Public slides

Lead team presentation Sofosbuvir-velpatasvir for treating chronic hepatitis C – STA

1st Appraisal Committee meeting (25 August 2016)

Background and Clinical Effectiveness

Committee D

Lead team: Carol Haigh, John Henderson, Malcolm Oswald

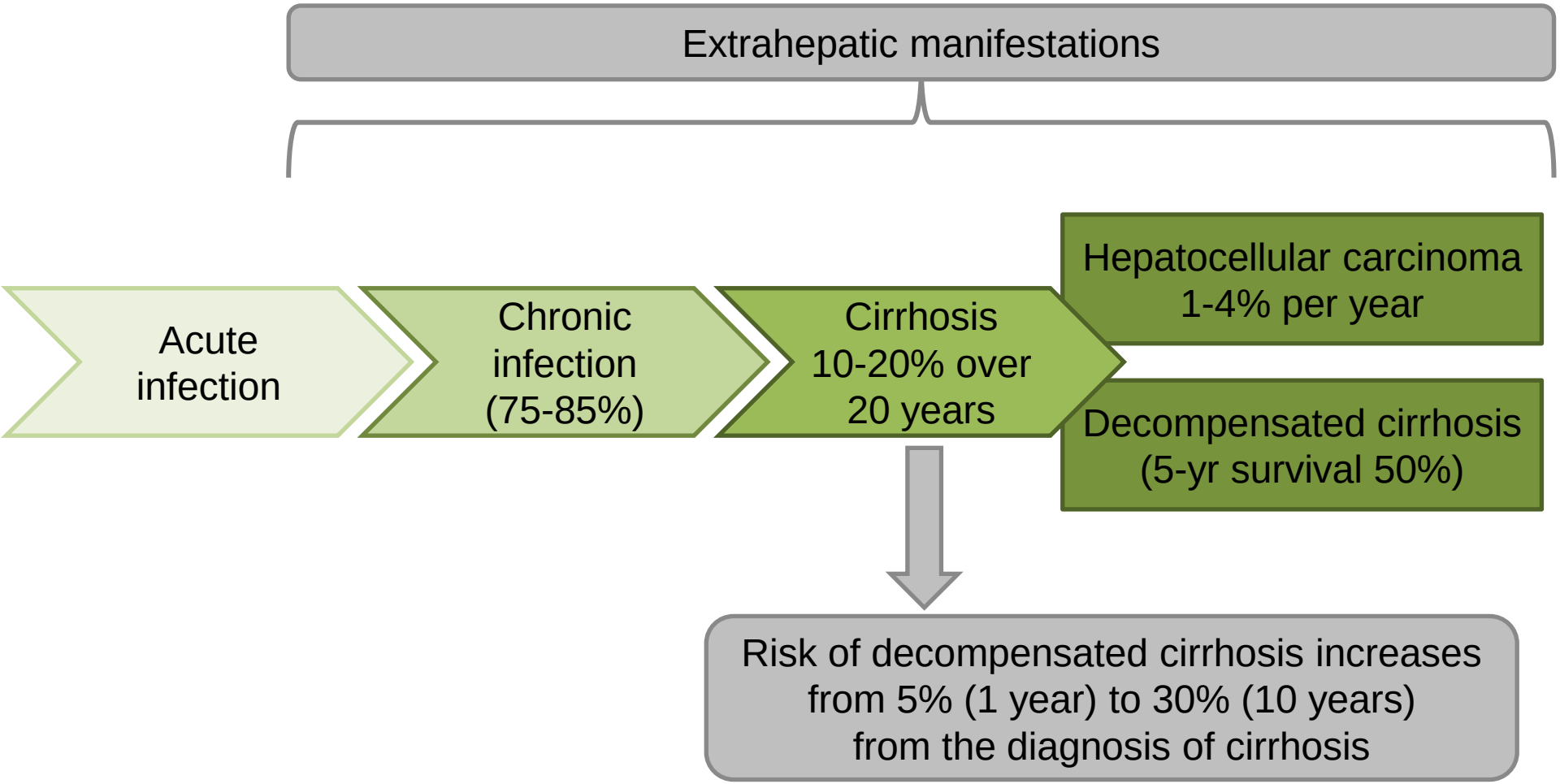
ERG: Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

NICE technical team: Sophie Cooper, Nwamaka Umeweni

Chronic hepatitis C (CHC)

- Blood borne virus (people who inject drugs major source ≈90%)
- Causes inflammation of liver, acute infection usually asymptomatic
- 214,000 people with CHC in UK, 160,000 in England (PHE, 2014)
- Six major genotypes (GT1-6)
  - GT1 and GT3 most common (approx. 90%)
  - GT3 (44%) highest risk of disease progression and death
- Aim of treatment is to cure the infection and to prevent liver disease progression and hepatocellular carcinoma development
  - Historically, treatment included peginterferon+ribavirin (TA75, 106, 200)
  - Now, direct-acting antivirals with improved efficacy and safety are used
    - sofosbuvir (TA330), simeprevir (TA331), ledipasvir-sofosbuvir (TA363) sofosbuvir +daclatasvir (TA364), ombitasvir/paritaprevir/ritonavir (TA365)
  - Mild disease may be managed by ‘watchful waiting’

Disease progression



Patient perspectives

Responses from Hepatitis C Trust and Liver4Life

- People with Hepatitis C can experience:
  - Differing symptoms, from mild to debilitating (chronic fatigue, mood swings, sexual dysfunction)
  - Liver damage even with mild symptoms
  - Uncertainty over who will be treated with new interferon-free therapies
  - Stigma & discrimination, job loss, substantial impact on relationships & social life
- Sofosbuvir-velpatasvir:
  - Potentially cures people who might otherwise transmit hepatitis C (avoids costs)
  - Fast-acting alternative to toxic interferon & ribavirin
  - Pan-genotypic – could benefit people with genotype 3, 5 and 6 who do not generally have access to interferon-free therapy
  - Simpler treatment protocol

