rates, transition probabilities, utilities
- Re-infection and transmission included as an exploratory analysis for DAA-naïve GT3 population only
- Most plausible ICER based on the committee's preferred assumptions?
- Innovation – any uncaptured health-related benefits?
- Potential equality issues?