Public Observer Slides

Lead team presentation
Glecaprevir/pibrentasvir for treating chronic hepatitis C

Clinical & cost effectiveness

1st Appraisal Committee meeting, 26 October 2017

Committee D

Lead team: Gillian Ells (clinical), Rebecca Harmston (patient perspective), Simon Dixon (cost)

Key Issues

1. Exclusion of the following comparators (slide 5)
   - DCV + SOF, with or without RBV (GT1 and 4)
   - PegIFNα + RBV (GT1; 2 TE, TN CC; 3 - 6)
   - SOF + RBV, with or without pegIFNα (GT1 and 4)
2. Results of the naïve indirect comparison given the ERG's concerns that the number of patients in the trials are very low and the choice of SVR rates are from only 1 source
3. Use of similar modelling assumptions and subgroup analysis as for previous Hep C appraisals
   - Comparator SVR 12 rates, Model structure, Transition probabilities
4. Use of Wright et al for HRQoL values (same as TA430 and other hep C appraisals) even though there is trial data available
5. Most plausible ICER based on the committee's preferred assumptions
6. Innovation – any health-related benefits not captured in the analysis
7. Potential equality issues

Hepatitis C

- Blood borne (people who inject drugs major source ≈90%)
- 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 (PHE, 2014)
- 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 peginterferon plus ribavirin regimens
  - Recently, direct-acting antivirals (DAAs) with better efficacy and improved safety profile have been recommended by NICE

DETAILS OF THE TECHNIOLOGY	
Technology	Glecaprevir/pibrentasvir (Maviret, AbbVie)
Marketing authorisation	For the treatment of chronic hepatitis C virus (HCV) infection in adults • All genotypes GT1-GT6 • No cirrhosis and compensated cirrhosis • Treatment naive and Treatment experienced* *(previous treatment does not include an NS5A and/or NS3/4A inhibitor)*
Mechanism of action	Fixed dose combination of 2 DAAs: • glecaprevir inhibits HCV NS3/4A protease • pibrentasvir inhibits HCV non-structural protein 5a (NS5A)
Administration	Oral, 100 mg/4 mg tablets, 3 tablets once per day for: • 8 weeks (TN, NC, all genotypes) and (TE, NC, GT1, 2, 4-6) • 12 weeks (TN, CC, all genotypes) and (TE, CC, GT1, 2, 4-6) • 16 weeks (TE, NC or CC, GT3)
Acquisition cost	List price per pack: £12,993.99 (£25,987.32 for 8 weeks treatment, £38,980.98 for 12 weeks treatment and £51,974.64 for 16 weeks treatment) The company have agreed a confidential pricing agreement with the commercial medicines unit

COMPANY'S DECISION PROBLEM & DEVIATIONS FROM FINAL SCOPE

	Final scope issued by NICE	Company submission	Rationale for deviations
Pop	People with chronic hepatitis C (treatment-naïve & experienced)		
Int.	Glecaprevir-pibrentasvir		
Com.	• BSC (GT1-6) • **DCV + SOF, with or without RBV (GT1, 3 or 4)** • EBR/GZR (GT1 or 4) • LDV/SOF (GT1 or 4) • OBV/PTV/RTV with or without DSV or RBV (GT1 or 4) • **PegIFNα + RBV (GT1– 6)** • **SOF + RBV, with or without pegIFNα (GT1–6)** • SOF + VEL (GT1-6)	• DCV + SOF without RBV **(for GT3 only)** • PegIFNα + RBV **GT2 (NC TN)** • SOF + RBV, with or without pegIFNα **(GT2, 3, 5 and 6** • Other comparators – as per scope	Not used in current NHS practice
Out.	SVR, resistance, mortality, adverse effects, HRQoL	Resistance not modelled	Resistance does not impact costs or QALYs

Patient perspective

Hepatitis C Trust

- Some patients experience minimal symptoms whilst others report chronic fatigue, sexual dysfunction and mood swings
- Patients may be unable to work or enjoy social situations and some experience discrimination due to the stigma of living with hepatitis
- Late diagnosis or treatment failure may lead to liver cancer and death within a few months
- Patients are experiencing uncertainty about if and when they will be able to access interferon-free therapy
- Unmet need in patients with genotype 2 who are not interferon tolerant, people needing retreatment and populations who need to be treated urgently due to access issues
- Patients think that glecaprevir-pibrentasvir has high cure rates and expands the range of treatment options available to treat Hepatitis C
- Alternative to interferons which can cause significant side effects in patients