Clinician perspective

Responses from nominated clinical experts and British Association for the Study of the Liver

- Comparators boceprevir, telaprevir and simeprevir are no longer used in the UK
- Hepatitis C treatment varies by genotype & geography:
  - Operational Delivery Network limits on new therapies vary
  - If limits removed, may be staff/diagnostic shortages
- Sofosbuvir-Velpatasvir advantages:
  - Good efficacy for all genotypes, all disease stages
  - Especially beneficial for genotype 3 and people with cirrhosis, current regimens sub-optimal (SVR 70-80%)
  - No adverse effects in trials or so far in clinical practice
  - Simple dosing regimen
  - Address inequality: disadvantaged groups and eg genotype 3

Technology being appraised

Technology	Sofosbuvir-velpatasvir (Epclusa)
Marketing authorisation	Chronic hepatitis C virus (HCV) infection in adults • Any genotype (GT1–6) • Includes people with/without compensated cirrhosis (CC) • Includes decompensated cirrhosis (DCC) • Includes HCV/HIV co-infection and post-liver transplant
Mechanism of action	SOF: NS5B inhibitor VEL: NS5A inhibitor
Administration	Oral, once daily for 12 weeks In combination with ribavirin for DCC and GT3 with CC
Acquisition cost	SOF/VEL 28 tablets: list price £12,993.33 (confidential simple discount agreement exists) Ribavirin 56 tablets: £246.65
Course of treatment	SOF/VEL 12 weeks: £38,980 (list price) SOF/VEL+RBV 12 weeks: £40,089.93 (list price)

Decision problem

	Final scope	Submission	Rationale
Pop.	People with chronic hepatitis C (treatment-naïve & experienced)		
Int.	Sofosbuvir-velpatasvir		
Com.	• BSC (GT1-6) • BOC + PR (GT1) • DCV + PR (GT4[a]) • DCV + SOF ± R (GT1, 3, 4[a]) • LDV/SOF (GT1, 4[a]) • OPR ± D ± R (GT1, 4) • PR (GT1-6) • SMV + PR (GT1, 4) • SOF + R ± P (GT1-6[a]) • TVR + PR (GT1)	Deviations: • BOC & TVR not included • Some only in scenarios • LDV/SOF in DCC	BOC and TVR not used DCV+PR and SMV+PR not used for GT4
Out.	SVR, resistance, mortality, adverse effects, HRQoL	Resistance not modelled	Does not impact costs/QALYs

[a] for specific people. Abbreviations: BOC, boceprevir; BSC, best supportive care; D, dasabuvir; DCC, decompensated cirrhosis; DCV, daclatasvir; HRQoL, health-related quality of life; LDV, ledipasvir; OPR, ombitasvir/paritaprevir/ritonavir; P, peginterferon; QALY, quality-adjusted life year; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virological response; TVR, telaprevir

Key clinical issues

- Are the following comparators relevant for this appraisal?
  - boceprevir and telaprevir
  - peginterferon alpha plus ribavirin (PR)
  - daclatsavir+PR and simeprevir+PR in GT4 patients

- Are the company's estimates of sustained virological response rate for each comparator treatment robust and appropriate?
  - 1 RCT for each comparator in each subgroup
  - eg SVR for PR in GT3 treatment-naïve non-cirrhotic = 71%

Clinical evidence for SOF/VEL: 3 phase III randomised controlled trials

Trial	Int.	Comp.	Population	Sites	Design
ASTRAL-1	SOF/VEL 12 weeks	Placebo 12 weeks	• GT 1, 2, 4-6 • TN & TE • NC & CC	81 sites (incl. 11 UK sites, n=104)	Double blind 5:1 randomisation except GT5 (n=35, SOF/VEL only)
ASTRAL-2	SOF/VEL 12 weeks	SOF + R 12 weeks	• GT2 • TN & TE • NC & CC	51 sites (USA only)	Open label 1:1 randomisation
ASTRAL-3	SOF/VEL 12 weeks	SOF + R 12 weeks	• GT3 • TN & TE • NC & CC	76 sites (incl. 11 UK sites, n=105)	Open label 1:1 randomisation
Abbreviations: CC, compensated cirrhosis; NC, no cirrhosis; R, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir					

Primary endpoint: SVR12 (HCV RNA <15 IU/mL, 12 weeks after treatment ends)
Secondary endpoints included: SVR4 and SVR24, drug resistance, virologic failure
HRQoL: SF-36, Chronic Liver Disease Questionnaire (CLDQ-HCV), Fatigue Index (FACIT-F) and Work Productivity and Activity Impairment (WPAI)

SVR12 in individual ASTRAL trials (1)

Study	GT	Subgroup	SVR12 with SOF/VEL (12 wks)		
			n/N	%	95% CI
ASTRAL-3	**GT3**	**All patients** p<0.001 compared with SOF+R 24 wks	264/277	95.3	**********
		TN, NC	160/163	98.2	**********
		TN, CC	40/43	93.0	**********
		TE, NC	31/34	91.2	**********
		TE, CC	33/37	89.2	**********
ASTRAL-2	**GT2**	**All patients** p=0.018 compared with SOF+R 24 wks	133/134	99.3	**********
		TN, NC	99/100	99.0	**********
		TN, CC	15/15	100.0	**********
		TE, NC	15/15	100.0	**********
		TE, CC	4/4	100.0	**********

SVR12 in individual ASTRAL trials (2)

Study	GT	Subgroup	SVR12 with SOF/VEL (12 wks)		
			n/N	%	95% CI
ASTRAL-1 p<0.001 compared with pre-defined performance goal of 85%	**GT1, GT2, GT4-6**	**All patients** (p<0.001)	618/624	99.0	**********
		TN	-	98.8	-
		TE	-	99.5	-
		NC	-	99.0	-
		CC	-	99.2	-
	GT1a		206/210	98.1	**********
	GT1b		117/118	99.2	**********
	GT2		104/104	100.0	**********
	GT4		116/116	100.0	**********
	GT5		34/35	97.1	**********
	GT6		41/41	100.0	**********

