CADTH THERAPEUTIC REVIEW

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[DRAFT FOR CONSULTATION]

Drugs for Chronic Hepatitis C Infection: Clinical Review

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ABBREVIATIONS AND GLOSSARY

AE	adverse event
BID	Twice daily
BOC	Boceprevir
CADTH	Canadian Agency for Drugs and Technologies in Health
CDEC	Canadian Drug Expert Committee
CDR	Common Drug Review
CHC	chronic hepatitis C
CI	confidence interval
CIHR	Canadian Institutes of Health Research
CrI	credible interval
DAA	direct-acting antiviral
DB	double blind
DIC	deviance information criterion
DSEN	Drug Safety and Effectiveness Network
EPO	epoetin alfa
EQ-5D	EuroQol 5 dimensions
eRVR	extended rapid virological response
FDA	Food and Drug Administration
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
Ic	incidence of the event in the control group
LOR	Logarithmic odds ratio
MAGIC	Methods and Applications Group for Indirect Comparisons
METAVIR	meta-analysis of histological data in viral hepatitis
NMA	network meta-analysis
NOC	notice of compliance
OR	odds ratio
PICO	population, intervention, comparator and outcome
PR	pegylated interferon plus ribavirin
PRISMA	preferred reporting items for systematic reviews and meta-analyses
q12	every 12 hours dosing regimen for DAA
q8	every 8 hours dosing regimen for DAA
QD	once daily
RCT	randomized controlled trial

RD	risk difference
RGT	response-guided therapy
RNA	ribonucleic acid
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SDT	standard (fixed) duration therapy
Ser139	protease active-site serine
SF-36	Short Form 36
SIM	Simeprevir
SOF	Sofosbuvir
SVR	sustained virologic response
SVR12	undetectable HCV RNA levels 12 weeks after the end of therapy
SVR24	undetectable HCV RNA levels 24 weeks after the end of treatment
TB	tuberculosis

TREATMENT REGIMEN NOMENCLATURE

ABT12	ABT-530 for 12 wks
ASU12	asunaprevir 12 wks
ASU24	asunaprevir 24 wks
B24 PR28	PR × 4 wks then boceprevir+PR × 24 wks
B24 PR28 RGT eRVR	PR × 4 wks then boceprevir +PR × 24 wks if eRVR achieved RGT
B24 PR28-48 RGT	PR × 4 wks then boceprevir +PR × 24 or 44 wks RGT
B32 PR36-48 RGT	PR × 4 wks then boceprevir × 32 wks with PR 32 to 44 wks RGT
B32 PR36 RGT eRVR	PR × 4 wks then boceprevir +PR × 32 wks if eRVR achieved RGT
B32 PR36-48 RGT no eRVR	PR × 4 wks then boceprevir +PR × 32 wks, then PR × 12 wks if no eRVR achieved RGT
B24 PR48 RGT no eRVR	PR × 4 wks then boceprevir +PR × 24 wks, then PR × 20 wks if no eRVR achieved RGT
B44 PR48	PR × 4 wks then boceprevir +PR × 44 wks
BEC12	beclabuvir 12 wks
BEC12 (75mg BID)	beclabuvir (75 mg BID) 12 wks
BEC12 (150mg BID)	beclabuvir (150 mg BID) 12 wks
DCV12	daclatasvir 12 wks
DCV24	daclatasvir 24 wks
DAS12	dasabuvir 12 wks
ELB8	elbasvir 8 wks
ELB12	elbasvir 12 wks
ELB12 (20mg QD)	elbasvir (20mg) 12 wks
ELB12 (50mg QD)	elbasvir (50mg) 12 wks
ELB18	elbasvir 18 wks
ELB18 (20mg QD)	elbasvir (20mg) 18 wks
ELB18 (50mg QD)	elbasvir (50mg QD) 18 wks
ELB8	elbasvir 8 wks
ELB8 (20mg QD)	elbasvir (20mg) 8 wks
ELB8 (50mg QD)	elbasvir (50mg) 8 wks
GALEXOS	simeprevir
GRA8	grazoprevir 8 wks
GRA8	grazoprevir (100mg QD) 8 wks
GRA12	grazoprevir 12 wks
GRA12	grazoprevir (100mg QD) 12 wks
GRA18	grazoprevir 18 wks
GRA18	grazoprevir (100mg QD) 18 wks
GS8	GS-5816 for 8 wks
GS-9451(6)	GS-9451 for 6 wks