Submissions from professional groups and clinical experts

Submissions from; British Society of Gastroenterology, Royal College of Pathologists, UK Clinical Pharmacy Association, 2 x clinical experts:

- Important pan-genotypic treatment
- Short treatment duration (8 weeks for some subgroups)
- Effective in people with renal failure
- Few side effects of treatment
- The regimen is contraindicated for patients with decompensated cirrhosis

Clinical trials used in the model (I)

Trial	Intervention/comparator
ENDURANCE-1	GT 1: G/P for 12 weeks (n=352) **vs** G/P for 8 weeks (n=351)
ENDURANCE-3	GT3: G/P for 12 weeks (n=233) **vs** SOF + DCV for 12 weeks (n=115)
EXPEDITION-1	GT1,2 4-6: G/P for 12 weeks (n=146)
SURVEYOR-II (Part 3)	**TE-PRS NC**: G/P for 12 weeks (n=22) **vs** G/P for 16 weeks (n=22) **TN CC**: G/P for 12 weeks (n=40) **TE-PRS CC**: G/P for 16 weeks (n=47)
SURVEYOR-II (Part 4)	3 fixed-dose combination tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir GT2 (n=145) and GT4, GT5 or GT6 (n=58)

Key: TE-PRS; treatment-experienced with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN

Clinical effectiveness - trials (II)

Trial	Intervention/comparator
SURVEYOR-II (Part 1)	**GT2 NC (for 12 weeks):** 3 x dose combinations (total number in all arms n= 74) **GT3 NC (for 12 weeks):** 4 x dose combinations (total number in all arms n=122)
SURVEYOR-II (Part 2)	**GT2 NC**: G/P for 8 weeks (n=54) **GT3 NC**: G/P for 8 (TN) or 12 (TE-PR) weeks (n=53) **GT3 TN CC**: G/P (n=28) vs G/P + RBV (n=27) for 12 weeks

- ERG noted patient numbers in the trials are very low therefore there is considerable uncertainty around SVR rates in most subgroups

Indirect treatment comparison

- 1 head-to-head trial for G/P compared with SOF/DCV (ENDURANCE-3)
- Therefore company used a naïve indirect comparison, using same SVR rates for comparator technologies that had been identified in a previous hep C appraisal (TA430 sofosbuvir-velpatasvir)

ERG comments

- Company followed same methodology which had been accepted in previous NICE guidance on HCV, therefore the same limitations apply:
  - Company selected sources for SVR rates of comparator technologies which results in bias similar to observational studies
  - Other study designs could have been included in the company's literature search including uncontrolled studies and case series
  - When multiple SVR rates were presented within a study the company selected one SVR rate to include in the analysis

SVR12 RATES % (n [where reported]) used in company model

		TN		TE	
GT	Treatment	NC	CC	NC	CC
1	G/P	[redacted]	[redacted]	[redacted]	[redacted]
	SOF/VEL	98.4% (251/255)	98.6% (72/73)	98.4% (251/255)	98.6% (72/73)
	EBR/GZR	93.2% (NR)	95.9% (NR)	93.4% (NR)	93.2% (NR)
	SOF/LDV: • F0–F1 • F2–F3	 95.2% (80/84) 94.4% (68/72)	94.1% (32/34)	95.4% (83/87)	86.4% (19/22)
	OBV/PTV/RTV + DSV ± RBV	[redacted]	96.4%(12/24)	97.4% (NR)	98.5% (12/24)
2	G/P	[redacted]	[redacted]	[redacted]	[redacted]
	Peg-IFN + RBV	**IFN-eligible patients:** 81.5% (44/54)	-	-	-
	SOF/VEL	99.0% (99/100)	100.0% (15/15)	100.0% (15/15)	100.0% (4/4)
	SOF/RBV	96.3% (180/187)	89.7% (26/29	88.5% (69/78)	77.3% (NR)