98.1% of people receiving SOF/VEL in ASTRAL 1-3 (n=1,035) had SVR12
1.3% (n=13) experienced virologic relapse after treatment

Adverse effects (AEs) of treatment

- No adverse drug reactions specific to SOF/VEL
- Type, incidence and severity of AEs comparable to placebo
- Most common (incidence ≥10%) treatment-emergent AEs across ASTRAL 1-3: headache, fatigue and nausea
- ASTRAL-2 and -3: lower % of patients in the SOF/VEL group experienced any AE (88%) compared with SOF+RBV (95%)
  - higher number of AEs known to be associated with RBV (e.g. fatigue, headache, nausea, insomnia)
- ASTRAL-4 (decompensated cirrhosis): AEs consistent with expected clinical sequelae of decompensated liver disease, or known AEs for ribavirin

Company network meta-analysis

- Only 2 networks could be formed:
  - **GT1 TN**: nearly all treatments showed a statistically significant increase in probability of SVR compared with PR
    - mean risk difference for SOF/VEL vs PR: 0.71 (95% CrI 0.51 to 0.89)
  - **GT3 TN**: no statistically significant difference in probability of SVR compared with PR for any treatment
    - mean risk difference for SOF/VEL vs PR: 0.15 (95% CrI −0.01 to 0.42)
- Company identified several limitations with the NMA:
  - Efficacy data could not be split by presence/absence of cirrhosis
  - No results for GT1a and GT1b
  - 1 trial essential to create GT3 network lacked face validity (ELECTRON)
  - Studies in GT3 network were heterogeneous for METAVIR fibrosis score
- Because of these limitations, and because NMA networks could not be formed for all subgroups, the company did not use the results of the NMA in its model
  - company extracted SVR data from individual RCTs identified in systematic literature review (1 source per comparator)

SVR12 rates, % (1)
(clinical data used in company model)

	GT1a				GT1b			
	TN		TE		TN		TE	
	NC	CC	NC	CC	NC	CC	NC	CC
SOF/VEL	97.5	100	97.5	100	100	95.8	100	95.8
SOF+PR	91.7	80.8	74.0	74.0	91.7	80.8	74.0	74.0
DCV+SOF±R	100	100	100	98.5	100	100	100	98.5
PR	43.6	23.6	17.6	10.0	43.6	23.6	17.6	10.0
LDV/SOF	94.0	94.1	95.4	86.4	94.0	94.1	95.4	86.4
OPR+D±R	97.0	92.9	96.0	95.4	99.0	100.0	100	97.8
SMV+PR	82.0	60.4	80.1	74.4	82.0	60.4	80.1	74.4

SVR12 rates, % (2)
(clinical data used in company model)

	GT1				GT2			
	TN		TE		TN		TE	
	NC	CC	NC	CC	NC	CC	NC	CC
SOF/VEL	98.4	98.5	98.4	98.5	99.0	100	100	100
SOF+R					95.8	93.3	81.3	100
SOF+PR	91.7	80.8	74.0	74.0				
DCV+SOF±R	100	100	100	100				
PR	43.6	23.6	17.6	10.0	80.6	71.5	35	35
LDV/SOF	94.0	94.1	95.4	86.4				
OPR+D±R		95.4						
SMV+PR	82.0	60.4	80.1	74.4				

SVR12 rates, % (3)
(clinical data used in company model)

	GT3				GT4			
	TN		TE		TN		TE	
	NC	CC	NC	CC	NC	CC	NC	CC
SOF/VEL	98.2	93.0	91.2	89.2	100	100	100	100
SOF+R	90.4	73.3	71.0	57.9				
SOF+PR	95.8	91.3	94.2	85.7	100	50	100	50
DCV+SOF±R	77.8	57.9	71.4	69.2				
PR	71.2	29.7	35.0	35.0	45.0	25.0	45	25
LDV/SOF					95.2	100	84.6	100
OPR+D+R					100	100	100	100
SMV+PR					84.4	66.7	63.6	46.4
DCV+PR					81.2	77.8	81.2	77.8

SVR12 rates, % (3)
(clinical data used in company model)

	GT5				GT6			
	TN		TE		TN		TE	
	NC	CC	NC	CC	NC	CC	NC	CC
SOF/VEL	96.6	100	100	100	100	100	100	100
SOF+PR	100	50	100	50	100	50	100	50
PR	45.0	25.0	-	-	45.0	25.0	-	-

SVR in decompensated cirrhosis:

- SOF/VEL + R: 94.3%
- LDV/SOF + R: 86.4%

ERG critique

Disagreed with company's estimation of SVRs for comparators (noting that the model was very sensitive to SVR rates):

- Only 1 source for each comparator in each population
  - company’s choice of study (and SVR from study) often arbitrary
- Open to the risks of bias associated with observational studies
- All types of study design (eg uncontrolled studies, non-randomised) should have been included (not just RCTs)

The company’s justifications for choosing each SVR were valid, but:

- equally valid justifications could be provided for alternative sources
- using multiple alternative sources across different interventions may have changed the results
- the company could have calculated a mean of all options.