GS-9669(6)	GS-9669 for 6 wks
Harvoni	ledipasvir/sofosbuvir
HOLKIRA PAK	ombitasvir/paritaprevir/ritonavir (fixed dose single tablet) and dasabuvir
INCIVEK	Telaprevir
LDV6	ledipasvir 6 wks
LDV8	ledipasvir 8 wks
LDV12	ledipasvir 12 wks
LDV24	ledipasvir 24 wks
OMB12	ombitasvir 12 wks
OMB24	ombitasvir 24 wks
PAR/RIT12	paritaprevir/ritonavir 12 wks
PEGASYS	peginterferon-alfa 2a
PEGASYS RBV	peginterferon-alfa 2a plus ribavirin
PEGETRON	peginterferon-alfa 2b plus ribavirin
PR12	pegylated interferon plus ribavirin 12 wks
PR24	peginterferon-alfa and ribavirin 24 wks
PR48	pegylated interferon 2a or 2b plus ribavirin administered for 48 wks
PR48 2a/2b	pegylated interferon 2a or 2b plus ribavirin for 48 wks
RBV8	ribavirin 8 wks
RBV12	ribavirin 12 wks
RBV16	ribavirin 16 wks
RBV18	ribavirin 18 wks
RBV24	ribavirin 24 wks
RBV(low-dose)24	low-dose RBV 600mg/day for 24 wks
SIM12 + PR24-48 RGT	simeprevir+PR × 12 wks then PR x12 or 36 wks RGT
SIM12 PR24 RGT eRVR	simeprevir +PR × 12 wks then PR x12 wks if eRVR achieved RGT
SIM12 PR48	simeprevir +PR × 12 wks then PR 36 wks
SIM12 PR48 RGT no eRVR	simeprevir +PR × 12 wks then PR × 36 wks if no eRVR RGT
SIM12	simeprevir 12 wks
SOF12 + PR12	sofosbuvir + PR × 12 wks
SOF12 + PR24-48 RGT	sofosbuvir + PR × 12 wks then PR × 12 or 36 wks RGT
SOF8	sofosbuvir 8 wks
SOF12	sofosbuvir 12 wks
SOF24	sofosbuvir 24 wks
SOF24	sofosbuvir 400mg/d for 24 wks
SOVALDI	sofosbuvir
T12 PR24 q8	teleprevir+PR × 12 wks, then PR × 12 wks q8h
T12 PR24 RGT eRVR q8	teleprevir +PR × 12 wks then PR x12 wks if eRVR achieved RGT q8h
T12 PR24 RGT eRVR q12	teleprevir +PR × 12 wks then PR x12 wks if eRVR achieved RGT q12h

T12 PR24-48 RGT q8	teleprevir +PR × 12 wks then PR x12 or 36 wks RGT q8h
T12 PR24-48 RGT q12	teleprevir +PR × 12 wks then PR x12 or 36 wks RGT q12h
T12 PR48 q8	teleprevir +PR × 12 wks then PR × 36 wks q8h
T12 PR48 RGT eRVR q8	teleprevir +PR × 12 wks then PR × 36 wks if eRVR achieved RGT q8h
T12 PR48 RGT no eRVR q8	teleprevir +PR × 12 wks then PR × 36 wks if no eRVR RGT q8h
T12 PR48 RGT no eRVR q12	teleprevir +PR × 12 wks then PR × 36 wks if no eRVR RGT q12h
VICTRELIS	boceprevir
VICTRELIS TRIPLE	boceprevir and peginterferon-alfa 2b plus ribavirin

EXECUTIVE SUMMARY

Chronic hepatitis C (CHC) is a common infection that can lead to chronic liver disease, liver failure, hepatocellular carcinoma, and requirement for liver transplantation. For many years, standard therapy for CHC infection consisted of pegylated interferon plus ribavirin (PR). In 2011, the first direct-acting antiviral agents (DAA), boceprevir and telaprevir, were approved for use in Canada. Treatment burden for patients is high with PR-based therapies due to drug-drug interactions, large pill burden, rigorous dosing requirements and significant side effects. Treatment regimens involving newer DAA agents have been developed and offer advantages to patients including shorter treatment duration, fewer side effects and interactions with other medicines, and the potential for interferon- and/or ribavirin-free treatment. They also may offer advantages to particular groups of patients who have historically been difficult to treat; however, any added benefit offered by these novel DAA treatment regimens must be considered in the context of high costs for these therapies.

