Web Annex 3.2. Adult hepatitis C virus treatment systematic review; supporting evidence

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PURPOSE

This ‘Supporting Document’ lists the studies that informed the pooled SVR12 estimates in the ‘all comer’ analyses for:

- Sofosbuvir + daclatasvir
- Sofosbuvir + velpatasvir
- Glecaprevir + pibrentasvir

Refer to Web Annex 3.1 (the complete report (v3)) for a summary of all SVR12 estimates and GRADE evidence summaries for all treatments and patient populations.

RESULTS

This Supporting Document is to accompany the main report (v3). The summaries presented in this section include a list of the studies which informed each analysis.

Efficacy outcomes (SVR12) – All comers

For each treatment in the all-comer population, the pooled proportions of patients achieving SVR12 are presented by genotype and treatment-experience. The number of treatment arms may represent subgroups of treatment arms in a single study, such as where outcomes are reported separately by prior treatment experience. The all-treatment experience analysis pools outcomes from patients who are treatment-naïve, treatment-experienced, and where previous treatment status was unclear.

Trial evidence refers to evidence coming from RCTs and other non-randomized or single-arm trials. This analysis is supplemented with an all evidence analysis, which also incorporates outcomes from observational studies.

Comparative evidence is not available and inferences on relative treatment effect should be avoided.

Daclatasvir + Sofosbuvir

All-treatment experience

In the all-treatment experience analysis of patients treated with daclatasvir + sofosbuvir, evidence was available for patients across all genotypes. The percentage of patients achieving SVR12 varied from 88% to 98%. Across outcomes, GRADE assessments varied from very low to high. A summary of the analyses is presented in Table 1.

Table 1: SVR12 in all patients treated with daclatasvir + sofosbuvir, arranged by genotype

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Genotype 1	Trial evidence AI444-040[187]	1	4	91	0.98 (0.96, 0.98)	⊕⊕⊕⊕
	All evidence Desnoyer 2016[41] Foster 2016[61] VASCUVALDIC 2[173,174] AI444-040[187] ANRS CO22 HEPATHER[55,164] Ji 2016[98]	6	19	773	0.96 (0.94, 0.98)	⊕⊕⊕⊕

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Genotype 2	Trial evidence	–	–	–	–	–
	All evidence VASCUVALDIC 2[173,174] Mangia 2016a[132]	2	4	21	0.94 (0.86, 1.00)	⊕
Genotype 3	Trial evidence Hezode 2017[79,80] ALLY-3[25,111,137,148,149] ENDURANCE-3[60]	3	4	293	0.92 (0.88, 0.97)	⊕⊕⊕⊕
	All evidence VASCUVALDIC 2[173,174] German Hepatitis C-Registry (GT3 patients)[36] Foster 2016[61] Mehta 2017[138] Lionetti 2017[128] Hezode 2017[79,80] ALLY-3[25,111,137,148,149] Bansal 2017[19] ENDURANCE-3[60]	9	16	895	0.89 (0.85, 0.94)	⊕⊕⊕
Genotype 4	Trial evidence Abdel-Aziz 2017[10] Yakoot 2017[223]	2	3	180	0.97 (0.95, 1.00)	⊕⊕⊕⊕
	All evidence VASCUVALDIC 2[173,174] Abdel-Aziz 2017[10] Yakoot 2017[223]	3	5	183	0.97 (0.95, 1.00)	⊕⊕⊕⊕
Genotype 5	Trial evidence	–	–	–	–	–
	All evidence Iwamoto 2017[93] VASCUVALDIC 2[173,174]	2	3	8	0.88 (0.70, 1.00)	⊕
Genotype 6	Trial evidence	–	–	–	–	–
	All evidence Iwamoto 2017[93]	1	4	123	0.94 (0.90, 0.98)	⊕⊕
Mixed genotype	Trial evidence	2	5	233	0.94 (0.88, 0.99)	⊕⊕⊕

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
	AI444-040[187] ALLY-2[24,131,137,220-222]					
	All evidence Foster 2016[61] Torres 2017[195] AI444-040[187] ALLY-2[24,131,137,220-222] Autorisation Temporaire d'Utilisation (ATU) Program[120]	5	9	591	0.92 (0.88, 0.97)	⊕⊕

Treatment-naïve patients only

In the analysis of treatment-naïve only patients treated with daclatasvir + sofosbuvir, evidence was available for patients with genotypes 1-5 infection, as well as an unknown or mixed genotype population. The percentage of patients achieving SVR12 varied from 75% to 98%. Across outcomes, GRADE assessments varied from very low to high. A summary of the analyses is presented in Table 2.

Table 2: SVR12 in treatment-naive patients treated with daclatasvir + sofosbuvir, arranged by genotype

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Genotype 1	Trial evidence AI444-040[187]	1	3	70	0.98 (0.96, 1.00)	⊕⊕⊕⊕
	All evidence Desnoyer 2016[41] VASCUVALDIC 2[173,174] AI444-040[187] ANRS CO22 HEPATHER[55,164]	4	8	196	0.94 (0.90, 0.99)	⊕⊕⊕
Genotype 2	Trial evidence	–	–	–	–	–
	All evidence VASCUVALDIC 2[173,174]	1	1	1	0.75 (0.15, 1.00)	⊕
Genotype 3	Trial evidence Hezode 2017[79,80]	3	3	242	0.94 (0.89, 0.98)	⊕⊕⊕⊕

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
	ALLY-3[25,111,137,148,149] ENDURANCE-3[60]					
	All evidence VASCUVALDIC 2[173,174] German Hepatitis C-Registry (GT3 patients)[36] Hezode 2017[79,80] ALLY-3[25,111,137,148,149] Bansal 2017[19] ENDURANCE-3[60]	6	7	470	0.93 (0.88, 0.98)	⊕⊕⊕⊕
Genotype 4	Trial evidence Abdel-Aziz 2017[10]	1	1	60	0.93 (0.87, 1.00)	⊕⊕⊕
	All evidence VASCUVALDIC 2[173,174] Abdel-Aziz 2017[10]	2	2	61	0.93 (0.87, 0.99)	⊕⊕⊕
Genotype 5	Trial evidence	–	–	–	–	–
	All evidence VASCUVALDIC 2[173,174]	1	1	2	0.83 (0.41, 1.00)	⊕
Genotype 6	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Mixed genotype	Trial evidence AI444-040[187] ALLY-2[24,131,137,220-222]	2	4	181	0.91 (0.82, 1.00)	⊕⊕⊕
	All evidence	Same as trial-only evidence				

Treatment-experienced patients only

In the analysis of treatment-experienced only patients treated with daclatasvir + sofosbuvir, evidence was available for patients with genotypes 1-4 infection, as well as an unknown or mixed genotype population. The percentage of patients achieving SVR12 varied from 75% to 98%. Across outcomes, GRADE assessments varied from very low to moderate. A summary of the analyses is presented in Table 3.