Key clinical issues

- Are the following comparators relevant for this appraisal?
  - boceprevir and telaprevir
  - peginterferon alpha plus ribavirin (PR)
  - daclatsavir+PR and simeprevir+PR in GT4 patients

- Are the company's estimates of sustained virological response rate for each comparator treatment robust and appropriate?
  - 1 RCT for each comparator in each subgroup
  - eg SVR for PR in GT3 treatment-naïve non-cirrhotic = 71%

BACK UP SLIDES

Relevant NICE guidance

Relevant NICE guidance (1)

Genotype	Recommended	Restrictions by cirrhosis & treatment history	NICE TA
GT1	P ± R	All	75, 106, 200
	TVR + PR	All	252
	BOC + PR	All	253
	SOF + PR	NC TN; NC TE; CC TN; CC TE	330
	SMV + PR	All	331
	LDV/SOF	NC TN; NC TE; CC TN; CC TE[a]	363
	DCV + SOF ± R	NC TN[b]; NC TE[b]; CC[c]	364
	OPR + D ± R	NC TN; NC TE; CC TN; CC TE	365
GT2	P ± R	All	75, 106, 200
	SOF + R	NC TN[c]; NC TE; CC TN[c]; CC TE	330
GT3	P ± R	All	75, 106, 200
	SOF + PR	NC TE; CC TN; CC TE	330
	SOF + R	CC TN[c]; CC TE[c]	330
	DCV + SOF ± R	NC[bc]; CC[c]	364

[a] If certain clinical criteria are met; [b] Only for significant fibrosis; [c] Only if IFN-ineligible/intolerant

BOC, boceprevir; CC, compensated cirrhosis; D, dasabuvir; DCV, daclatasvir; LDV, ledipasvir; NC, no cirrhosis; OPR, ombitasvir/paritaprevir/ritonavir; P, peginterferon; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; TVR, telaprevir

Relevant NICE guidance (2)

Genotype	Recommended	Restrictions by cirrhosis & treatment history	NICE TA
GT4	P ± R	All	75, 106, 200
	SOF + PR	CC TN; CC TE	330
	SMV + PR	All	331
	LDV/SOF	NC TE; CC TN; CC TE[a]	363
	DCV + PR	NC TN[b]; NC TE[b]; CC TN[b]; CC TE[b]	364
	DCV + SOF ± R	NC TE[b]; CC[c]	364
	OPR + R	NC TN; NC TE; CC TN; CC TE	365
GT5/6	P ± R	All	75, 106, 200
	SOF + PR	CC TN; CC TE	330

[a] If certain clinical criteria are met; [b] Only for significant fibrosis; [c] Only if IFN-ineligible/intolerant

BOC, boceprevir; CC, compensated cirrhosis; D, dasabuvir; DCV, daclatasvir; LDV, ledipasvir; NC, no cirrhosis; OPR, ombitasvir/paritaprevir/ritonavir; P, peginterferon; R, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; TVR, telaprevir

Lead team presentation Sofosbuvir-velpatasvir for treating chronic hepatitis C – STA

1st Appraisal Committee meeting (25 August 2016)

Cost Effectiveness

Committee D

Lead team: Carol Haigh, John Henderson, Malcolm Oswald

ERG: Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

NICE technical team: Sophie Cooper, Nwamaka Umeweni

Summary of cost-effectiveness issues

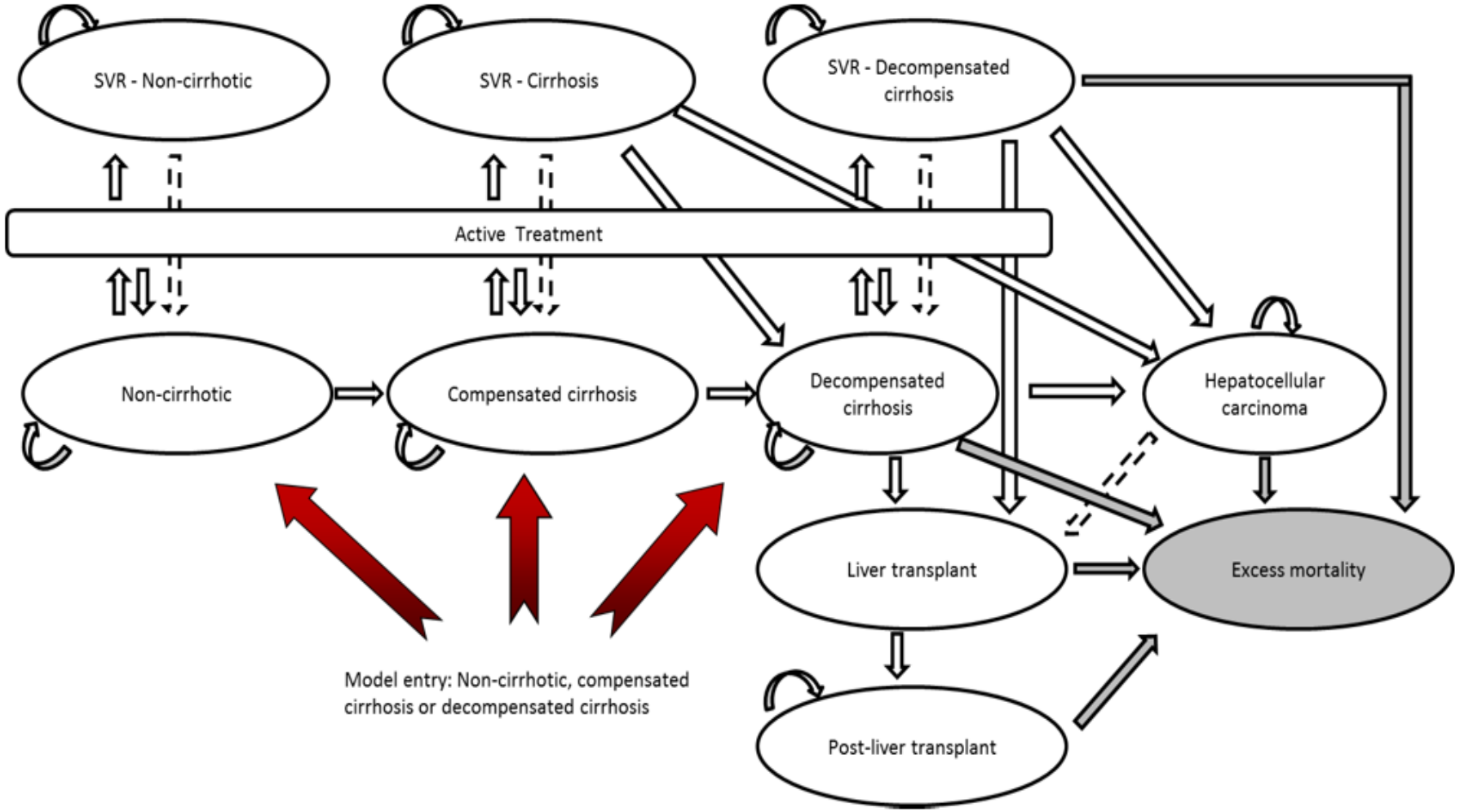
Similar modelling assumptions as for previous appraisals