In 2014, CADTH completed a Therapeutic Review evaluating the clinical and cost-effectiveness of treatments for CHC genotype 1 infection that included the DAA-based regimens available in Canada at the time. Clinical data for the novel DAA treatments for CHC infection have evolved quickly since then. Some of these regimens are or will be approved for only genotype 1 CHC infection, and others for multiple genotypes.

The original CADTH Therapeutic Review focused on regimens approved in Canada for the treatment of genotype 1 CHC infection at the time of writing. This meant that only treatment regimens with pegylated interferon plus ribavirin were included in these reports. In anticipation of the need and demand for supporting evidence and information regarding the comparative effectiveness of new regimens for CHC infection, CADTH has updated its Therapeutic Review to include recently approved and emerging regimens for the treatment of CHC infection (Genotypes 1 through 6), including interferon-free regimens.

Objective

The objective of this systematic review was to assess the comparative efficacy and safety of currently available and emerging regimens for the treatment of CHC infection (Genotypes 1 to 6).

Policy Questions

There are three policy questions for the project. These reflect the information needs of provincial and territorial decision- and policy-makers.

1. How should interferon-free DAA regimens be listed for reimbursement for CHC infection (Genotypes 1 to 6)?
2. Should reimbursement of regimens for CHC infection be guided by fibrosis staging and limited to fibrosis stages ≥ F2?
3. Should re-treatment with a DAA regimen be reimbursed for patients with CHC infection who fail to achieve SVR on another DAA regimen?

Research Questions

Five research questions were developed to address the aforementioned policy issues.

1. What is the comparative efficacy and safety of treatment regimens for patients with CHC infection (Genotypes 1 to 6) who are treatment-naive?
2. What is the comparative cost-effectiveness of treatment regimens for patients with CHC infection (Genotypes 1 to 4) who are treatment-naive?
3. What is the comparative efficacy and safety of treatment regimens for patients with CHC infection (Genotypes 1 to 6) who have relapsed or had a partial or null response to prior PR or DAA + PR or DAA-only therapy?
4. What is the comparative cost-effectiveness of treatment regimens for patients with CHC infection (Genotypes 1 to 4) who have relapsed or had a partial or null response to prior PR or DAA + PR or DAA-only therapy?
5. For questions 1 to 4, how do the comparative efficacy, safety, and cost-effectiveness of treatment regimens vary across population subgroups based on fibrosis level (METAVIR score ≤ F1, F2, F3, or F4), cirrhosis stage (e.g., compensated versus decompensated), genotype subtype, post-liver transplant, baseline viral load, HIV/CHC coinfection, hepatitis B (HBV)/CHC coinfection, and tuberculosis (TB)/CHC coinfection?

This Clinical Review addresses questions the questions related to comparative efficacy and safety. Questions related to cost effectiveness are addressed in the accompanying Cost Effectiveness Analysis Report.

Methods

This report is an update to CADTH's previous Therapeutic Review on DAA agents for CHC genotype 1 infection published in October 2014. This review specifically expands the scope of the previous review to include HCV Genotypes 2 to 6, as well as recently approved and emerging regimens.

The literature search from the 2014 CADTH Therapeutic Review on DAAs for CHC genotype 1 infection, originally conducted on January 9, 2014, was updated for this review on February 4, 2015. The updated search incorporated several additional DAAs that were not included in the original report. Alerts were run monthly and regular search updates were performed on databases not providing alert services. The last alert from which studies were selected for inclusion in the review was run on May 1, 2015. A protocol and list of included studies was posted in April 2015, with stakeholder feedback sought on the latter. Both were vetted by clinical experts and methodologists.

