Ledipasvir-sofosbuvir for treating chronic hepatitis C

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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Description of additional analyses undertaken by the ERG

Gilead's response to the NICE appraisal consultation document included new cost-effectiveness analyses results. Additional analyses were undertaken by the ERG to verify the company's results.

The details of the analyses undertaken are as below:

- 12 weeks LDV/SOF for GT1 and GT4 treatment experienced patients with cirrhosis
- GT3 patients who are intolerant to or ineligible for interferon
    - 12 weeks LDV/SOF+RBV for treatment naïve GT3 IFN intolerant or ineligible patients without cirrhosis
    - 24 weeks LDV/SOF+RBV for treatment naïve GT3 IFN intolerant or ineligible patients with compensated cirrhosis
    - 24 weeks LDV/SOF+RBV for treatment experienced GT3 IFN intolerant or ineligible patients without cirrhosis
    - 24 weeks LDV/SOF+RBV for treatment experienced GT3 IFN intolerant or ineligible patients with compensated cirrhosis

The analysis was run for the following scenarios

- ERG base case
- *Additional analysis:* Alternative transition probabilities based on the sofosbuvir STA model

It should be noted that these analyses use the ERG-preferred base case analysis as a starting point. As noted in the ERG report, all analyses were undertaken using point estimates of parameters due to the excessive computation time and complexity associated with running the probabilistic version of the model. As before, total costs and QALYs for LDV/SOF and each comparator are reported to two decimal places, which may produce some rounding error in the calculation of ICERs.

SVR rates

The SVR rates used for LDV/SOF and LDV/SOF+RBV are presented in Table 1.

Table 1: SVR rates used in the new analyses

Treatment	**SVR (%)**	**Source**	**Details**
HCV genotype 1/4, treatment-experienced cirrhotic patients			
LDV/SOF 12 weeks	86.4%	ION-2	The company states that in the 12 week LDV/SOF arm, 86% (19/22) of cirrhotic patients achieved SVR12
HCV genotype 3 IFN intolerant or ineligible patients			

TN without cirrhosis	LDV/SOF+RBV 12 weeks	100.0%	ELECTRON-2 (Phase-II study)	All 19 TN GT3 patients without cirrhosis achieved SVR12 with 12 weeks LDV/SOF+RBV
TN with CC	LDV/SOF+RBV 24 weeks	100.0%	ELECTRON-2 (Phase-II study)	All 5 TN GT3 patients with cirrhosis achieved SVR12 with 12 weeks LDV/SOF+RBV
TE without cirrhosis	LDV/SOF+RBV 24 weeks	89.3%	ELECTRON-2 (Phase-II study)	SVR12 of 89% (25/28) observed in TE non-cirrhotic patients with 12 weeks LDV/SOF+RBV
TE with CC	LDV/SOF+RBV 24 weeks	72.7%*	ELECTRON-2 (Phase-II study)	SVR12 of 73% (16/22) observed in TE cirrhotic patients with 12 weeks LDV/SOF+RBV

SVR – sustained virologic response, TN - treatment-naïve, TE – treatment-experienced, CC –compensated cirrhosis

Results

The cost-effectiveness analyses results estimated from the company's model are presented in Table 2. It should be noted that the SVR rates for LDV/SOF and LDV/SOF+RBV are from Table 1, whilst the SVR rates for the comparators are the same as those considered in the company's base case analysis.

Table 2: Central estimates of cost-effectiveness results estimated by ERG

(i) Genotype 1/4 treatment-experienced cirrhotic patients					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	9.19	£62,363.64	4.00	£21,712.84	**£5,434**
SOF+PEG-IFN2a+RBV	8.59	£63,193.43	-	-	dominated
SMV+PEG-IFN2a+RBV	8.31	£62,045.65	-	-	ext dom
TVR+PEG-IFN2a+RBV*	7.46	£63,324.53	-	-	dominated
BOC+PEG-IFN2b+RBV*	6.95	£68,413.45	-	-	dominated
PEG-IFN2a+RBV	5.74	£47,441.22	-	-	ext dom
No treatment	5.19	£40,650.80	-	-	-
(ii) Genotype 3 treatment-naïve IFN intolerant or ineligible patients without cirrhosis					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	17.24	£42,997.49	2.67	£28,069.48	**£10,513**
No treatment	14.57	£14,928.01	-	-	-
(iii) Genotype 3 treatment-naïve cirrhotic IFN intolerant or ineligible patients					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	10.23	£102,644.92	0.36	£6,697.89	**£18,605**
SOF+RBV	9.87	£95,947.03	4.62	£54,694.01	**£11,839**
No treatment	5.25	£41,253.02	-	-	-
(iv) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic patients					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	15.97	£84,108.64	2.09	£70,172.93	**£33,576**
No treatment	13.88	£13,935.71	-	-	-
(v) Genotype 3 treatment-experienced IFN-ineligible cirrhotic patients					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	8.55	£106,734.85	3.36	£66,084.05	**£19,668**
SOF+RBV	8.01	£101,108.73	-	-	ext dom
No treatment	5.19	£40,650.80	-	-	-

**not applicable for genotype 4 patients*
Inc. – incremental; ICER – incremental cost-effectiveness ratio; ext dom – extended dominance; IFN – interferon

ERG critique

The ERG urges caution in interpreting cost-effectiveness analyses results presented in Table 2, the reasons are outlined below.