Table 3: SVR12 in treatment-experienced patients treated with daclatasvir + sofosbuvir, arranged by genotype

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Genotype 1	Trial evidence AI444-040[187]	1	1	21	0.98 (0.92, 1.00)	⊕⊕
	All evidence Desnoyer 2016[41] VASCUVALDIC 2[173,174] AI444-040[187] ANRS CO22 HEPATHER[55,164] Ji 2016[98]	5	10	573	0.97 (0.95, 0.98)	⊕⊕⊕
Genotype 2	Trial evidence	–	–	–	–	–
	All evidence VASCUVALDIC 2[173,174]	1	1	1	0.75 (0.15, 1.00)	⊕
Genotype 3	Trial evidence ALLY-3[25,111,137,148,149]	1	1	51	0.86 (0.77, 0.96)	⊕⊕⊕
	All evidence VASCUVALDIC 2[173,174] German Hepatitis C-Registry (GT3 patients)[36] ALLY-3[25,111,137,148,149]	3	5	110	0.85 (0.78, 0.92)	⊕⊕⊕
Genotype 4	Trial evidence	–	–	–	–	–
	All evidence VASCUVALDIC 2[173,174]	1	1	2	0.83 (0.41, 1.00)	⊕
Genotype 5	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Genotype 6	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Mixed genotype	Trial evidence ALLY-2[24,131,137,220-222]	1	1	52	0.98 (0.94, 1.00)	⊕⊕⊕
	All evidence	Same as trial-only evidence				

Glecaprevir + Pibrentasvir

All-treatment experience

In the all-treatment experience analysis of patients treated with glecaprevir + pibrentasvir, evidence was available for patients across all genotypes. The percentage of patients achieving SVR12 varied from 83% to 98%. Across outcomes, GRADE assessments varied from very low to high. A summary of the analyses is presented in Table 4.

Table 4: SVR12 in all patients treated with glecaprevir + pibrentasvir, arranged by genotype

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Genotype 1	Trial evidence MAGELLAN-1, Part 1[165,166] SURVEYOR-I[65,118] EXPEDITION-1[56-58]	3	6	231	0.98 (0.97, 1.00)	⊕⊕⊕⊕
	All evidence	Same as trial-only evidence				
Genotype 2	Trial evidence CERTAIN-1, Sub-study 2[30,31,198] SURVEYOR-II[65,118] EXPEDITION-1[56-58] CERTAIN-2[31,198]	4	6	242	0.98 (0.96, 1.00)	⊕⊕⊕⊕
	All evidence	Same as trial-only evidence				
Genotype 3	Trial evidence SURVEYOR-II[65,118] ENDURANCE-3[60]	2	7	533	0.95 (0.93, 0.97)	⊕⊕⊕⊕
	All evidence	Same as trial-only evidence				
Genotype 4	Trial evidence EXPEDITION-1[56-58]	1	1	16	0.97 (0.89, 1.00)	⊕
	All evidence	Same as trial-only evidence				
Genotype 5	Trial evidence EXPEDITION-1[56-58]	1	1	2	0.83 (0.41, 1.00)	⊕
	All evidence	Same as trial-only evidence				
Genotype 6	Trial evidence EXPEDITION-1[56-58]	1	1	7	0.94 (0.77, 1.00)	⊕

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
	All evidence	Same as trial-only evidence				
Mixed genotype	Trial evidence EXPEDITION-2[171] SURVEYOR-I[65,118] MAGELLAN-1, Part 2[167,168]	3	5	276	0.97 (0.93, 1.00)	⊕⊕⊕⊕
	All evidence	Same as trial-only evidence				

Treatment-naïve patients only

In the analysis of treatment-naïve only patients treated with glecaprevir + pibrentasvir, evidence was available only for patients with genotype 3 infection (N=419). The percentage of patients achieving SVR12 was 95%, with a GRADE assessment of high. A summary of the analyses is presented in Table 5.

Table 5: SVR12 in treatment-naïve patients treated with glecaprevir + pibrentasvir, arranged by genotype

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Genotype 1	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Genotype 2	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Genotype 3	Trial evidence SURVEYOR-II[65,118] ENDURANCE-3[60]	2	3	419	0.95 (0.93, 0.97)	⊕⊕⊕⊕
	All evidence	Same as trial-only evidence				
Genotype 4	Trial evidence					
	All evidence	–	–	–	–	–
Genotype 5	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Genotype 6	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Mixed genotype	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–

Treatment-experienced patients only

In the analysis of treatment-experienced only patients treated with glecaprevir + pibrentasvir, evidence was available only for patients with genotype 3 infection (N=24). The percentage of patients achieving SVR12 was 92%, with a GRADE assessment of very low. A summary of the analyses is presented in Table 6.

Table 6: SVR12 in treatment-experienced patients treated with glecaprevir + pibrentasvir, arranged by genotype

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Genotype 1	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Genotype 2	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Genotype 3	Trial evidence SURVEYOR-II[65,118]	1	1	24	0.92 (0.81, 1.00)	⊕
	All evidence	Same as trial-only evidence				
Genotype 4	Trial evidence					
	All evidence	–	–	–	–	–
Genotype 5	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Genotype 6	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Mixed genotype	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–

Sofosbuvir + Velpatasvir

All-treatment experience

In the all-treatment experience analysis of patients treated with sofosbuvir + velpatasvir, evidence was available for patients across all genotypes. The percentage of patients achieving SVR12 varied from 89% to 99%. GRADE assessments varied from low to high across outcomes. A summary of the analyses is presented in Table 7.