SVR12 RATES % (n [where reported]) used in company model

		TN		TE	
GT	Treatment	NC	CC	NC	CC
3	G/P	94.9% (149/157)	[redacted]	95.5% (21/22)	[redacted]
	SOF/VEL	98.2% (160/163)	96.7% (116/120)	91.2% (31/34)	89.9% (62/69)
	SOF+DCV	96.8% (184/190)		94.1% (32/34)	
	SOF+DCV+ RBV	-	100% (5/5)	-	100% (5/5)
	SOF + peg-IFN + RBV	-	91.3% (21/23)	NR	85.7% (30/35)
	SOF+RBV	-	77.6% (45/58)	-	59.0% (49/83
4	G/P	[redacted]	[redacted]	[redacted]	[redacted]
	SOF/VEL	100.0% (89/89)	100.0% (27/27)	100.0% (89/89)	100.0% (27/27)
	EBR/GZR	100.0% (16.71/16.71)	100.0% (1.29/1.29)	100.0% (3/3)	66.7% (4/6)
	SOF/LDV	-	100.0% (1/1)	84.6% (11/13)	100.0% (9/9)
	OBV/PTV/RTV + RBV	100.0% (42/42)	96.7% (29/30)	100.0% (49/49	98.2% (N=29)

SVR12 RATES % (n [where reported]) used in company model					
		Treatment (duration in weeks)			
		TN		TE	
GT	Treatment	NC	CC	NC	CC
5	G/P	[redacted]	[redacted]	[redacted]	[redacted]
	SOF/VEL	96.6% (28/29)	100.0% (5/5)	100.0% (11/11)	100.0% (11/11)
	SOF + peg-IFN + RBV	-	50% (1/2)	-	50% (1/2)
6	G/P	[redacted]	[redacted]	[redacted]	[redacted]
	SOF/VEL	100.0% (35/35)	100.0% (6/6	100.0% (35/35)	100.0% (6/6)
	SOF + peg-IFN + RBV	-	50% (1/2)	-	50% (1/2)

Adverse effects of treatment from G/P trials

- SmPC lists headache and fatigue as the most common adverse effects
- In 21 arms of the phase II/III studies [redacted]
- patients experienced AEs that were Grade ≥3 (severe)
- Of the [redacted]
- patients who experienced an AE of Grade ≥3 severity, [redacted]
- patients had AEs considered study drug-related, these were:

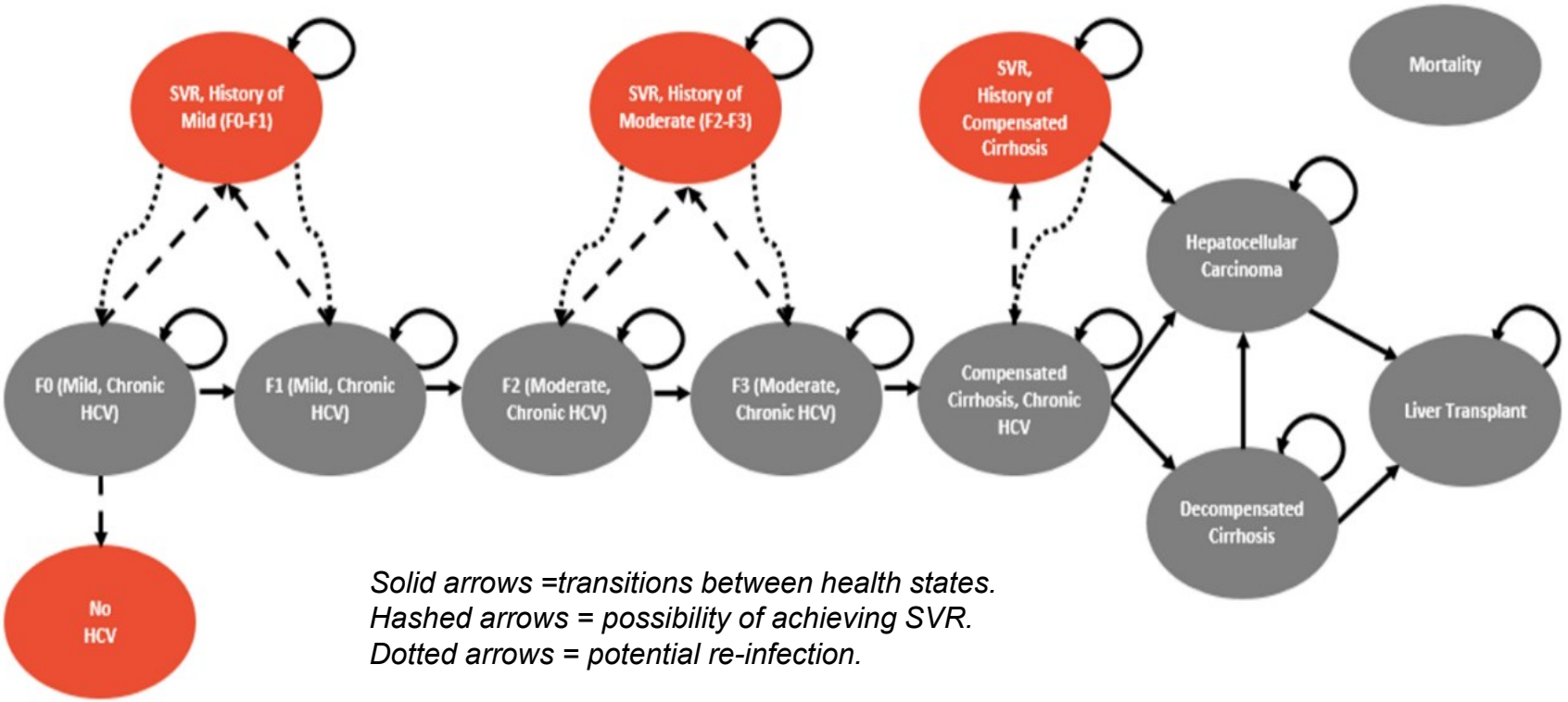
[redacted]