The strategy for building and analyzing the evidence base for the treatment of CHC infection consisted of two fundamental steps. First, a broad systematic review of the available evidence in the published literature for the outcomes specified in the protocol was undertaken to update the previous Therapeutic Review literature search for genotype 1, and to identify all studies for genotypes 2 to 6. The systematic review followed a protocol written a priori and was conducted in line with the Cochrane Handbook for Systematic Reviews of Interventions. Second, a network meta-analysis was conducted comparing the available treatment regimens reporting outcomes of interest.

The main regimens of interest for this review were those:

- Currently approved by Health Canada for the populations of interest in this review

- Considered of clinical relevance based on inclusion in Canadian (1) or US clinical practice guidelines (2), or
- Considered to have a high likelihood of regulatory approval in Canada in the near future (i.e., within approximately 12 months) based upon information available to CADTH as of February 2015.

The main efficacy outcome of interest was sustained virologic response (SVR) at 12 or 24 weeks. Key safety outcomes were rash, depression, and anemia.

Assessment of bias in comparative randomized studies was completed using the Cochrane Risk of Bias tool (Appendix H). When data were sufficient for appraisal, we evaluated single-arm studies using criteria applicable for the evaluation of case series

The lack of head-to-head trials in this therapeutic area, combined with the use of single-arm cohort studies, makes it difficult to compare the relative efficacy of the different treatment regimens. We performed a network meta-analysis (NMA) (also known as an indirect treatment comparison) to assess the various treatment options for CHC infection. This method allows for the comparison of the direct and indirect evidence for a number of therapies in this population. We also made adjustments to conventional NMA methodology in order to incorporate the single-arm evidence. The single-arm studies were included into the NMA by creating a "virtual" study where a comparator arm matched for patient characteristics was selected for a single arm in single-arm studies. Where the available studies for a particular genotype could not be assembled into a NMA due to the lack of a common reference treatment, supplemental literature searches were conducted to identify evidence from meta-analyses or key primary studies (including observational studies if needed) for a clinically appropriate reference treatment that would allow construction of a network.

Separate analyses were performed for each genotype for SVR, and within each genotype, analyses were separated by subpopulations based on prior treatment experience with PR (with or without DAA) or DAA alone, as follows:
- Treatment-naive
- Treatment-experienced
- Treatment-experienced with prior relapse
- Treatment-experienced with prior partial response
- Treatment-experienced with prior null response.

Within each of these 5 subpopulations, analyses were further separated by the presence or absence of cirrhosis. The analyses for genotype 1 were further separated by genotype subtype 1a and 1b.

Summary of Findings

A total of 67 studies reported in 63 publications were included in this review. Included studies predominantly reported on patients with CHC genotype 1 infection, or a mix of patients with genotype 1 and other genotypes. Eleven studies reported on patients with CHC genotype 2 infection, 11 on genotype 3, and eight on genotype 4, two on genotype 5, and three on genotype 6. Only two studies included patients with CHC Genotypes 5 and 6 infection.

Efficacy – Sustained Virologic Response at 12 Weeks

While this review was comprehensive in its scope with respect to available and emerging regimens of interest, Harvoni, Holkira Pak and daclatasvir-based regimens were the main focus. A summary of the NMA results for CHC patients with genotype 1 infection with particular reference to these regimens is provided in Exhibit 1. This table provides a summary of results by patient subgroup and previous treatment experience, and highlights treatment regimens that significantly improved SVR compared to other regimens listed in the table.

In particular:

- For treatment-naive patients, Harvoni, Holkira Pak, and daclatasvir-based regimens were superior to PR-based treatments, with Harvoni and Holkira Pak significantly achieving SVR more often compared to simeprevir and sofosbuvir-based regimens with PR or RBV alone. In some cases, Harvoni and Holkira Pak were better than daclatasvir-based regimens. There was less evidence for patients with cirrhosis.
- For treatment-experienced patients, all three regimens were superior to PR-based treatments, specifically Harvoni and Holkira Pak. There was limited evidence for patients with cirrhosis. Once again, Harvoni and Holkira Pak were superior to daclatasvir-based regimens in some cases (in particular, Holkira Pak was better for genotype 1b and for patients without cirrhosis).
- For treatment-experienced patients with prior relapse, prior partial response or null response, Holkira Pak demonstrated improved SVR rates compared to PR-based treatments, and compared to Harvoni and daclatasvir-based regimens.

