

# A cost-effectiveness analysis of shortened direct-acting antiviral treatment in genotype 1 non-cirrhotic treatment-naïve patients with chronic hepatitis C virus

Appendices 1-5

## Appendix 1 – Calculating SVR12 by treatment duration

Kowdley et al. [1] is the only study comparing treatment duration using the 3D regimen assumed in our model. Kowdley et al. [1] report SVR12 comparing 12 weeks and 8 weeks treatment durations. We take a Bayesian approach to estimation to enable us to easily combine evidence from multiple sources and reflect uncertainty in our estimates. Assuming a Binomial likelihood for the number of patients achieving an SVR12, we can estimate a log-odds-ratio for 8 weeks compared with 12 weeks treatment,  $LOR_{12v8}$ , (by putting a model on the log-odds scale and giving diffuse priors for the log-odds of SVR). We can also estimate the probability of SVR12 for 12 weeks,  $p_{12}$ , and apply the log-odds ratio to obtain the probability of SVR at 8 weeks:

$$\text{logit}(p_8) = \text{logit}(p_{12}) + LOR_{12v8} \quad (1)$$

together with uncertainty in these estimates.

However, Kowdley et al. [1] does not include shorter treatment durations than 8 weeks. Sulkowski et al. [2] compare SVR12 for 6 weeks and 4 weeks treatment duration, however this is for a different drug regimen, DCV-TRIO+SOF, and they do not include longer treatment durations. We use the approach described above to estimate the log-odds ratio of an SVR for 6 weeks duration compared with 4 weeks,  $LOR_{6v4}$  based on the Sulkowski et al. [2] data. We make the assumptions that:

- (i) the log-odds ratios seen for DCV-TRIO+SOF are the same as would be seen for 3D. Note this does not mean that the absolute probability of SVR12 is the same under both regimens.
- (ii) the log-odds ratio for 6 compared with 8 weeks duration,  $LOR_{8v6}$ , is a simple average of  $LOR_{6v4}$  and  $LOR_{12v8}$ , so  $LOR_{8v6} = (LOR_{12v8} + LOR_{6v4}) / 2$

We can then form the probabilities  $p_6$  and  $p_4$  of SVR for 6 and 4 weeks treatment that we predict for 3D using:

$$\text{logit}(p_6) = \text{logit}(p_8) + \text{LOR}_{8v6} \quad (2)$$

and

$$\text{logit}(p_4) = \text{logit}(p_6) + \text{LOR}_{6v4} \quad (3)$$

All the calculations described above are performed simultaneously using Markov Chain Monte Carlo simulation, so that all uncertainties are propagated and reflected in the resulting posterior distribution for the SVR12 probabilities. The posterior distributions for the probabilities are approximated by Beta distributions, using the method of matching moments to the marginal posterior summaries (Table 1).

**Table 1** Estimated SVR12 by first-line treatment and retreatment

	Mean	Distribution	Alpha	Beta	Source
First-line treatment					
12 weeks	0.96	Beta	76	3	[1]
8 weeks	0.87	Beta	69	10	[1]
6 weeks	0.64	Beta	6	3	[1, 2]
4 weeks	0.38	Beta	1	2	[1, 2]

## Appendix 2 – Probability of adverse events

**Table 2** Probability of common and serious adverse events by treatment duration

	Probability	Rate (weekly) <sup>a</sup>	Probability (12 weeks) <sup>b</sup>	Probability (8 weeks)	Probability (6 weeks)	Probability (4 weeks)	Source
Anaemia	0.039	0.003	0.039	0.026	0.020	0.013	[3]
Rash	0.079	0.007	0.079	0.053	0.040	0.027	[3]
Depression	0.000	0.000	0.000	0.000	0.000	0.000	[3]
Neutropenia	0.001	0.000	0.001	0.001	0.001	0.000	[3]
Thrombocytopenia	0.001	0.000	0.001	0.001	0.001	0.000	[3]