The frequency of serious AEs and grade ≥3 AEs was [redacted]

Cost-effectiveness evidence

Model structure

- Cohort Markov state-transition model that distinguishes between NC/CC (NC patients are further subdivided into fibrosis severity)
- Lifetime horizon with annual cycle length
- Assumes no onward HCV transmission or re-infection
- *ERG used alternative probabilities for re-infection from SVR states but this had no impact on the overall results*



Solid arrows =transitions between health states.
Hashed arrows = possibility of achieving SVR.
Dotted arrows = potential re-infection.

Model inputs – transition probabilities (I)

Variable	Source	TA430 source	ERG comments
SVR12 rates	Company trials and naïve indirect comparison (see slides 11-13)	Same SVR12 rates for comparator technologies	See slide 10 for ERG critique
Fibrosis progression	GT1: Thein et al. (2008) GT2 – GT6: GT-specific multipliers from Kanwal et al. (2014) applied to rates for GT1 to account for faster progression	Did not distinguish between different non-cirrhotic fibrosis health states, and transition probabilities from fibrosis to CC were calculated from Kanwal et al. (2014)	NICE TA253 and TA364 used Thein et al. (2008). ERG explored alternative transition probabilities in its scenario analysis from Grischenko et al. (2009). **This had no impact on the results**

Key: SVR; sustained virologic response, CC; compensated cirrhosis, DCC; decompensated cirrhosis, HCC; hepatocellular carcinoma

Model inputs – transition probabilities (II)

Variable	Source	TA430 source	ERG comments
Non fibrosis progression			
CC to HCC (SVR with history of CC)	Cardoso et al. (2010)	Same	-
CC to DCC	Fattovich et al. (1997)	Cardoso et al. (2010)	Fattovich et al. (1997) has been accepted by committee as being generalisable to the UK in previous NICE TA guidance
CC to HCC (GT1)			
DCC to HCC (GT1)			
CC to HCC (GT2 – GT6)	GT-specific multipliers from Kanwal et al. (2014) applied to rates for GT1	Not applied	-
DCC to HCC (GT2 – GT6)	Same as CC to HCC	Not applied	-

Model inputs - transition probabilities (III)

Variable	Source	TA430 source	ERG comments
Liver transplantation			
DCC to LT (1st year)	Siebert et al. (2003)	Siebert et al. (2005)	-
HCC to LT (1st year)		Transition not allowed in model	-
Liver mortality			
DCC to liver death	Fattovich et al. (1997)	EAP data (EASL 2016)	In TA430, a single transition probability for liver transplant to death was used from Bennett et al. which is higher than those used in this model. However, the value used in this model is consistent with TA365 and TA364
LT (1st year) to liver death	Grieve et al. (2006)	Bennett et al. (1997)	
LT (subsequent year) to liver death	Bennett et al. (1997)	Same	
HCC to liver death	Fattovich et al. (1997)	Same	
DCC to HCC (GT1)	Fattovich et al. (1997)	Cardoso et al. (2010)	