Exhibit 1: Genotype 1 Patients: Summary of the Results for SVR With Reference to Harvoni, Holkira Pak and Daclatasvir

Patient Population	Harvoni (SOF12 + LDV12) Significantly Improved SVR Compared With	Holkira Pak (PAR/RIT12 + OMB12 + DAS12) Significantly Improved SVR Compared With	Daclatasvir (DCV24 + ASU24) Significantly Improved SVR Compared With
Treatment-Naive Patients			
All	PR48 SOF24 + RBV24 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24	PR48 SOF24 + RBV24 SIM12 + PR24-48 RGT (with RBV12) PR48 SOF24 + RBV24 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24	PR48 SIM12 + PR24-48 RGT (for DCV12 + SOF12) PR48
Genotype 1a	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT	(with RBV12) PR48 SOF12 + PR12	
Genotype 1b	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24	PR48	PR48 SIM12 + PR24-48 RGT
Cirrhotic	PR48 SOF24 + RBV24 SIM12 + PR24-48 RGT		PR48
Non-Cirrhotic	PR48 SOF24 + RBV24 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24	PR48 (with RBV12) PR48 SOF24 + RBV24	PR48 SIM12 + PR24-48 RGT (for DCV12 + SOF12) PR48

Exhibit 1: Genotype 1 Patients: Summary of the Results for SVR With Reference to Harvoni, Holkira Pak and Daclatasvir			
Patient Population	**Harvoni (SOF12 + LDV12) Significantly Improved SVR Compared With**	**Holkira Pak (PAR/RIT12 + OMB12 + DAS12) Significantly Improved SVR Compared With**	**Daclatasvir (DCV24 + ASU24) Significantly Improved SVR Compared With**
		SIM12 + PR24-48 RGT	
Treatment-Experienced Patients			
All	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SIM12 + PR48 DCV24 + ASU24 (24 weeks) PR48	PR48 (with RBV12) PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SIM12 + PR48 DCV24 + ASU24	PR48 SIM12 + PR48 (with PR24) PR48 SIM12 + PR48 SIM12 + PR24-48 RGT
Genotype 1a	PR48 SIM12 + PR24-48 RGT SIM12 + PR48 (24 weeks) PR48	(with RBV12) PR48 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12	(with PR24) PR48
Genotype 1b	PR48 (24 weeks) PR48	PR48 SIM12 + PR24-48 RGT (with RBV12) PR48 SOF12 + LDV12 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12 DCV24 + ASU24	PR48 (with PR24) PR48 SOF12 + LDV12 SOF24 + LDV24 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12 DCV24 + ASU24
Cirrhotic	PR48 (24 weeks) PR48		PR48 (with PR24) PR48 SIM12 + PR48
Non-Cirrhotic	PR48 SIM12 + PR24-48 RGT	PR48 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12 DCV24 + ASU24 SIM12 + SOF12 (with RBV12) PR48 SOF12 + LDV12 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12 DCV24 + ASU24 DCV24 + ASU24 + PR24 SIM12 + SOF12	PR48 (with PR24) PR48 SIM12 + PR24-48 RGT
Treatment-Experienced Patients With Prior Relapse			
All	PR48	PR48 SIM12 + PR24-48 RGT (with RBV12) PR48 SIM12 + PR24-48 RGT	