<sup>a</sup>  $e^{-\gamma t} = 1 - p$

<sup>b</sup>  $p(12) = (1 - e^{-\gamma 12})$

## Appendix 3 – Sensitivity analyses with alternative DAA regimens

**Table 3** Cost-effectiveness findings of sensitivity analyses with different first-line treatment regimens

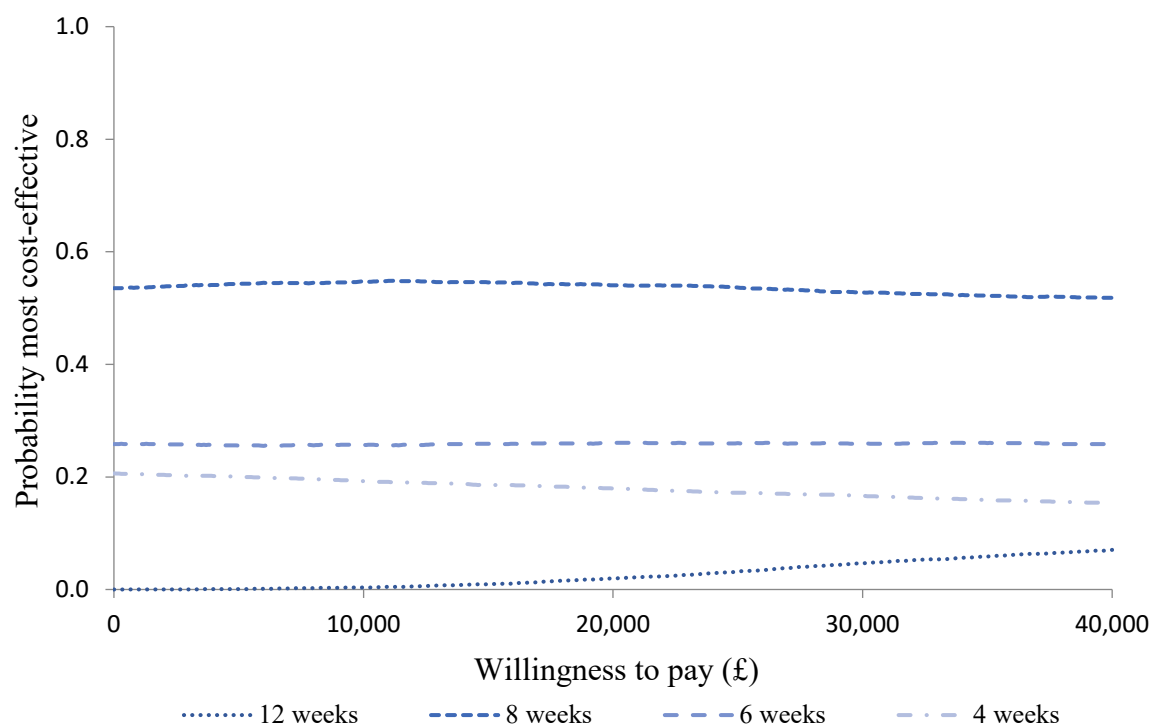
	<b>Costs (95% CI)</b>	<b>QALYs (95% CI)</b>	<b>Cost per cure (95% CI)</b>	<b>INMB (95% CI)<sup>a,b</sup></b>
<b>LDV/SOF<sup>c</sup></b>				
12 weeks	£44095 (£41899 to £47205)	15.5 (15 to 16.16)	£44247 (£41962 to £47529)	-
8 weeks	£34969 (£31634 to £39011)	15.48 (14.97 to 16.14)	£35369 (£31807 to £39859)	£8780 (£4260 to £12777)
6 weeks	£39153 (£26984 to £53772)	15.43 (14.91 to 16.11)	£40588 (£27214 to £57807)	£3576 (£-12800 to £17008)
4 weeks	£44250 (£21503 to £60494)	15.38 (14.82 to 16.07)	£47213 (£21725 to £68887)	£-2653 (£-22253 to £22202)
<b>DCV/SOF<sup>c</sup></b>				
12 weeks	£64261 (£62023 to £67400)	15.48 (14.97 to 16.14)	£64481 (£62111 to £67835)	-
8 weeks	£48405 (£45053 to £52586)	15.47 (14.96 to 16.13)	£48955 (£45293 to £53614)	£15646 (£11189 to £19551)
6 weeks	£49171 (£37161 to £63695)	15.43 (14.9 to 16.1)	£50917 (£37472 to £68149)	£13942 (£-2347 to £27099)
4 weeks	£50989 (£28516 to £67402)	15.37 (14.8 to 16.06)	£54359 (£28809 to £77171)	£11038 (£-8691 to £36039)
<b>ELB/GZR<sup>c</sup></b>				
12 weeks	£41635 (£39417 to £44649)	15.51 (15.01 to 16.16)	£41779 (£39466 to £44922)	-
8 weeks	£33334 (£29986 to £37396)	15.49 (14.99 to 16.15)	£33718 (£30164 to £38149)	£7917 (£3463 to £11804)
6 weeks	£38040 (£25951 to £52555)	15.44 (14.91 to 16.11)	£39461 (£26135 to £56520)	£2156 (£-14466 to £15564)
4 weeks	£43418 (£20895 to £59804)	15.38 (14.82 to 16.07)	£46321 (£21157 to £68155)	£-4322 (£-23850 to £20449)