Table 7: SVR12 in all patients treated with sofosbuvir + velpatasvir, arranged by genotype

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Genotype 1	Trial evidence Everson 2015[48] Pianko 2015[163] POLARIS-4[21,242] ASTRAL-4[29,37,38,146,157,228] ASTRAL-5[109,146,218,219,232] POLARIS-2[96] ASTRAL-1[49,71,73,94,146,219,229]	7	12	1011	0.96 (0.95, 0.98)	⊕⊕⊕⊕
	All evidence	Same as trial-only evidence				
Genotype 2	Trial evidence ASTRAL-4[29,37,38,146,157,228] ASTRAL-5[109,146,218,219,232] Everson 2015[48] POLARIS-4[21,242] POLARIS-2[96] ASTRAL-1[49,71,73,94,146,219,229] ASTRAL-2[59,71,73,94,146,185,219,231]	7	9	395	0.99 (0.97, 1.00)	⊕⊕⊕⊕
	All evidence	Same as trial-only evidence				
Genotype 3	Trial evidence ASTRAL-4[29,37,38,146,157,228] ASTRAL-5[109,146,218,219,232] Pianko 2015[163] Everson 2015[48] POLARIS-3[96] POLARIS-4[21,242] ASTRAL-3[59,71,73,94,146,219,231] POLARIS-2[96]	8	15	776	0.89 (0.85, 0.93)	⊕⊕⊕
	All evidence	Same as trial-only evidence				

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Genotype 4	Trial evidence ASTRAL-4[29,37,38,146,157,228] ASTRAL-5[109,146,218,219,232] POLARIS-2[96] ASTRAL-1[49,71,73,94,146,219,229]	4	5	184	0.99 (0.98, 1.00)	⊕⊕⊕⊕
	All evidence	Same as trial-only evidence				
Genotype 5	Trial evidence ASTRAL-1[49,71,73,94,146,219,229]	1	1	35	0.97 (0.92, 1.00)	⊕⊕
	All evidence	Same as trial-only evidence				
Genotype 6	Trial evidence ASTRAL-4[29,37,38,146,157,228] POLARIS-2[96] ASTRAL-1[49,71,73,94,146,219,229]	3	3	51	0.99 (0.95, 1.00)	⊕⊕⊕⊕
	All evidence	Same as trial-only evidence				
Mixed genotype	Trial evidence Everson 2015[48] POLARIS-2[96]	2	4	485	0.99 (0.97, 1.00)	⊕⊕⊕⊕
	All evidence Torres 2017[195] Everson 2015[48] POLARIS-2[96]	3	5	489	0.99 (0.97, 1.00)	⊕⊕⊕⊕

Treatment-naïve patients only

In the analysis of treatment-naïve only patients treated with sofosbuvir + velpatasvir, evidence was available for patients with genotypes 1-3 infection, as well as an unknown or mixed genotype population. The percentage of patients achieving SVR12 varied from 84% to 98%. GRADE assessments varied from very low to high across outcomes. A summary of the analyses is presented in Table 8.

Table 8: SVR12 in treatment-naïve patients treated with sofosbuvir + velpatasvir, arranged by genotype

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Genotype 1	Trial evidence	1	4	114	0.95 (0.90, 1.00)	⊕⊕

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
	Everson 2015[48]					
	All evidence	Same as trial-only evidence				
Genotype 2	Trial evidence Everson 2015[48]	1	2	52	0.84 (0.73, 0.95)	⊕
	All evidence	Same as trial-only evidence				
Genotype 3	Trial evidence Everson 2015[48] POLARIS-3[96] ASTRAL-3[59,71,73,94,146,219,231]	3	4	337	0.98 (0.96, 0.99)	⊕⊕⊕⊕
	All evidence	Same as trial-only evidence				
Genotype 4	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Genotype 5	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Genotype 6	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Mixed genotype	Trial evidence Everson 2015[48]	1	2	45	0.96 (0.90, 1.00)	⊕
	All evidence	Same as trial-only evidence				

Treatment-experienced patients only

In the analysis of treatment-experienced only patients treated with sofosbuvir + velpatasvir, evidence was available for patients with genotypes 1-3 infection. The percentage of patients achieving SVR12 varied from 85% to 97%. GRADE assessments varied from low to high across outcomes. A summary of the analyses is presented in Table 9.

Table 9: SVR12 in treatment-experienced patients treated with sofosbuvir + velpatasvir, arranged by genotype

	Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Genotype 1	Trial evidence Pianko 2015[163] POLARIS-4[21,242]	2	3	120	0.96 (0.92, 1.00)	⊕⊕⊕⊕
	All evidence	Same as trial-only evidence				
Genotype 2	Trial evidence POLARIS-4[21,242]	1	1	33	0.97 (0.91, 1.00)	⊕⊕
	All evidence	Same as trial-only evidence				
Genotype 3	Trial evidence Pianko 2015[163] POLARIS-3[96] POLARIS-4[21,242] ASTRAL-3[59,71,73,94,146,219,231]	4	7	312	0.85 (0.78, 0.92)	⊕⊕⊕
	All evidence	Same as trial-only evidence				
Genotype 4	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Genotype 5	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Genotype 6	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–
Mixed genotype	Trial evidence	–	–	–	–	–
	All evidence	–	–	–	–	–

Safety outcomes

The number of patients experiencing each adverse event outcome category was pooled across studies, arranged by treatment. When possible, outcomes were extracted from each study based on the safety analysis set (i.e. number of patients who received ≥1 dose). Comparative evidence is not available and inferences on relative treatment effect should be avoided.

Discontinuations due to adverse events

Evidence on the number of patients who experienced a DAE was available for every treatment. The analyses for daclatasvir + sofosbuvir + ribavirin and sofosbuvir + ribavirin was restricted to patients with cirrhosis and genotype 2 or 3 infection. Across treatments and studies, the number of DAEs was very low, with the pooled percentages varying from 0% to 0.04%. GRADE was assessed as moderate in all cases. As very few studies blinded patients or outcome assessors, GRADE was lowered by one level due to the perceived subjectivity of labelling a discontinuation as a DAE (Risk of Bias). A summary of the analyses is presented in Table 10.