Exhibit 1: Genotype 1 Patients: Summary of the Results for SVR With Reference to Harvoni, Holkira Pak and Daclatasvir			
Patient Population	**Harvoni (SOF12 + LDV12) Significantly Improved SVR Compared With**	**Holkira Pak (PAR/RIT12 + OMB12 + DAS12) Significantly Improved SVR Compared With**	**Daclatasvir (DCV24 + ASU24) Significantly Improved SVR Compared With**
Genotype 1a		(with RBV12) PR48	
Genotype 1b		(with RBV12) PR48	
Cirrhotic			
Non-Cirrhotic		PR48 SIM12 + PR24-48 RGT (with RBV12) PR48 SIM12 + PR24-48 RGT	
Treatment-Experienced Patients With Prior Partial Response			
All		PR48 (with RBV12) PR48 SIM12 + PR48	PR48 (with PR24) PR48
Genotype 1a		(with RBV12) PR48 SIM12 + PR48	
Genotype 1b		(with RBV12) PR48	
Cirrhotic			
Non-Cirrhotic		PR48 (with RBV12) PR48	
Treatment-Experienced Patients With Prior Null			
All		PR48 (with RBV12) PR48 SOF12 + PR12 SIM12 + PR48	PR48 SOF12 + PR12 (with PR24) PR48 SOF12 + PR12
Genotype 1a		(with RBV12) PR48 SIM12 + PR48 (24 weeks with RBV24) PR48 SIM12 + PR48	
Genotype 1b		(with RBV12) PR48 SIM12 + PR48 DCV24 + ASU24	
Cirrhotic			
Non-Cirrhotic		PR48 SIM12 + PR48 (with RBV12) PR48 SIM12 + PR48	(with PR24) SIM12 + PR48

NMA was also conducted in patients with genotype 2, 3 or 4 CHC infection. The data available were more limited compared with genotype 1 and, with fewer treatment strategies being evaluated, the networks were simpler. Therefore, a limited number of treatment comparisons resulted from the analysis.

In Exhibit 2, the SVR results for specific treatments that have been compared and reported in this review are summarized.

In particular:

- For patients with genotype 2 infection, SOF12 + RBV12 significantly improved SVR rates over PR24 in treatment-naive patients, but SOF12 + PR12 did not. In treatment-experienced patients, neither SOF16 + RBV16 nor SOF12+PR12 were significantly different from SOF12+ RBV12.
- For patients with genotype 3 infection and regardless of treatment experience, SOF24 + RBV24, DCV12 + SOF12, and SOF12 + PR12 significantly improved SVR compared with PR48, and there were no significant differences between these regimens.
- For patients with genotype 4 infection, DCV24 + ASU24 + PR24 significantly improved SVR compared to SOF12 + RBV12 in treatment-experienced patients overall, and for patients with and without cirrhosis. SOF12 + PR12 significantly improved SVR compared to SOF12 + RBV12 in treatment-naive patients overall.

Exhibit 2: Genotype 2 to 4 Patients: Summary of the Results for SVR With Reference to Reported Treatment Regimens

Patient Population	Genotype 2			Genotype 3			Genotype 4			
	SOF12 + RBV12	SOF12 + PR12	SOF16 + RBV16	SOF24 + RBV24	SOF12 + DCV12	SOF12 + PR12	SOF12 + RBV12	SOF24 + RBV24	SOF12 + PR12	DCV24 + ASU24 + PR24
Treatment-Naive Patients (PR24 Reference for Genotype 2) (PR48 Reference for Genotypes 3/4)										
All	PR24	NS[a]	[c]	PR48	PR48		NS	PR48	PR48 SOF12+ RBV12	
Cirrhotic	PR24			PR48			NS	PR48		
Non-Cirrhotic	PR24	NS		PR48	PR48		NS	NS		
Treatment-Experienced Patients (SOF12 + RBV12 Reference for Genotypes 2/4) (PR48 Reference for Genotype 3)										
All	---[b]	NS SOF16+ RBV16	NS	PR48	PR48	PR48	---	NS		SOF12+ RBV12
Cirrhotic	---	NS	NS	PR48		PR48	---	NS		SOF12+ RBV12
Non-Cirrhotic	---	NS		PR48	PR48	NS	---	NS		SOF12+ RBV12

[a] NS indicates that no significant difference was found.
[b] Dashes (---) indicates that the treatment was the reference standard.
[c] Blank cell indicates that the treatment was not considered for this patient population.

The data for CHC genotype 5 and 6 infections were insufficient for analysis. All six patients with genotype 6 and the one patient with genotype 5 who received SOF12 + PR12 in the NEUTRINO study achieved SVR12. Eight out of the 10 (80%) patients with genotype 6 who received grazoprevir/elbasvir in the C-EDGE study achieved SVR12. Two patients experienced virologic relapse.