<sup>a</sup> Versus 12 weeks

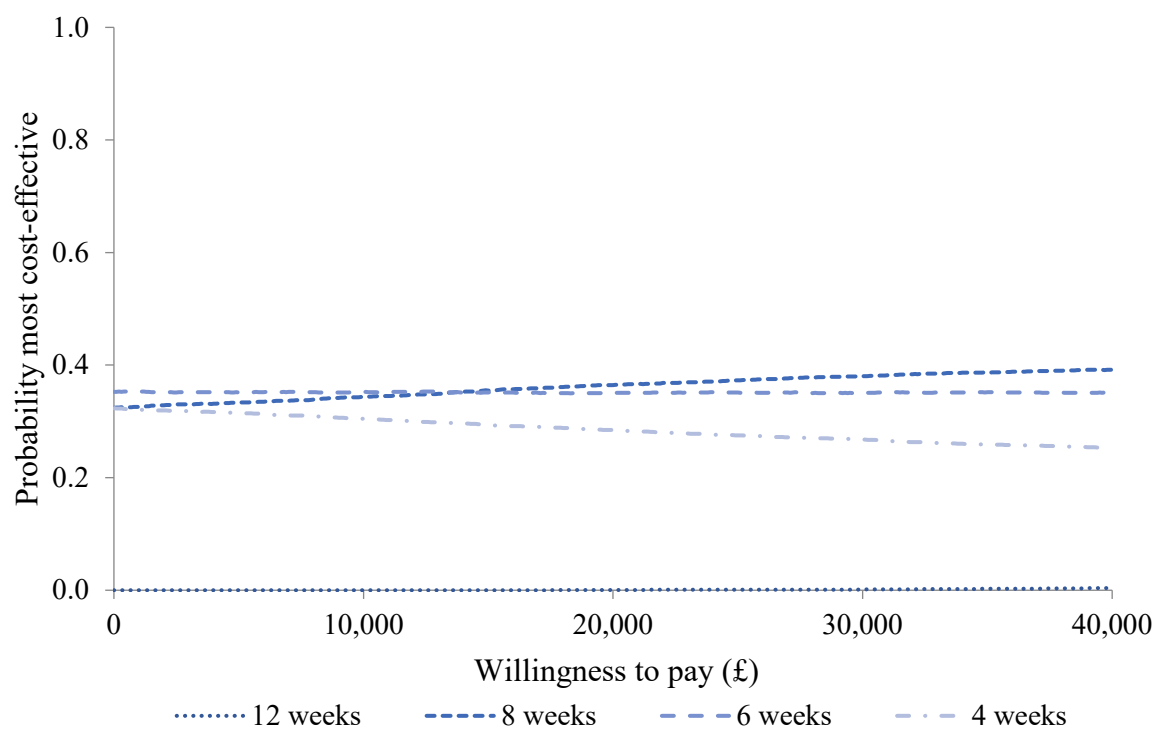
<sup>b</sup> At £20,000 willingness-to-pay

<sup>c</sup> See Tables 4 and 5 for cost and quality of life inputs, respectively.