Table 10: Discontinuations due to adverse events, arranged by treatment

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Daclatasvir + sofosbuvir	Trial evidence ALLY-2[24,131,137,220-222] Abdel-Aziz 2017[10] Yakoot 2017[223] ENDURANCE-3[60] ALLY-3[25,111,137,148,149]	5	8	650	0.01 (0.00, 0.01)	⊕⊕⊕
	All evidence Iwamoto 2017[93] Mangia 2016a[132] Lionetti 2017[128] Chen 2017[32] Ji 2016[98] Abdel-Aziz 2017[10] Yakoot 2017[223] ALLY-2[24,131,137,220-222] ENDURANCE-3[60] ALLY-3[25,111,137,148,149] ANRS CO22 HEPATHER[55,164] Autorisation Temporaire d'Utilisation (ATU) Program[120]	12	20	1955	0.01 (0.01, 0.01)	⊕⊕⊕
Glecaprevir + pibrentasvir	Trial evidence MAGELLAN-1, Part 1[165,166] MAGELLAN-1, Part 2[167,168]	10	14	1333	0.01 (0.00, 0.01)	⊕⊕⊕

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
	EXPEDITION-2[171] CERTAIN-1, Sub-study 2[30,31,198] Kwo 2016[119] CERTAIN-2[31,198] SURVEYOR-I[65,118] SURVEYOR-II[65,118] EXPEDITION-1[56-58] ENDURANCE-3[60]					
	All evidence	Same as trial-only evidence				
Sofosbuvir + velpatasvir	Trial evidence Everson 2015[48] Pianko 2015[163] ASTRAL-4[29,37,38,146,157,228] ASTRAL-5[109,146,218,219,232] POLARIS-3[96] ASTRAL-2[59,71,73,94,146,185,219,231] POLARIS-4[21,242] ASTRAL-3[59,71,73,94,146,219,231] POLARIS-2[96] ASTRAL-1[49,71,73,94,146,219,229]	10	15	2445	0.00 (0.00, 0.01)	⊕⊕⊕
	All evidence	Same as trial-only evidence				

Serious adverse events

Evidence on the number of patients who experienced a SAE was available for every treatment with the exception of daclatasvir + sofosbuvir + ribavirin, where inclusion in this review was restricted to patients with cirrhosis and genotype 2 or 3 infection. Across treatments and studies, the number of SAEs was very low, with the pooled percentage varying 1% to 5% and GRADE assessments varying from moderate to high. A summary of the analyses is presented in Table 11.

Table 11: Serious adverse events, arranged by treatment

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Daclatasvir + sofosbuvir	Trial evidence ALLY-2[24,131,137,220-222] Abdel-Aziz 2017[10] Yakoot 2017[223] ENDURANCE-3[60] ALLY-3[25,111,137,148,149]	5	8	650	0.01 (0.00, 0.02)	⊕⊕⊕⊕
	All evidence Desnoyer 2016[41] VASCUVALDIC 2[173,174] Ji 2016[98] ALLY-2[24,131,137,220-222] Abdel-Aziz 2017[10] Yakoot 2017[223] ENDURANCE-3[60] ALLY-3[25,111,137,148,149] ANRS CO22 HEPATHER[55,164] Autorisation Temporaire d'Utilisation (ATU) Program[120]	10	19	1875	0.03 (0.01, 0.05)	⊕⊕⊕
Glecaprevir + pibrentasvir	Trial evidence MAGELLAN-1, Part 1[165,166] EXPEDITION-2[171] CERTAIN-1, Sub-study 2[30,31,198] MAGELLAN-1, Part 2[167,168] SURVEYOR-I[65,118] SURVEYOR-II[65,118] CERTAIN-2[31,198] EXPEDITION-1[56-58] ENDURANCE-3[60]	9	14	1309	0.02 (0.01, 0.02)	⊕⊕⊕⊕
	All evidence	Same as trial-only evidence				
Sofosbuvir + velpatasvir	Trial evidence	10	15	2445	0.03 (0.02, 0.04)	⊕⊕⊕⊕

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
	Everson 2015[48] Pianko 2015[163] ASTRAL-4[29,37,38,146,157,228] ASTRAL-5[109,146,218,219,232] POLARIS-3[96] ASTRAL-2[59,71,73,94,146,185,219,231] POLARIS-4[21,242] ASTRAL-3[59,71,73,94,146,219,231] POLARIS-2[96] ASTRAL-1[49,71,73,94,146,219,229]					
	All evidence	Same as trial-only evidence				

Mortality

Evidence on mortality was available for every treatment. Incidence was very low across treatments, with the pooled morality percentage varying from 0% to 4%. GRADE assessments were high for all treatments and evidence types. A summary of the analyses is presented in Table 12.

Table 12: Mortality, arranged by treatment

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
Daclatasvir + sofosbuvir	Trial evidence ALLY-2[24,131,137,220-222] Abdel-Aziz 2017[10] Yakoot 2017[223] ALLY-3[25,111,137,148,149]	4	7	535	0.01 (0.00, 0.01)	⊕⊕⊕⊕
	All evidence Iwamoto 2017[93] Mangia 2016a[132] VASCUVALDIC 2[173,174] Mehta 2017[138] Ji 2016[98] ALLY-2[24,131,137,220-222] Abdel-Aziz 2017[10] Yakoot 2017[223] ALLY-3[25,111,137,148,149] ANRS CO22 HEPATHER[55,164] Autorisation Temporaire d'Utilisation (ATU) Program[120]	11	22	2156	0.01 (0.00, 0.01)	⊕⊕⊕⊕
Glecaprevir + pibrentasvir	Trial evidence SURVEYOR-I[65,118] SURVEYOR-II[65,118] EXPEDITION-1[56-58]	3	4	539	0.01 (0.00, 0.02)	⊕⊕⊕⊕
	All evidence	Same as trial-only evidence				
Sofosbuvir + velpatasvir	Trial evidence Everson 2015[48] Pianko 2015[163] ASTRAL-4[29,37,38,146,157,228] ASTRAL-5[109,146,218,219,232] POLARIS-3[96] ASTRAL-2[59,71,73,94,146,185,219,231] POLARIS-4[21,242] ASTRAL-3[59,71,73,94,146,219,231] POLARIS-2[96]	10	15	2445	0.00 (0.00, 0.00)	⊕⊕⊕⊕

		Number of studies	Number of arms	Total N	Pooled proportion (95% CI)	GRADE
	ASTRAL-1[49,71,73,94,146,219,229]					
	All evidence	Same as trial-only evidence				

Appendix A: Included studies from all analyses

Table A1: List of included studies, with treatments and study design categorization