Model inputs – HRQoL

Health state	Utility values	Source
No cirrhosis - F0	0.77	Wright et al. 2006 *(used in previous Hep C appraisals)*
No cirrhosis - F1	0.77	
No cirrhosis - F2	0.66	
No cirrhosis - F3	0.66	
Compensated cirrhosis - F4	0.55	
DCC, HCC and liver transplant (1st year)	0.45	(Ratcliffe et al. 2002, used in the model by Wright et al. 2006) *(used in previous Hep C appraisals)*
Liver transplant (subsequent years)	0.67	

- Did not use trial utility values in base-case due to small UK patient numbers
- Utility increment after SVR: 0.05 from Wright et al. 2006
- Treatment-related utility changes were applied to adjust for the impact on HRQoL of treatment, e.g. due to adverse events.
  - For comparators, these (dis)utilities were derived from previous NICE submissions
- Separate utility decrements not applied for each adverse event to avoid double counting

ERG comments on HRQoL

- Using utility values from the literature is consistent with other Hep C appraisals however
  - questionable whether the values from Wright et al. are relevant to UK practice in this DAA era
  - difference in utility of a health state with or without SVR ranges from 0.025 to 0.029 using trial data, substantially lower than the increment of 0.05 from the literature
  - applying ‘no gain’ in utility after SVR in ERG exploratory analysis had **no impact** on the results
- Changes in utility for treatment-related HRQoL values were based on the same studies used in the company's naïve indirect comparison which included studies with very small patient numbers
  - ERG explored no treatment specific health utility changes in its scenario analyses, and this had **no impact** on the results
- No age based utility decrements were applied
  - Applying age based utility decrements derived from Ara and Brazier (2010) had **no impact** on the results

Model inputs – Resource use and costs

- Company model included costs associated with treatment, monitoring and adverse events
- Company used same data (inflated to 2017 prices) as TA430 to inform health state costs
- G/P has a confidential commercial pricing arrangement
- Confidential commercial pricing arrangements also exist for:
  - Daclatavir (TA364)
  - Ombitasvir/paritaprevir/ritonavir with or without dasabuvir – 3D and 2D (TA365)
  - Elbasvir/grazoprevir (TA413)
  - Sofosbuvir /velpatasvir (TA430)