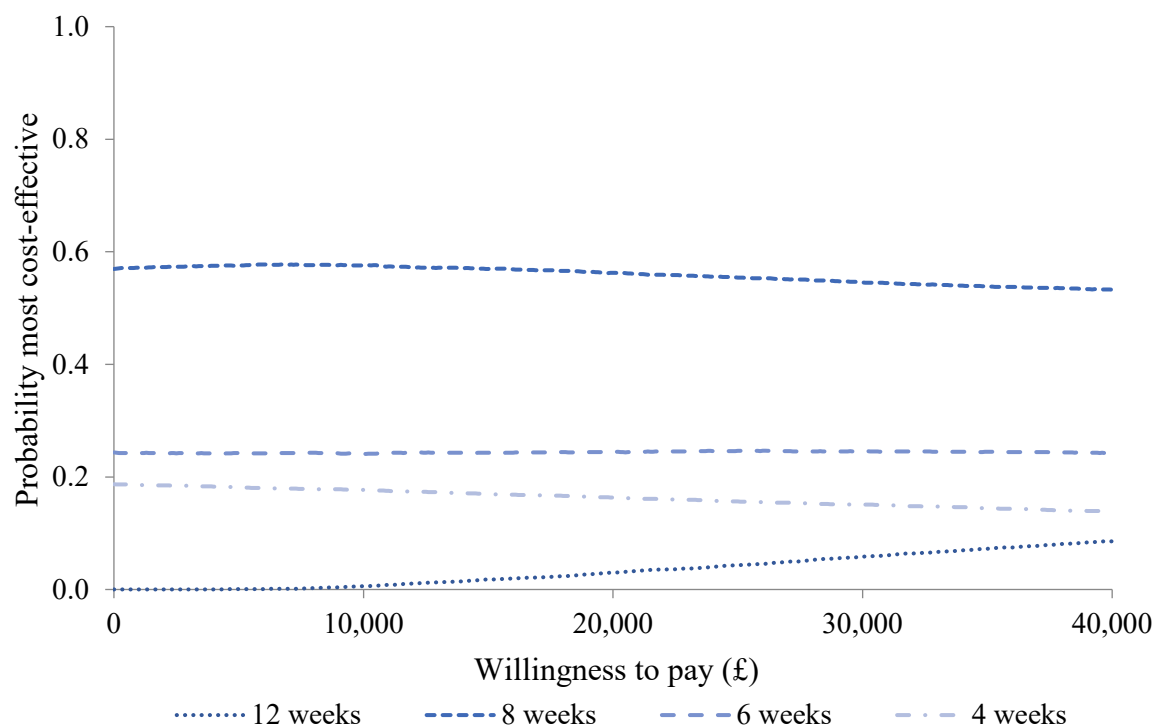
QALYs, quality-adjusted life years; INMB, incremental net monetary benefit



**Figure 1** Probability that any treatment strategy is the most cost-effective treatment strategy with LDV/SOF-based regimen assumed for first-line treatment



**Figure 2** Probability that any treatment strategy is the most cost-effective treatment strategy with DCV/SOF-based regimen assumed for first-line treatment



**Figure 3** Probability that any treatment strategy is the most cost-effective treatment strategy with ELB/GZR-based regimen assumed for first-line treatment

**Table 4** Alternative DAA costs

	Cost	Source
Ledipasvir / sofosbuvir 4 week course	£13,225.20	[4]
Daclatasvir plus sofosbuvir 4 week course	£20,187.60	[5]
Elbasvir / Grazoprevir 4 week course	£12,383.78	[6]