- No differentiations between mild and moderate disease
- Utility estimates
- HIV co-infection treated the same as mono-infection
- Not including re-infection and transmission in base case

Differences from other appraisals

- Faster progression in GT3 than in other genotypes
- Transition probabilities for disease progression from Cardoso
- SVR in decompensated cirrhosis ↑ utility and ↓ mortality
- LDV/SOF+R as a comparator for treating DCC

Company's 10-state Markov model



Lifetime horizon up to 100 years, starting age of 40 or 45 years
2 week cycles for 72 weeks, one 24-week cycle, yearly cycles thereafter

Company model inputs & assumptions

Similarities to previous Hep C NICE appraisals

- 1 health state for mild & moderate disease (non-cirrhotic)
  - Some of the previous TAs separated the non-cirrhotic states
- SVR, treatment duration and AEs from individual comparator studies
- HIV co-infection treated the same as mono-infection
- Re-infection after SVR not in base case (scenario only)
- Utility estimates
  - Fibrosis health state utility values from Wright et al., 2006
  - SVR-related increment (0.04) from Vera-Llonch et al. 2013
    - Consistent with TA330 and TA363
    - Other appraisals used 0.05 from Wright et al. 2006
  - Treatment-specific utility increments/decrements applied (consistent with TA330 and TA363); removing them has little impact on results
- Broadly the same cost sources as in TA330 and TA363

Company model inputs & assumptions

Differences from previous Hep C NICE appraisals

- Transition probability from non-cirrhotic → compensated cirrhosis:
  - assumed to be faster in GT3 (40% faster than in GT1)
  - based on Kanwal study of 8,337 US veterans (unadjusted HR)
- Transition probability from compensated or decompensated cirrhosis → hepatocellular carcinoma
  - based on Cardoso et al. 2010 (0.0631)
  - committee previously concluded that TPs for disease progression were between Fattovich et al. 1997 and Cardoso
- Short 2-week cycles initially
  - most other models start with yearly cycles
  - some used monthly, TA253 used weekly
- Patients do not die of non-hepatitis C causes during the treatment period (consistent with TA363)
- Previous models have included boceprevir and telaprevir

Company model inputs: TPs

From	To	Annual TP	Source
NC	CC	GT1 0.0213 GT2 0.0165 GT3 0.0296 GT4 0.0202 GT5 0.0202 GT6 0.0202	Kanwal et al 2014 (unadjusted hazard ratios)
CC	DCC	0.0438	Cardoso et al 2010
	HCC	0.0631	Cardoso et al 2010
CC SVR	DCC	0.0064	Cardoso et al 2010
	HCC	0.0128	Cardoso et al 2010
DCC	HCC	0.0631	Cardoso et al 2010
	Liver transplant	0.022	Siebert 2005
	Death	0.24	EAP data (EASL 2016)
DCC SVR	HCC	0.0631	Assumption
	Liver transplant	0.022	Assumption
	Death	0.049	EAP data (EASL 2016)
HCC	Death	0.4300	Fattovich et al 1997
Liver transplant	Death, year 1	0.2100	Bennett et al 1997

CC, compensated cirrhosis; DCC, decompensated cirrhosis; EAP, Expanded Access Programme; HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability

Company model inputs
Health-state utilities

Health state	**Utility**
Baseline: non-cirrhotic	0.75 (Wright et al. 2006)
Baseline: compensated cirrhosis	0.55 (Wright et al. 2006)
Baseline: decompensated cirrhosis, hepatocellular carcinoma and liver transplant	0.45 (Wright et al. 2006)
Post liver transplant	0.47 (Wright et al. 2006)

- Utility increment after SVR: 0.04 (Vera-Llonch 2013, US EQ-5D tariff)
- No time-dependent utility change within health states
- Adverse events reduce utility
- Once treatment stops: no quality of life, adverse event (AE) or cost implications persist
  - Patients utility returns to that of the post treatment health state they are in, and future AEs and their associated costs cannot occur

Company model inputs
Treatment-specific utilities

- Data sourced from trials where possible but some assumptions e.g.:
  - on-treatment utility values for SOF/VEL based on LDV/SOF SF-36 data because of lack of evidence from ASTRAL trials
- Treatment-specific utility decrements applied for regimens containing interferon or ribavirin to reflect adverse events
  - ribavirin-containing regimens: −1.00% to −6.88%
  - interferon-containing regimens: −14.27% to −14.77%
- Treatment-specific utility increment of 4.43% applied for direct-acting antivirals because they:
  - are not associated with the AEs of interferon and ribavirin
  - improve quality of life due to rapid early suppression of the virus
- Impact of removing treatment-specific utilities is negligible

Application of price discounts

- 2 comparators are recommended by NICE with confidential price discounts agreed with the Commercial Medicines Unit:
  - ombitasvir/paritaprevir/ritonavir (OPR) (TA365)
  - daclatasvir (DCV) (TA364)
- Company's cost-effectiveness analyses where OPR or DCV are comparators (GT1 & 4) use the list prices for OPR, DCV and SOF/VEL
  - does not reflect true cost effectiveness; not presented here for discussion
- The ERG reproduced the company base case and using the confidential discounted prices for OPR, DCV and SOF/VEL
  - Note that fully incremental results with discounted prices for OPR and DCV are not available because the ERG presented only pairwise comparisons

Cost-effectiveness results based on company's base case assumptions (1)

Fully incremental results using discounted price for SOF/VEL

The ICER for SOF/VEL compared with the next non-dominated comparator was between:

- £2,379 and £32,595 for **GT2** (TN NC, TN CC, TE NC and TE CC)
  - ICER of £32,595 was compared with PR in GT2 TN NC
  - excluding GT2 TN NC, the maximum ICER was £12,384
- £3,893 and £15,199 for **GT3** (TN NC, TN CC, TE NC and TE CC)
  - does not include IFN-ineligible population (where DCV is a comparator)
- £2,395 and £6,229 for **GT5/6** (TN NC, TN CC, TE NC and TE CC)

In DCC, SOF/VEL plus ribavirin dominated LDV/SOF plus ribavirin

Note regarding GT1 and GT4: fully incremental results with the discounted prices for OPR for DCV are not available

Cost-effectiveness results based on company's base case assumptions (2)

Pairwise results using discounted prices for SOF/VEL, OPR & DCV

- At a willingness-to-pay threshold of £20,000/QALY
  - SOF/VEL cost effective compared with all treatments in all populations
  - **except** compared with PR for GT2 TN NC (ICER £32,595/QALY)

- Compared with no treatment or PR
  - the ICER for SOF/VEL ranged from £1,144–£32,595/QALY
  - excluding the ICER of £32,595, maximum ICER £15,199/QALY

- Compared with the DAAs
  - SOF/VEL was cost effective (threshold of £20,000/QALY)

Company's deterministic and probabilistic sensitivity analyses

Deterministic sensitivity analyses

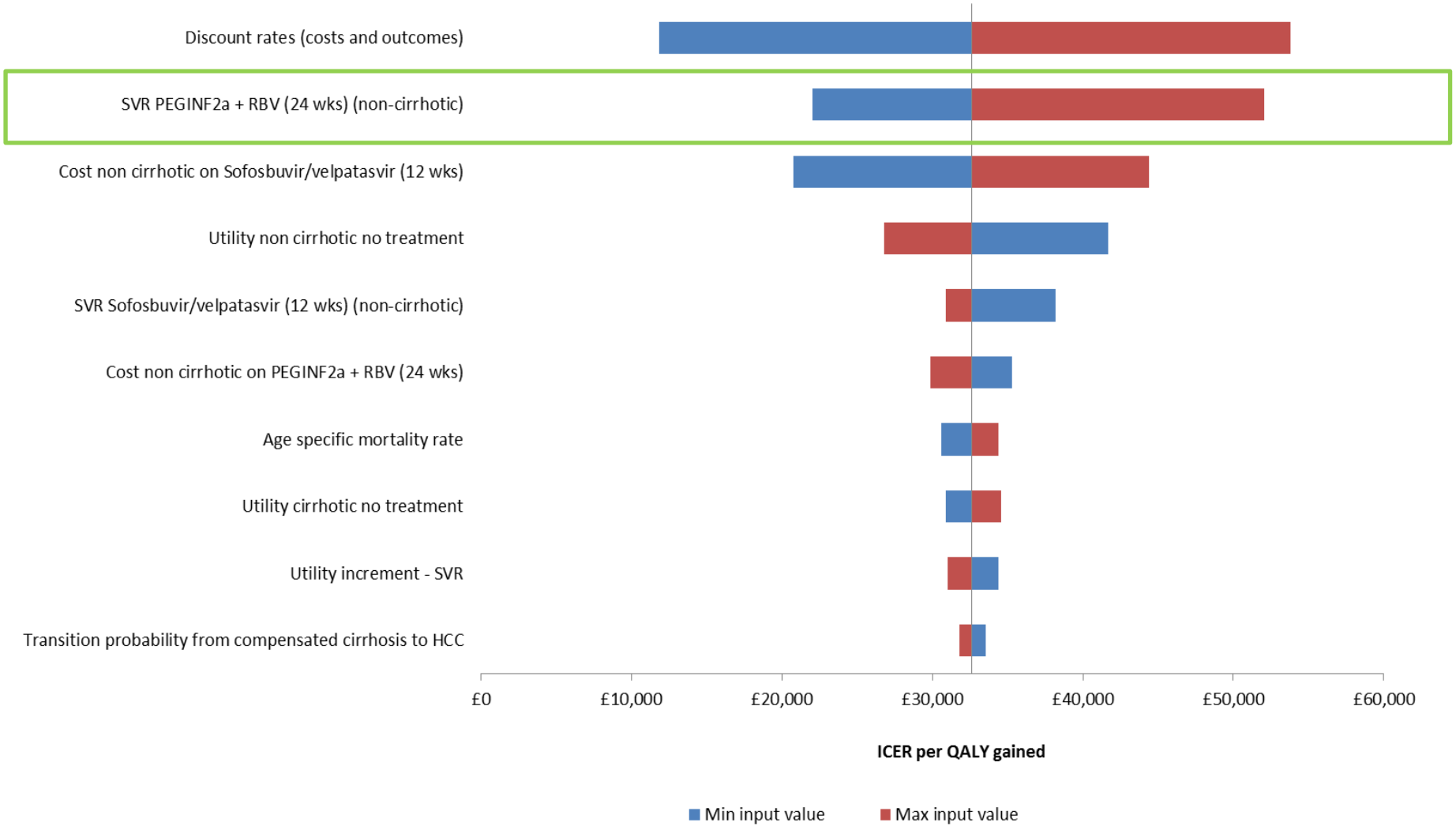
- Company only presented DSA for TN NC GT1-GT4
- ICER most sensitive to:
  - Treatment costs (for LDV/SOF and SOF/VEL)
  - Discount rates (costs and outcomes)
  - SVR probability (for LDV/SOF, PR and SOF/VEL)
  - Utility non cirrhotic (baseline)
- Not sensitive to including a risk of re-infection after SVR

Probabilistic sensitivity analyses

- Probabilistic ICERs appeared similar to deterministic ICERs
- Probability SOF/VEL cost effective: 18%-93% (threshold £20,000/QALY); 23%-95% (threshold £30,000/QALY)
  - *Note: not all analyses include confidential discounts*