			Study design	
Study name	Registration	Treatment arms	Trial	Observational study
Abdel-Aziz 2017[10]	–	DAC 60 mg qd 12 weeks + SOF 400 mg qd 12 weeks	Yes	–
AI444-040[187]	NCT01359644	DAC 60 mg 24 weeks + SOF 400 mg 24 weeks	Yes	–
		DAC 60 mg 12 weeks + SOF 400 mg 12 weeks		
AI447-017[139,191,225]	NCT01051414	DAC 60 mg 24 weeks + ASV 200 mg bid 24 weeks	Yes	–
AI447-031[102]	NCT01718145	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	Yes	–
ALLY 3+[126,137]	NCT02319031	DAC 60 mg qd 12 weeks + SOF 400 mg qd 12 weeks + RBV 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg), 12 weeks	Yes	–
		DAC 60 mg qd 16 weeks + SOF 400 mg qd 16 weeks + RBV 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg), 16 weeks		
ALLY-2[24,131,137,220-222]	NCT02032888	DAC 60 mg qd 8 weeks + SOF 400 mg qd 8 weeks	Yes	–
		DAC 60 mg qd 12 weeks + SOF 400 mg qd 12 weeks		
ALLY-3[25,111,137,148,149]	NCT02032901	DAC 60 mg 12 weeks + SOF 400 mg 12 weeks	Yes	–
ANRS CO22 HEPATHER[55,164]	NCT01953458	DAC 60 mg qd 12 weeks + SOF 400 mg qd 12 weeks	–	Yes
		DAC 60 mg qd 24 weeks + SOF 400 mg qd 24 weeks		
ASCEND[103]	–	LDV 2, 3, or 6 months + SOF 2, 3, or 6 months	Yes	–
ASTRAL-1[49,71,73,94,146,219,229]	NCT02201940	SOF 400 mg qd 12 weeks + VEL 100 mg qd 12 weeks	Yes	–
		PBO		
ASTRAL-2[59,71,73,94,146,185,219,231]	NCT02220998	SOF 400 mg qd 12 weeks + VEL 100 mg qd 12 weeks	Yes	–
		SOF 400 mg qd 12 weeks + RBV bid 12 weeks for 1000 mg daily (body weight <75 kg) or 1200 mg daily (body weight ≥75 kg)		
ASTRAL-3[59,71,73,94,146,219,231]	NCT02201953	SOF 400 mg qd 12 weeks + VEL 100 mg qd 12 weeks	Yes	–
		SOF 400 mg qd 24 weeks + RBV bid 24 weeks for 1000 mg daily (body weight <75 kg) or 1200 mg daily (body weight ≥75 kg)		
ASTRAL-4[29,37,38,146,157,228]	NCT02201901	SOF 400 mg qd 12 weeks + VEL 100 mg qd 12 weeks	Yes	–
		SOF 400 mg qd 24 weeks + VEL 100 mg qd 24 weeks		
ASTRAL-5[109,146,218,219,232]	NCT02480712	SOF 400 mg qd 12 weeks + VEL 100 mg qd 12 weeks	Yes	–

			Study design	
Study name	Registration	Treatment arms	Trial	Observational study
Autorisation Temporaire d'Utilisation (ATU) Program[120]	–	DAC 30/60/90 qd 12 weeks + SOF 400 mg qd 12 weeks	–	Yes
		DAC 30/60/90 qd 24 weeks + SOF 400 mg qd 24 weeks		
Backus 2016[18]	–	LDV ≤12 weeks + SOF ≤12 weeks	–	Yes
		PTV/r ≤12 weeks + OMV ≤12 weeks + DBV ≤12 weeks		
Bansal 2017[19]	–	DAC 60 mg 12 weeks + SOF 400 mg 12 weeks	–	Yes
		DAC 60 mg 12 weeks + SOF 400 mg 12 weeks + RBV 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg), twice per day 12 weeks		
		DAC 60 mg 24 weeks + SOF 400 mg 24 weeks + RBV 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg), twice per day 24 weeks		
BOSON[62,63]	–	SOF 400 mg qd 16 weeks + RBV 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg), twice per day 16 weeks	Yes	–
		SOF 400 mg qd 24 weeks + RBV 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg), twice per day 24 weeks		
C-CORAL[72,205,212]	–	ESV 50 mg qd 12 weeks + GZR 100 mg qd 12 weeks	Yes	–
		PBO 12 weeks		
C-EDGE CO-INFECTION[172]	NCT02105662	ESV 50 mg qd 12 weeks + GZR 100 mg qd 12 weeks	Yes	–
C-EDGE CO-STAR[45,46]	NCT02105688	ESV 50 mg qd 12 weeks + GZR 100 mg qd 12 weeks	Yes	–
		PBO		
C-EDGE HEAD-2-HEAD[179,180]	NCT02358044	ESV 50 mg qd 12 weeks + GZR 100 mg qd 12 weeks	Yes	–
C-EDGE IBLD[75-78,181]	NCT02252016	ESV 50 mg qd 12 weeks + GZR 100 mg qd 12 weeks	Yes	–
		PBO		
C-EDGE Treatment-Experienced[115-117]	NCT02105701	ESV 50 mg qd 12 weeks + GZR 100 mg qd 12 weeks	Yes	–
		ESV 50 mg qd 16 weeks + GZR 100 mg qd 16 weeks		
C-EDGE Treatment-Naïve[152,224,243-245]	NCT02105467	ESV 50 mg qd 12 weeks + GZR 100 mg qd 12 weeks	Yes	–
		PBO		
CERTAIN-1, Sub-study 2[30,31,198]	NCT02707952	GCR 300 mg qd 12 weeks + PBV 120 mg qd 12 weeks	Yes	–
CERTAIN-2[31,198]	NCT02723084	GCR 300 mg qd 8 weeks + PBV 120 mg qd 8 weeks	Yes	–
Chamorro-de-Vega 2016[28]	–	PTV/r 150/100 mg qd 12 weeks + OMV 25 mg qd 12 weeks + DBV 250 mg bid 12 weeks	–	Yes