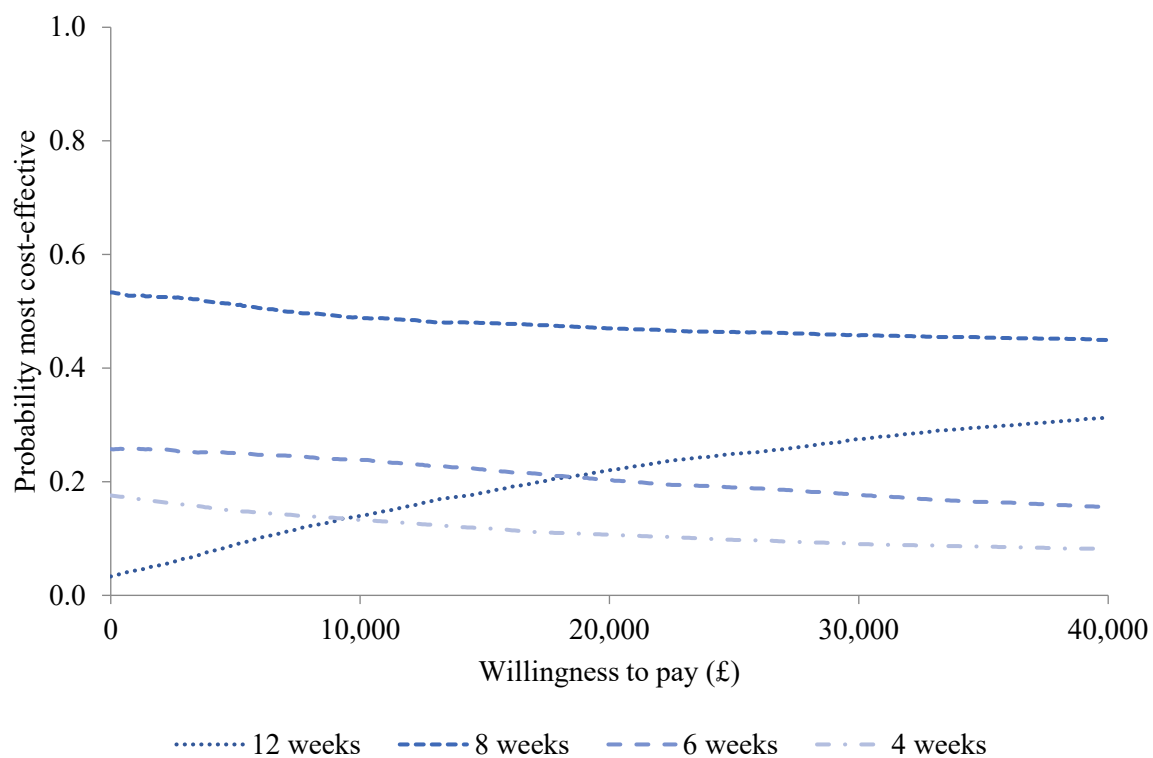
DAA, direct-acting antiviral

**Table 5** Alternative quality of life estimates

	Mean	Source
Ledipasvir / sofosbuvir Mild (F0-F1)	-0.002	[7]
Moderate (F2-F3)	-0.002	[7]
Daclatasvir plus sofosbuvir Mild (F0-F1)	-0.035	[7]
Moderate (F2-F3)	-0.035	[7]
Elbasvir / Grazoprevir* Mild (F0-F1)	0.000	[8]
Moderate (F2-F3)	0.000	[8]

\* Corman et al. [8] assumed ELB/GZR was not associated with any deterioration or penalty in quality of life

#### Appendix 4 – Sensitivity analysis with 80% reduction in drug prices



**Figure 4** Probability that any treatment strategy is the most cost-effective treatment strategy with 80% reduction in drug prices



## Appendix 5 – Sensitivity analysis with lower (1.5%) and higher (5.0%) discount rates

**Table 6** Sensitivity analysis using different discount rates

	<b>Costs (95% CI)</b>	<b>QALYs (95% CI)</b>	<b>Cost per cure (95% CI)</b>	<b>INMB<sup>ab</sup> (95% CI)</b>	<b>p(CE)<sup>b</sup></b>
<i>1.5% discount rate</i>					
12 weeks	£13,675 (£11,098 to £17,637)	21.86 (20.9 to 23.15)	£13,722 (£11,127 to £17,694)	-	0.303
8 weeks	£11,984 (£9,281 to £15,988)	21.83 (20.88 to 23.12)	£12,121 (£9,367 to £16,180)	£1,108 (£-1,242 to £2,825)	0.456
6 weeks	£13,304 (£9,124 to £18,571)	21.75 (20.78 to 23.06)	£13,786 (£9,245 to £19,949)	£-1,846 (£-10,162 to £3,166)	0.161
4 weeks	£14,841 (£8,451 to £21,177)	21.66 (20.65 to 23)	£15,818 (£8,569 to £24,206)	£-5,146 (£-17,466 to £4,064)	0.081
<i>5% discount rate</i>					
12 weeks	£10,444 (£9,358 to £11,995)	12.47 (12.13 to 12.88)	£10,479 (£9,372 to £12,049)	-	0.1692
8 weeks	£8,742 (£7,490 to £10,432)	12.46 (12.12 to 12.87)	£8,843 (£7,537 to £10,598)	£1,441 (£20 to £2,595)	0.4952
6 weeks	£9,830 (£6,912 to £13,268)	12.42 (12.07 to 12.84)	£10,190 (£6,980 to £14,311)	£-404 (£-5,446 to £3,187)	0.2223
4 weeks	£11,107 (£5,971 to £15,273)	12.38 (12 to 12.82)	£11,852 (£6,021 to £17,567)	£-2,507 (£-9,676 to £4,211)	0.1133

<sup>a</sup> Versus 12 weeks

<sup>b</sup> At £20,000 willingness-to-pay

QALYs, quality-adjusted life years; INMB, incremental net monetary benefit; p(CE), probability most cost-effective; CI, confidence interval

## References

1. Kowdley KV, Lawitz E, Poordad F, Cohen DE, Nelson DR, Zeuzem S, Everson GT, Kwo P, Foster GR, Sulkowski MS *et al*: Phase 2b Trial of Interferon-free Therapy for Hepatitis C Virus Genotype 1. *New England Journal of Medicine* 2014, 370(3):222-232.
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8. Corman S, Elbasha EH, Michalopoulos SN, Nwankwo C: Cost-Utility of Elbasvir/Grazoprevir in Patients with Chronic Hepatitis C Genotype 1 Infection. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2017, 20(8):1110-1120.