Safety

Three key adverse events were identified — rash, anemia and depression — based on their impact on patients' quality of life and health care resources. These events were analyzed using NMA methods with patients from all Genotypes combined in the analysis. Separate analyses stratified by previous treatment experience were also conducted.

A summary of the NMA results with specific reference to Harvoni, Holkira, and the daclatasvir-based regimens is provided in Exhibit 3. This table provides a summary, by treatment history, of when these regimens were significantly associated with fewer adverse events (i.e., rash, anemia and depression) compared to the other treatments listed in the table.

In particular:

For treatment-naive patients:

- All three regimens were associated with significantly lower risks for rash and anemia than PR-based treatments, but only Harvoni and daclatasvir-based regimens were significantly associated with less depression compared to PR-based treatments.
- For rash, Holkira Pak with RBV was less favourable than Harvoni, Holkira Pak without RBV and daclatasvir-based regimens.
- For anemia, Holkira Pak with or without RBV was less favourable than Harvoni.
- For depression, Holkira Pak with RBV and daclatasvir were less favourable than Harvoni.

For treatment-experienced patients:

- All three regimens were associated with significantly less rash and anemia than PR-based treatments, but evidence was limited for depression.
- For rash, daclatasvir with PR was less favourable than Harvoni, Holkira Pak and daclatasvir without PR.
- For anemia, Holkira Pak with RBV was less favourable than Harvoni and Holkira Pak without RBV.

Exhibit 3: All Patients: Summary of the Results for Rash, Anemia and Depression With Reference to Harvoni, Holkira Pak and Daclatasvir

Safety Event	Harvoni (SOF12 + LDV12) Significantly Associated With Less Events Compared With	Holkira Pak (PAR/RIT12 + OMB12 + DAS12) Significantly Associated With Less Events Compared With	Daclatasvir (DCV24 + ASU24) Significantly Associated With Less Events Compared With
Treatment-Naive Patients – All Genotypes			
Rash	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT PAR/RIT12 + OMB12 + DAS12 + RBV12	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT PAR/RIT12 + OMB12 + DAS12 + RBV12	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT PAR/RIT12 + OMB12 + DAS12 + RBV12
Anemia	PR48 SOF12 + PR12 SOF24 + RBV24 SIM12 + PR24-48 RGT PAR/RIT12 + OMB12 + DAS12 ± RBV12	PR48 SOF12 + PR12 SOF24 + RBV24 SIM12 + PR24-48 RGT (with RBV12) PR48 SOF12 + PR12	(with DCV12 + SOF12) PR48 SOF12 + PR12 SOF24 + RBV24 SIM12 + PR24-48 RGT

Exhibit 3: All Patients: Summary of the Results for Rash, Anemia and Depression With Reference to Harvoni, Holkira Pak and Daclatasvir			
Safety Event	Harvoni (SOF12 + LDV12) Significantly Associated With Less Events Compared With	Holkira Pak (PAR/RIT12 + OMB12 + DAS12) Significantly Associated With Less Events Compared With	Daclatasvir (DCV24 + ASU24) Significantly Associated With Less Events Compared With
Depression	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SOF24 + RBV24 DCV24 + ASU24 DCV12 + SOF12 PAR/RIT12 + OMB12 + DAS12 + RBV12		PR48
Treatment-Experienced Patients – All Genotypes			
Rash	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SOF24 + RBV24 DCV24 + ASU24 + PR24	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24 +PR24 PAR/RIT12 + OMB12 + DAS12 + RBV12 (with RBV12) PR48 DCV24 + ASU24 + PR24	PR48 DCV24 + ASU24 + PR24 SOF12 + PR12
Anemia	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SOF214 + RBV24 DCV24 + ASU24 +PR24 PAR/RIT12 + OMB12 + DAS12 + RBV12	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SOF24 + RBV24 DCV24 + ASU24 +PR24 PAR/RIT12 + OMB12 + DAS12 + RBV12 (with RBV12) PR48 SOF12 + PR12	(with PR24) PR48 SOF12 + PR12
Depression		(with RBV12) PR48	PR48

In addition to rash, anemia and depression, other safety events were considered. The data available and/or the frequency of these safety events were not sufficient for NMA.