			Study design	
Study name	Registration	Treatment arms	Trial	Observational study
Chen 2017[32]	–	DAC 60 mg/day 12 or 24 weeks + SOF 400 mg/day 12 or 24 weeks	–	Yes
		LDV 90 mg/day 12 or 24 weeks + SOF 400 mg/day 12 or 24 weeks		
Chuang 2016 - Korea[34,127,186]	NCT02021656	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	Yes	–
Chuang 2016 - Taiwan[34,127,186]	NCT02021656	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	Yes	–
C-WORTHY[70,121,184,224]	NCT01717326	ESV 50 mg qd 12 weeks + GZR 100 mg qd 12 weeks	Yes	–
		ESV 50 mg qd 18 weeks + GZR 100 mg qd 18 weeks		
Dashtseren 2017[39,40]	–	LDV 80 mg qd 12 weeks + SOF 400 mg qd 12 weeks	Yes	–
Desnoyer 2016[41]	–	DAC 60 mg qd 12 weeks + SOF 400 mg qd or tiw 12 weeks	–	Yes
		DAC 60 mg qd 24 weeks + SOF 400 mg qd or tiw 24 weeks		
Deterding 2015[42,83]	–	SOF + RBV	–	Yes
ELECTRON[69]	NCT01260350	SOF 400 mg 12 weeks + LDV 90 mg 12 weeks	Yes	–
ELECTRON-2[64,66,67,125]	NCT01826981	SOF 400 mg 12 weeks + LDV 90 mg 12 weeks	Yes	–
ENDURANCE-3[60]	NCT02640157	GCR 300 mg qd 12 weeks + PBV 120 mg qd 12 weeks	Yes	–
		DAC 60 mg qd 12 weeks + SOF 400 mg qd 12 weeks		
		GCR 300 mg qd 8 weeks + PBV 120 mg qd 8 weeks		
ERADICATE[158,159,196,197]	NCT01878799	SOF 400 mg 12 weeks + LDV 90 mg 12 weeks	Yes	–
Everson 2015[48]	NCT01858766	SOF 400 mg qd 12 weeks + VEL 25 mg qd 12 weeks	Yes	–
		SOF 400 mg qd 12 weeks + VEL 100 mg qd 12 weeks		
		SOF 400 mg qd 8 weeks + VEL 25 mg qd 8 weeks		
		SOF 400 mg qd 8 weeks + VEL 100 mg qd 8 weeks		
EXPEDITION-1[56-58]	NCT02642432	GCR 300 mg qd 12 weeks + PBV 120 mg qd 12 weeks	Yes	–
EXPEDITION-2[171]	NCT02738138	GCR 300 mg qd 8 weeks + PBV 120 mg qd 8 weeks	Yes	–
		GCR 300 mg qd 12 weeks + PBV 120 mg qd 12 weeks		
Fierer 2017[54]	–	LDV 8 weeks + SOF 8 weeks	Yes	–
Foster 2016[61]	–	DAC 60 mg qd 12 weeks + SOF 400 mg qd 12 weeks	–	Yes
		LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks		

			Study design	
Study name	Registration	Treatment arms	Trial	Observational study
		DAC 60 mg qd 12 weeks + SOF 400 mg qd 12 weeks + RBV Clinician discretion		
FUSION[26,52,147,234]	NCT01604850	SOF 400 mg qd 12 weeks + RBV 1000-1200 mg/day 12 weeks	Yes	–
		SOF 400 mg qd 16 weeks + RBV 1000-1200 mg/day 16 weeks		
Gane 2017[68]	NCT02202980	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	Yes	–
		LDV 90 mg qd 8 weeks + SOF 400 mg qd 8 weeks		
GARNET[213,214]	NCT02582632	PTV/r 150 mg/100 mg qd 8 weeks + OMV 25 mg qd 8 weeks + DBV 250 mg bid 8 weeks	Yes	–
GECCO-01[89]	–	LDV 8 weeks + SOF 8 weeks	–	Yes
German Hepatitis C-Registry (GT1 patients)[202]	–	LDV 12 weeks + SOF 12 weeks	–	Yes
		LDV 8 weeks + SOF 8 weeks		
German Hepatitis C-Registry (GT2 patients)[136,192]	–	SOF 12 weeks + RBV 12 weeks	–	Yes
German Hepatitis C-Registry (GT3 patients)[36]	–	SOF 24 weeks + RBV 24 weeks	–	Yes
		DAC 12 weeks + SOF 12 weeks		
		DAC 12 weeks + SOF 12 weeks + RBV 12 weeks		
		DAC 24 weeks + SOF 24 weeks		
		DAC 24 weeks + SOF 24 weeks + RBV 24 weeks		
GS-US-334-0118/ GS-US-337-0113 (Pooled)[230,239]	–	LDV 12 weeks + SOF 12 weeks	Yes	–
GS-US-337-1119 [Genotype 4][12,66]	NCT02081079	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	Yes	–
GS-US-337-1119 [Genotype 5][11,66]	NCT02081079	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	Yes	–
HALLMARK DUAL[100,101,135]	NCT01581203	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	Yes	–
		PBO		
HCV Research UK (HCVRUK)[33]	–	DAC 12 weeks + SOF 12 weeks	–	Yes
HCV-TARGET[50,161,169,194,215,227]	NCT01474811	SOF 400 mg qd 12 weeks + RBV Clinician discretion 12 weeks	–	Yes
		SOF 400 mg qd 16 weeks + RBV Clinician discretion 16 weeks		
		SOF 24 weeks + RBV Clinician discretion 24 weeks		

			Study design	
Study name	Registration	Treatment arms	Trial	Observational study
		LDV 90 mg qd 8, 12, or 24 weeks + SOF 400 mg qd 8, 12, or 24 weeks		
		ESV + GZR		
		SOF + VEL + VEL		
HepNet Acute HCV IV Study[43,44]	NCT02309918	LDV 90 mg qd 6 weeks + SOF 400 mg qd 6 weeks	Yes	–
Hezode 2017[79,80]	–	DAC 60 mg qd 8 weeks + SOF 400 mg qd 8 weeks	Yes	–
Hlaing 2017[81]	–	SOF 400 mg qd 24 weeks + RBV 15 mg/kg/day 24 weeks	–	Yes
		LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks		
		DAC 60 mg qd 12 weeks + SOF 400 mg qd 12 weeks + RBV 15 mg/kg/day 12 weeks		
Ide 2016a[84]	–	DAC 24 weeks + ASV 24 weeks	–	Yes
		LDV 12 weeks + SOF 12 weeks		
Ide 2016b[85]	–	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	Yes	–
Iio 2017a[86]	–	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	Yes	–
Iio 2017b[87]	–	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	Yes	–
Ikeda 2017[88]	–	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	Yes	–
ION-1[14-16,74,216,233,235]	NCT01701401	LDV 90 mg 12 weeks + SOF 400 mg 12 weeks	Yes	–
		LDV 90 mg 24 weeks + SOF 400 mg 24 weeks		
ION-2[13,15,16,74,216,233,235]	NCT01768286	LDV 90 mg 12 weeks + SOF 400 mg 12 weeks	Yes	–
		LDV 90 mg 24 weeks + SOF 400 mg 24 weeks		
ION-3[15,16,74,110,216,233,235]	NCT01851330	LDV 90 mg 12 weeks + SOF 400 mg 12 weeks	Yes	–
		LDV 90 mg 8 weeks + SOF 400 mg 8 weeks		
ION-4[144,145,236]	NCT02073656	SOF 400 mg 12 weeks + LDV 90 mg 12 weeks	Yes	–
Isakov 2016[90,247]	–	LDV 90 mg qd 8 weeks + SOF 400 mg qd 8 weeks	Yes	–
Ishigami 2017[91]	–	DAC + ASV	–	Yes
Itoh 2016[92]	–	ESV qd 12 weeks + GZR qd 12 weeks	Yes	–
Iwamoto 2017[93]	–	DAC 12 weeks + SOF 12 weeks	–	Yes
		DAC 24 weeks + SOF 24 weeks		