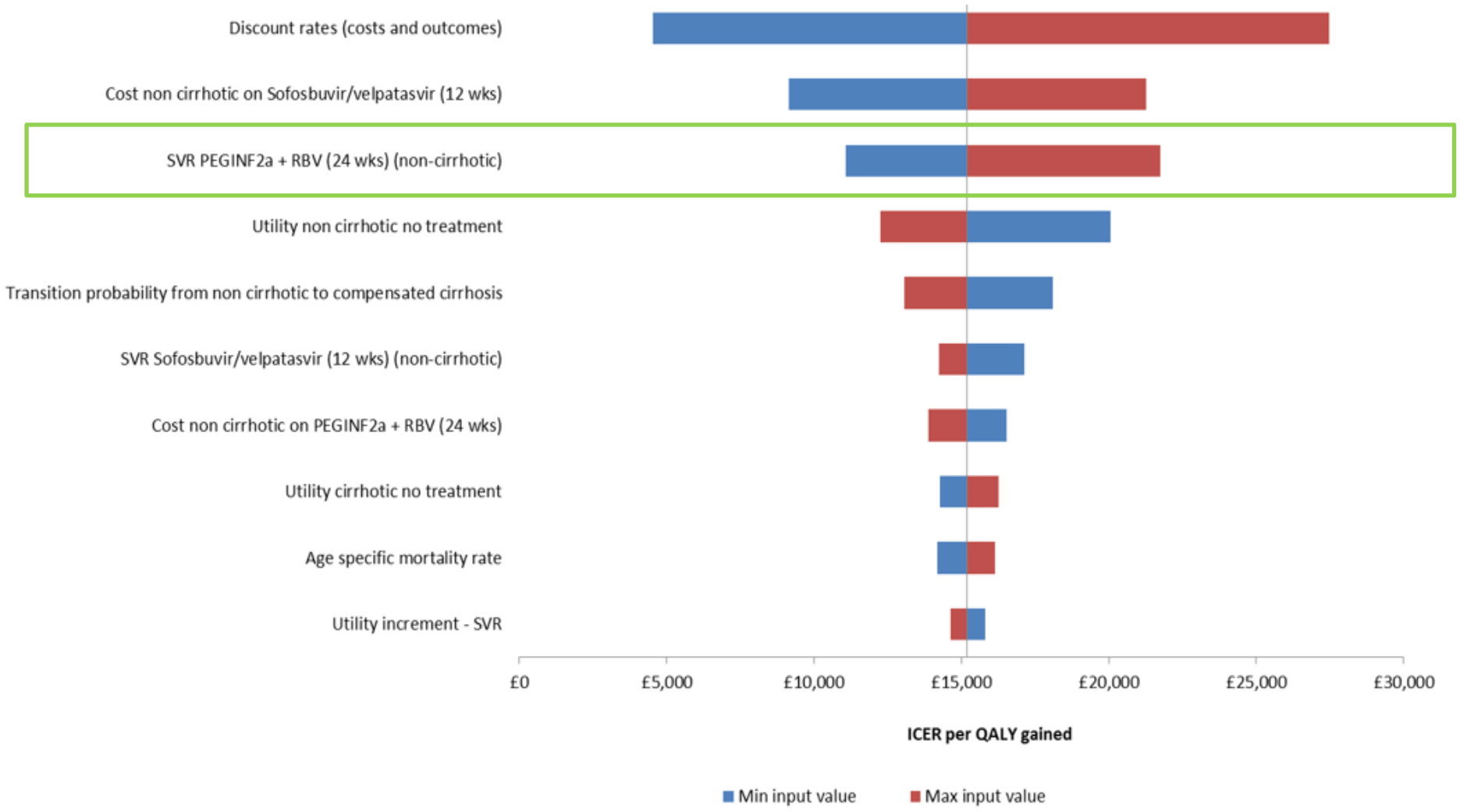
Deterministic sensitivity analyses

tornado diagram for GT2 treatment-naïve non-cirrhotic



Deterministic sensitivity analyses

tornado diagram for GT3 treatment-naïve non-cirrhotic



ERG critique
Differences from previous appraisals

- Company did not systematically identify transition probabilities
- Calculation errors in transition probabilities
- The following assumptions **not supported** by published literature:
  - Other than progression to compensated cirrhosis, TPs are independent of prior treatment and genotype
  - An SVR in people with decompensated cirrhosis leads to:
    - improved health-related quality of life (utility increment)
    - reduced mortality risk
  - 83% of people without cirrhosis have mild disease, 17% have moderate
- Model lacked face/internal validity
- Probabilistic sensitivity analyses biased and difficult to interpret
- ERG could not model the comparators excluded by the company

ERG alternative base case

The ERG made the following changes to the company's base case:

- incorporated an annual reinfection probability of 2.4%
  - the model was most sensitive to this change
- corrected calculation errors in company transition probabilities (TPs)
  - the model was not sensitive to these changes
  - the ERG subsequently noted that its corrections to TPs were wrong:
    - TPs from Kanwal 2014: the company's estimates were correct
    - TPs from Cardoso 2010: neither the company's nor the ERG's TPs were correct
- removed utility increment for SVR from decompensated cirrhosis
  - the model was not sensitive to this change
  - only relevant to analyses of subgroups with DCC

The ERG presented results for GT1a and GT1b combined

ERG alternative base case

Pairwise results using discounted prices for SOF/VEL, OPR & DCV

Includes re-infection, new estimates of treatment-independent TPs (incorrect, but minimal impact on ICERS) and no utility increment for SVR in DCC

- At a willingness-to-pay threshold of £20,000/QALY SOF/VEL was cost effective compared with all treatments in all populations **except** compared with PR in:
  - GT2 TN NC (ICER £44,545/QALY)
  - GT3 TN NC (ICER £21,479/QALY)
- Compared with no treatment or PR
  - the ICER for SOF/VEL ranged from £2,897–£44,545/QALY
  - excluding the non cost-effective ICERs, maximum ICER £17,947/QALY
- Compared with the DAAs
  - SOF/VEL was cost effective (threshold of £20,000/QALY)

ERG additional analyses in GT2/3 TN NC
Methods (ERG addendum)