Genotype 1/4 treatment-experienced cirrhotic patients

The results for genotype 1/4 treatment-experienced cirrhotic patients are estimated assuming all the patients receive 12 weeks of LDV/SOF. While the EMA suggests that "12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options", clinical advice received by the ERG suggests that there is no clear definition that can be used to identify this subgroup of patients. It should be noted that the EMA recommended duration for patients with compensated cirrhosis is 24 weeks LDV/SOF, which results in an ICER of £32,458/QALY for LDV/SOF compared with SOF+PEG-IFN2a+RBV.

Genotype 3 treatment-naïve IFN intolerant or ineligible patients

The ERG is unclear regarding the plausibility of the "treatment-naïve IFN intolerant or ineligible" patient subgroup. Given the definition of the patient group as treatment-naïve (i.e. no prior treatment), the ERG is concerned about the accurate identification of patients who would be 'intolerant' or 'ineligible' for IFN treatment. Furthermore, the SVR results of LDV/SOF+RBV for the treatment naïve GT3 patients are based on Phase-II trial with low patient numbers (19 non-cirrhotic and 5 cirrhotic patients).

Genotype 3 treatment-experienced IFN intolerant or ineligible patients with cirrhosis

The ERG is concerned that the company has not included 'no treatment' option in their analysis; this makes LDV/SOF+RBV appear more cost-effective. If a 'no treatment option' was included in the analysis, the ICER of LDV/SOF+RBV is £19,668/QALY. However, the SVR results of LDV/SOF+RBV for the treatment naïve GT3 patients are based on Phase-II trial with low patient numbers. Furthermore, it should be noted that the company has updated the SVR rate for this patient group since their original submission – the new SVR12 rate is 72.7% (16/22) compared to SVR4 rate of 77.3% (17/22) used in their original submission. Given the small numbers of patients in this Phase II trial and the use of deterministic results (i.e. no inclusion of uncertainty), the ERG urges caution in interpreting these cost-effectiveness results.

Table 3 presents the central estimates of cost-effectiveness results of the additional analysis; which uses the ERG-preferred base case analysis in combination with transition probabilities taken from the previous sofosbuvir STA model.

Table 3: Central estimates of cost-effectiveness (additional analysis 1, use of alternative transition probabilities based on the sofosbuvir STA model) estimated by ERG

(i) Genotype 1/4 treatment-experienced cirrhotic patients					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	9.51	£64,496.01	2.13	£13,698.98	**£6,432**
SOF+PEG-IFN2a+RBV	9.19	£66,473.04	-	-	dominated
SMV+PEG-IFN2a+RBV	9.03	£65,803.66	-	-	dominated
TVR+PEG-IFN2a+RBV*	8.59	£68,854.52	-	-	dominated
BOC+PEG-IFN2b+RBV*	8.33	£74,964.16	-	-	dominated
PEG-IFN2a+RBV	7.68	£56,386.16	-	-	ext dom
No treatment	7.38	£50,797.03	-	-	-
(ii) Genotype 3 treatment-naïve IFN intolerant or ineligible patients without cirrhosis					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	17.24	£42,997.49	2.27	£26,567.89	**£11,704**
No treatment	14.97	£16,429.60	-	-	-
(iii) Genotype 3 treatment-naïve cirrhotic IFN intolerant or ineligible patients					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	10.26	£103,591.07	0.18	£5,933.84	**£32,966**
SOF+RBV	10.08	£97,657.23	2.52	£45,207.09	**£17,939**
No treatment	7.56	£52,450.14	-	-	-
(iv) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic patients					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	16.01	£84,234.47	1.78	£69,124.36	**£38,834**
No treatment	14.23	£15,110.11	-	-	-
(v) Genotype 3 treatment-experienced IFN-ineligible cirrhotic patients					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	9.17	£110,132.57	1.79	£59,335.54	**£33,148**
SOF+RBV	8.89	£105,607.67	-	-	ext dom
No treatment	7.38	£50,797.03	-	-	-

**not applicable for genotype 4 patients*
Inc. – incremental; ICER – incremental cost-effectiveness ratio; ext dom – extended dominance; IFN – interferon