			Study design	
Study name	Registration	Treatment arms	Trial	Observational study
Jargalsaikhan 2017[97]	–	LDV 12 weeks + SOF 12 weeks	Yes	–
Ji 2016[98]	–	DAC 60 mg/day 12 weeks + SOF 400 mg/day 12 weeks	–	Yes
		LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks		
Johnson 2017[99]	–	LDV 8 weeks + SOF 8 weeks	–	Yes
		LDV 12 weeks + SOF 12 weeks		
		LDV 24 weeks + SOF 24 weeks		
Kawada 2015[104]	–	ESV 50 mg qd 12 weeks + GZR 50 mg qd 12 weeks	Yes	–
		ESV 50 mg qd 12 weeks + GZR 100 mg qd 12 weeks		
Kawakami 2016[105]	UMIN000015539	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	–	Yes
Korenaga 2017[108]	–	LDV 12 weeks + SOF 12 weeks	Yes	–
Kumada 2014[113,139,225]	NCT01497834	DAC 60 mg 24 weeks + ASV 100 mg bid 24 weeks	Yes	–
Kumada 2016a[112]	NCT01718145	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	Yes	–
Kumada 2016b[114,190]	NCT02203149	ESV 50 mg qd 12 weeks + GZR 50 mg qd 12 weeks	Yes	–
		ESV 50 mg qd 12 weeks + GZR 100 mg qd 12 weeks		
Kwo 2016[119]	–	GCR 300 mg qd 12 weeks + PBV 120 mg qd 12 weeks	Yes	–
Lawitz 2017[122,124]	NCT02536313	SOF 400 mg qd 12 weeks + VEL 100 mg qd 12 weeks + VOX 100 mg qd 12 weeks	Yes	–
Lionetti 2017[128]	–	DAC 24 weeks + SOF 24 weeks + RBV 922 ± 200 mg/day 24 weeks	–	Yes
		DAC 24 weeks + SOF 24 weeks		
Liu 2017[129]	–	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	Yes	–
Lok 2012[130]	NCT01012895	DAC 60 mg 24 weeks + ASV 600 mg bid 24 weeks	Yes	–
LONESTAR[123]	NCT01726517	LDV 90 mg 12 weeks + SOF 400 mg 12 weeks	Yes	–
		LDV 90 mg 8 weeks + SOF 400 mg 8 weeks		
MAGELLAN-1, Part 1[165,166]	NCT02446717	GCR 200 mg qd 12 weeks + PBV 80 mg qd 12 weeks	Yes	–
		GCR 300 mg qd 12 weeks + PBV 120 mg qd 12 weeks		
MAGELLAN-1, Part 2[167,168]	NCT02446717	GCR 300 mg qd 12 weeks + PBV 120 mg qd 12 weeks	Yes	–
		GCR 300 mg qd 16 weeks + PBV 120 mg qd 16 weeks		

			Study design	
Study name	Registration	Treatment arms	Trial	Observational study
MALACHITE-I[35,47]	NCT01854697	PTV/r 150 mg/100 mg qd 12 weeks + OMV 25 mg qd 12 weeks + DBV 250 mg bid 12 weeks	Yes	–
Mangia 2016a[132]	–	DAC 60 mg qd 12 weeks + SOF 400 mg qd 12 weeks	–	Yes
		DAC 60 mg qd 24 weeks + SOF 400 mg qd 24 weeks		
Mangia 2017a[133]	EUDRACT 2015-002401-1	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	Yes	–
Mangia 2017b[134]	–	SOF 400 mg qd 16 weeks + RBV 1000 or 1200 mg/day 16 weeks	–	Yes
		SOF 400 mg qd 20 weeks + RBV 1000 or 1200 mg/day 20 weeks		
Mehta 2017[138]	–	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	–	Yes
		DAC 60 mg qd 12 weeks + SOF 400 mg qd 12 weeks		
		DAC 60 mg qd 24 weeks + SOF 400 mg qd 24 weeks		
		DAC 60 mg qd 24 weeks + SOF 400 mg qd 24 weeks + RBV 1000 mg/day (<75 kg) or 1200 mg/day (>75 kg), divided doses 24 weeks		
Mizokami 2015[140]	NCT01975675	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	Yes	–
Nagao 2017[143]	–	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	–	Yes
Nguyen 2017[150,151]	–	LDV 90 mg qd 8 weeks + SOF 400 mg qd 8 weeks	Yes	–
		LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks		
Ogawa 2016[155]	–	SOF 400 mg qd 12 weeks + RBV Weight-adjusted (600-1000 mg/day) 12 weeks	–	Yes
Ogawa 2017a[156]	UMIN000015627	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	Yes	–
Ogawa 2017b[153,154]	UMIN000024007	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	–	Yes
ONYX-I[206,207]	–	PTV/r 12 weeks + OMV 12 weeks + DBV 12 weeks	Yes	–
		PBO 12 weeks		
PEARL-II[17,208]	NCT01674725	PTV/r 150/100 mg 12 weeks + OMV 25 mg 12 weeks + DBV 250 mg bid 12 weeks	Yes	–
PEARL-III[53,208]	NCT01767116	PTV/r 150/100 mg 12 weeks + OMV 25 mg 12 weeks + DBV 250 mg bid 12 weeks	Yes	–
PEARL-IV[53]	NCT01833533	PTV/r 150/100 mg 12 weeks + OMV 25 mg 12 weeks + DBV 250 mg bid 12 weeks	Yes	–
Persico 2017[162]	–	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	–	Yes
PHOTON-2[141,142,234]	NCT01783678	SOF 400 mg qd 24 weeks + RBV 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg), twice per day 24 weeks	Yes	–
		SOF 400 mg qd 12 weeks + RBV 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg), twice per day 12 weeks		