Committee previously concluded (TA363) that TPs for disease progression were between Fattovich et al. 1997 and Cardoso et al. 2010

From	To	Cardoso	Fattovich
CC	DCC	0.0438	0.039
	HCC	0.0631	0.014
DCC	HCC	0.0631	0.014

CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; NC, non-cirrhotic; TN, treatment-naive

In its addendum (GT2/3 TN NC only), the ERG applied Fattovich TPs to:

A. the company base case

B. the 'corrected ERG base case': includes reinfection but reverts to company TP estimates for NC→CC (based on Kanwal, unadjusted HRs)
   - includes corrections to Cardoso TPs, but these do not impact results when Fattovich TPs are included

C. a scenario including reinfection and new TP estimates for NC→CC using **adjusted** hazard ratios from Kanwal et al.

Note: Kanwal unadjusted HRs suggest progression is 40% faster in GT3 than in GT1 (company base case); adjusted HRs assume progression is 31% faster (ERG scenario)

ERG additional analyses in GT2 TN NC
Results (ERG addendum)

ICERs for SOF/VEL compared with PR (£/QALY)		
	Treatment-independent TPs[a]	
	Cardoso 2010	Fattovich 1997
Company base case	£32,595	£37,125
Company base case with: • New TPs for NC→CC (Kanwal adjusted HR)	£35,091	£39,783
Corrected ERG base case: • Annual re-infection rate • Corrections to Cardoso TPs • Company TPs for NC→CC (Kanwal unadjusted HR)	£45,348	£50,812
ERG scenario analysis: • Annual re-infection rate • Corrections to Cardoso TPs • New TPs for NC→CC (Kanwal adjusted HR)	Not reported	£54,237

[a] except from non-cirrhotic to compensated cirrhosis (taken from Kanwal 2014)
CC, compensated cirrhosis; HR, hazard ratio; NC, non-cirrhotic; PR, TPs, transition probabilities

ERG additional analyses in GT3 TN NC
Results (ERG addendum)

ICERs for SOF/VEL compared with PR (£/QALY)		
	Treatment-independent TPs[a]	
	Cardoso 2010	Fattovich 1997
Company base case	£15,199	£17,540
Company base case with: • New TPs for NC→CC (Kanwal adjusted HR)	£15,923	£18,362
Corrected ERG base case: • Annual re-infection rate • Corrections to Cardoso TPs • Company TPs for NC→CC (Kanwal unadjusted HR)	£22,099	£25,157
ERG scenario analysis: • Annual re-infection rate • Corrections to Cardoso TPs • New TPs for NC→CC (Kanwal adjusted HR)	Not reported	£26,239

[a] except from non-cirrhotic to compensated cirrhosis (taken from Kanwal 2014)
CC, compensated cirrhosis; HR, hazard ratio; NC, non-cirrhotic; PR, TPs, transition probabilities

ERG analyses: limitations

- Because the company's executable model did not include all comparators, the ERG was not able to include them in its analyses:
  - DCV+SOF+R 24w in GT4 IFN-ineligible cirrhotic
    - dominated by SOF/VEL at list prices (company scenario)
  - DCV+SOF±R 12w in GT4 patients
    - dominated by SOF/VEL, or more costly for the same QALY gains, at list prices (company scenario)
  - DCV+PR in GT4 patients
    - the ICER for SOF/VEL was substantially >£30,000/QALY in GT4 TN NC, at list prices (company scenario)
  - SMV+PR in GT4 patients
    - dominated by SOF/VEL at list prices, except in TN CC where SOF/VEL was dominated (company base case)
- For the comparison with DCV+SOF+RBV (GT1 CC), the ERG assumed the results for DCV+SOF+RBV were equal to DCV+SOF

Equality issues

The following potential equality issues were raised by the company and professional organisations:

- A higher prevalence of disease or specific genotypes (genotypes 3 and 4) in people who inject drugs
  - *Note from technical team: NICE do not consider this to be an equalities issue and people who inject drugs are assumed to be included in any guidance published for the treatment*
- A higher prevalence of disease or specific genotypes (genotypes 3 and 4) among minority ethnic groups
  - *Note from technical team: committee will consider whether there is potential for its preliminary recommendations to have an adverse impact on minority ethnic groups, and if so it will consider whether anything can be done to remove/reduce disproportionate impact for protected groups*

Innovation

- First pan-genotypic, all-oral, interferon- and ribavirin-free regimen
  - unmet need for interferon-free regimen in treatment-experienced people with GT3 and cirrhosis
  - only ribavirin-free treatment for GT2 and GT3
- Also treats decompensated cirrhosis
- >94% SVR12 rates across all genotypes and subgroups
- Meets a need identified as important by NHS
  - NHS Outcomes Framework commitment to reducing mortality due to liver disease in people under 75 years of age
- Benefits not captured in QALY:
  - reduction in onward transmission of HCV
  - reversal of liver fibrosis once cured

Key cost-effectiveness issues (1)

Does the committee accept similar modelling assumptions as for previous appraisals?

- Combining mild and moderate disease into 1 health state
- Utilities:
  - Source of utilities (Wright et al. 2006, Vera-Llonch et al. 2013)
  - Use of treatment-specific utility increments
- HIV co-infection treated the same as mono-infection
- Not including re-infection and transmission in base case

Key cost-effectiveness issues (2)

Views on other assumptions (differences from other appraisals)?

- Faster progression in GT3 than in other genotypes
  - is Kanwal et al. generalisable to the UK?
  - adjusted or unadjusted HRs from Kanwal more appropriate?
- TPs for disease progression from Cardoso 2010 (not Fattovich)
- SVR in people with decompensated cirrhosis leads to:
  - improved utility value
  - reduced probability of death
- LDV/SOF+R as a comparator for treating DCC (licensed, but no NICE recommendation)

Appropriateness of ERG's analyses?

- Presenting pairwise comparisons instead of fully incremental analyses, and combining GT1a and 1b
- Including reinfection probability & no utility increment for SVR DCC