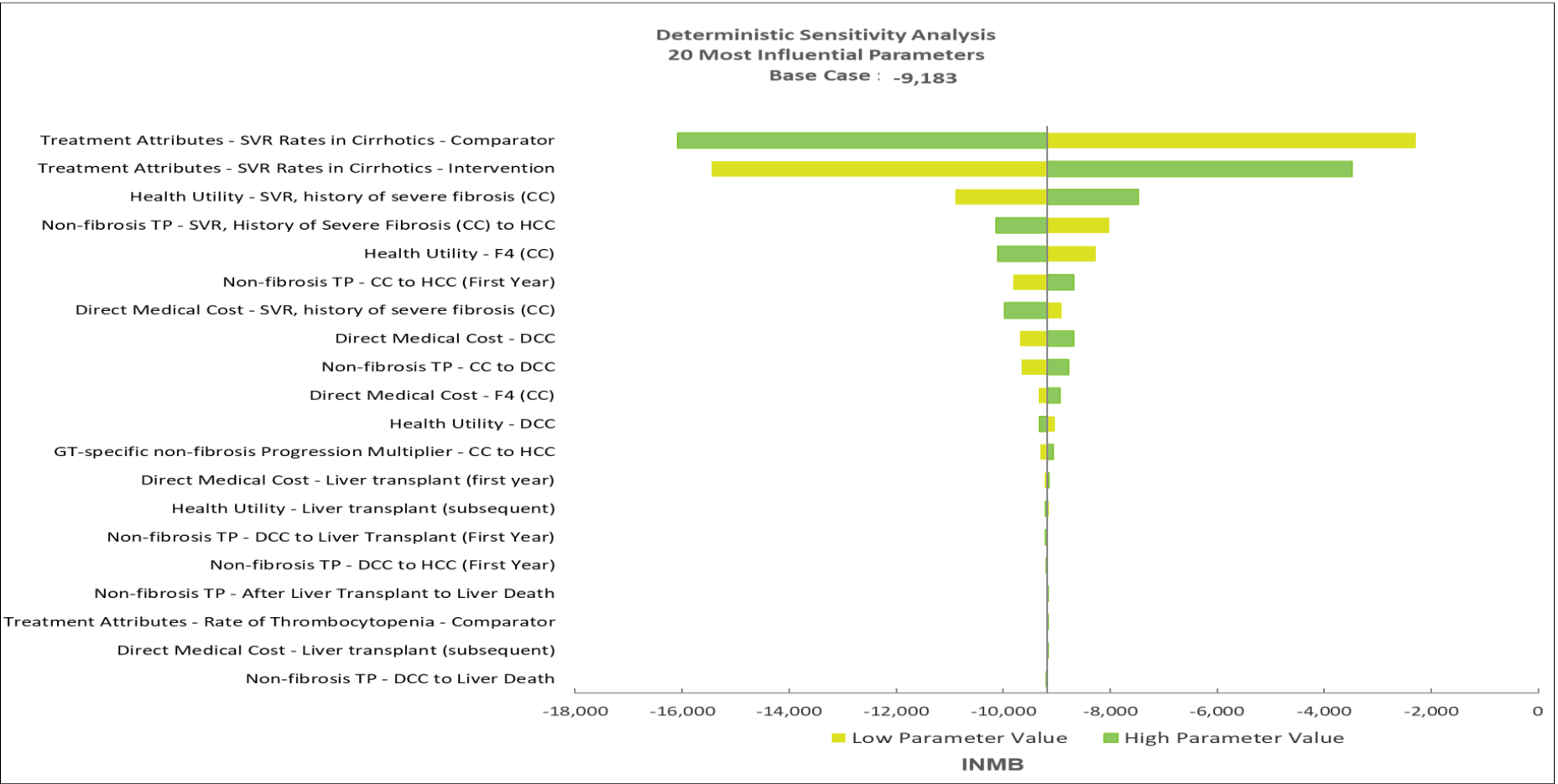
Company's base case results (list prices)

- **13** out of the 26 subgroups the ICER for G/P was lower than £20,000/QALY
  - ICER range £2281 - £5813 per QALY gained
- In NC patients, the ICERs for G/P were all **below** £20,000/QALY except for:
  - GT2 TN IFN-eligible (£36,936/QALY)
  - GT3 TE (ICER > £167,731/QALY)
- In CC patients, the ICERs for G/P were all **above** £20,000/QALY except for:
  - GT1 TN
  - GT3 TN

Results using confidential commercial pricing arrangements for G/P and comparators presented in part 2

Company's deterministic sensitivity analyses

- Showed that SVR rates had the biggest impact on the cost-effectiveness of G/P
- Example below GT3 TE CC, G/P vs. SOF/VEL:



Innovation *(company comments)*

- 8-week regimen meaning treatment cessation 4 weeks sooner than comparator DAA-based therapies
- G/P is suitable for specific patient groups with an unmet need in the UK:
  - Patients with GT2, GT3, GT5 or GT6 with chronic kidney disease (Stage 4/5)
  - Patients with GT3 previously treated with peg-IFN, RBV and/or SOF
- A positive recommendation in all patients regardless of IFN-eligibility would remove the need for baseline resistance associated variance (RAV) and viral load testing
- Favourable safety profile which suggests minimal monitoring may be required
- Oral, once-daily regimen used in primary care could help those groups who are recognised to have difficulty engaging with secondary care services

Equalities

- During the scoping process it was noted that HCV disproportionately affects certain populations such as certain immigrant populations, prison populations, and drug users, which leads to poor quality care and potential discrimination in these groups

NICE response

- Any recommendations on the use of glecaprevir-pibrentasvir would be irrespective of whether or not the person is in prison, or uses injectable drugs
- Related technology appraisals have already addressed the higher representation of minority ethnic groups in certain HCV genotypes, giving consideration to whether anything could be done to remove or reduce the disproportionate impact on the protected groups. The Committee may need to discuss similar equality issues for glecaprevir-pibrentasvir, where applicable

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