			Study design	
Study name	Registration	Treatment arms	Trial	Observational study
Pianko 2015[163]	NCT01909804	SOF 400 mg qd 12 weeks + VEL 25 mg qd 12 weeks	Yes	–
		SOF 400 mg qd 12 weeks + VEL 100 mg qd 12 weeks		
POLARIS-1[21,22]	NCT02607735	SOF 400 mg qd 12 weeks + VEL 100 mg qd 12 weeks + VOX 100 mg qd 12 weeks	Yes	–
		PBO		
POLARIS-2[96]	NCT02607800	SOF 400 mg qd 8 weeks + VEL 100 mg qd 8 weeks + VOX 100 mg qd 8 weeks	Yes	–
		SOF 400 mg qd 12 weeks + VEL 100 mg qd 12 weeks		
POLARIS-3[96]	NCT02639338	SOF 400 mg qd 8 weeks + VEL 100 mg qd 8 weeks + VOX 100 mg qd 8 weeks	Yes	–
		SOF 400 mg qd 12 weeks + VEL 100 mg qd 12 weeks		
POLARIS-4[21,242]	NCT02639247	SOF 400 mg qd 12 weeks + VEL 100 mg qd 12 weeks + VOX 100 mg qd 12 weeks	Yes	–
		SOF 400 mg qd 12 weeks + VEL 100 mg qd 12 weeks		
POSITRON[26,95]	NCT01542788	SOF 400 mg qd 12 weeks + RBV 1000-1200 mg/day 12 weeks	Yes	–
Reddy 2017[170]	–	DAC + ASV	–	Yes
Sezaki 2017[175]	–	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	–	Yes
Shah 2016[176]	NCT02074514	SOF 400 mg qd 16 weeks + RBV 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg), twice per day 16 weeks	Yes	–
		SOF 400 mg qd 24 weeks + RBV 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg), twice per day 24 weeks		
Shiha 2017[177]	–	LDV 8 weeks + SOF 8 weeks	Yes	–
		LDV 12 weeks + SOF 12 weeks		
SIRIUS[20,23,27,203,237,238]	NCT01965535	SOF 400 mg 24 weeks + LDV 90 mg qd 24 weeks	Yes	–
Slash C[160]	–	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	Yes	–
Suda 2016[182]	UMIN000016355	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	–	Yes
Suda 2017[183]	UMIN000020301	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	–	Yes
Sung 2016[188]	–	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	–	Yes
SURVEYOR-I[65,118]	NCT02243280	GCR 200 mg qd 12 weeks + PBV 120 mg qd 12 weeks	Yes	–
		GCR 200 mg qd 12 weeks + PBV 40 mg qd 12 weeks		
		GCR 300 mg qd 8 weeks + PBV 120 mg qd 8 weeks		
		GCR 300 mg qd 12 weeks + PBV 120 mg qd 12 weeks		

			Study design	
Study name	Registration	Treatment arms	Trial	Observational study
SURVEYOR-II[65,118]	NCT02243293	GCR 300 mg qd 12 weeks + PBV 120 mg qd 12 weeks	Yes	–
		GCR 200 mg qd 12 weeks + PBV 120 mg qd 12 weeks		
		GCR 200 mg qd 12 weeks + PBV 40 mg qd 12 weeks		
		GCR 300 mg qd 8 weeks + PBV 120 mg qd 8 weeks		
Suzuki 2017[189]	–	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	–	Yes
SYNERGY[66,106,107,178,197,217]	NCT01805882	LDV 90 mg qd 12 weeks + SOF 400 mg qd 12 weeks	Yes	–
Terashita 2017[193]	–	DAC + ASV	Yes	–
Torres 2017[195]	–	LDV + SOF	–	Yes
		SOF + VEL		
		DAC + SOF		
Toyoda 2016[200]	UMIN000017023	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	Yes	–
Toyoda 2017[199]	UMIN000017020	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	Yes	–
TURQUOISE-III[51]	NCT02219503	PTV/r 150/100 mg qd 12 weeks + OMV 25 mg qd 12 weeks + DBV 250 mg bid 12 weeks	Yes	–
UNITY-3[201]	NCT02123654	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	Yes	–
VALENCE[125,234,241,246]	NCT01682720	SOF 400 mg qd 12 weeks + RBV 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg), twice per day 12 weeks	Yes	–
		SOF 400 mg qd 24 weeks + RBV 1000 mg/day (<75 kg) or 1200 mg/day (≥75 kg), twice per day 24 weeks		
		PBO		
VALOR-HCV[82]	NCT02128542	SOF 400 mg qd 12 weeks + RBV Weight-adjusted (1000-1200 mg/day divided doses) 12 weeks	Yes	–
VASCUVALDIC 2[173,174]	NCT02856243	DAC 60 mg qd 12 weeks + SOF 400 mg qd 12 weeks	–	Yes
		DAC 60 mg qd 24 weeks + SOF 400 mg qd 24 weeks		
Vierling 2015[204]	–	ESV 50 mg 8 weeks + GZR 100 mg 8 weeks	Yes	–
Wei 2016[211]	NCT01995266	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	Yes	–
Wei 2017a[210]	–	SOF 400 mg 12 weeks + RBV 1000-1200 mg divided daily dose 12 weeks	Yes	–
		SOF 400 mg 24 weeks + RBV 1000-1200 mg divided daily dose 24 weeks		
Wei 2017b[209]	–	DAC 60 mg qd 24 weeks + ASV 100 mg bid 24 weeks	Yes	–

			Study design	
Study name	Registration	Treatment arms	Trial	Observational study
		PBO		
Yakoot 2017[223]	ACTRN 12617000263392	DAC (generic) 60 mg/day 12 weeks + SOF (generic) 400 mg/day 12 weeks	Yes	–
		DAC (generic) 60 mg/day response-tailored duration + SOF (generic) 400 mg/day response-tailored duration		
Younossi 2016[226]	–	LDV 12 weeks + SOF 12 weeks	Yes	–
Zeng 2017[240]	–	LDV (generic) 90 mg qd 8 weeks + SOF (generic) 400 mg qd 8 weeks	–	Yes

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