In particular, for treatment-naive patients:

- Withdrawals due to adverse events, mortality (all cause), mortality (liver-related), suicidal ideation, hepatocellular carcinoma and liver transplants were infrequently reported for all treatment regimens
- Adverse events, fatigue and pruritus were frequently reported across treatment regimens
- PR48 was often associated with harms, and
- SOF12 + PR12, SOF12 + RBV12, SOF24 + RBV24, SIM12 + PR24-48 RGT were associated with several harms.

For treatment-experienced patients:

- Withdrawals due to adverse events, mortality (all cause), mortality (liver-related), suicidal ideation, hepatocellular carcinoma and liver transplants were infrequent reported for all treatment regimens

- Adverse events, fatigue and pruritus were frequently reported across all treatments
- PR48 was often associated with harms, and
- SOF12 + PR12, SOF12 + RBV12, SOF24 + RBV24, SIM12 + PR24-48 RGT were associated with several harms.

Strengths and Limitations

The systematic review was limited by the quality of the included studies. Of the 67 studies included in the systematic review, overall quality was adequate; however, all but two studies had one or more methodological domains with an unclear or high risk of bias. Moreover, data for some DAAs in specific populations were limited to open-label, uncontrolled (or historically controlled) studies, thus limiting our ability to assess comparative efficacy and safety using standard Bayesian indirect comparison methodologies. No individual patient data were available for analyses, so it was not possible to use comparative effectiveness methods, such as propensity scores weighting, for matching studies and identifying a comparator arm or conducting an adjusted analysis. Instead, single-arm studies were incorporated into the NMA by creating a "virtual" study where a comparator arm matched for baseline patient characteristics was identified for the single arm.

NMAs were not conducted for all outcomes of interest in the systematic review. The outcomes analyzed were selected based on their clinical importance to the research questions and the economic model. The adverse events analyzed were limited to those specific events deemed to have the greatest impact on patients' quality of life or ability to complete treatment regimens, or those that required additional interventions or incurred substantial costs to manage.

Limited data were available for severity of fibrosis by METAVIR score for the interferon-free DAA treatment regimens. Instead, the more recent studies define patients according to whether they have cirrhosis or not. In order to maintain the most robust network possible for SVR12, analyses were stratified by non-cirrhosis (i.e., METAVIR score 1 to 3) and cirrhosis (i.e., METAVIR score of 4). This classification method resulted in 6 studies reporting fibrosis scores of 3 and 4 combined, being excluded from the NMA for SVR12. In addition, due to sparse data, our subgroup analyses for patients with cirrhosis may lack power, and the uncertainty in the findings are reflected in the wide CrIs.

A large majority of included studies excluded patients with TB, hepatitis B coinfection, decompensated cirrhosis, or other significant illnesses; as such, we were unable to perform NMA for these special patient populations. The primary outcome for most studies was SVR12, but some of the earlier studies reported SVR24, and some studies reported both. No studies reported long- term outcomes.

The number of trials that contributed to some of the NMAs was limited which may have yielded less precise estimates than if we were able to create more robust evidence networks. Data were insufficient to conduct an NMA for some subpopulations of interest and in Genotypes 5 and 6. Specifically, small numbers of patients with cirrhosis, patients previously treated (with PR, DAA+PR or DAA alone), and patients coinfected with HIV were included. Limited data was especially an issue in the analysis of genotype 1 patients with cirrhosis and all analyses for Genotypes 2 to 4; thus, the results showed wide CrIs. Results should be interpreted with caution.

We were unable to perform regression analyses to determine whether the proportion of patients with specific baseline characteristics or epidemiological factors in the trials had an impact on our findings.

We were unable to analyze adverse events according to their severity, as data on severity were not consistently reported. In addition, different definitions of adverse events may have been used across studies, but due to the lack of detailed descriptions and study protocols, we were unable to assess potential differences.

A strength of this review was its comprehensiveness in identifying and assessing clinically relevant regimens for the treatment of CHC infection that are currently approved in Canada, recommended by major guidelines, or likely to be available in the near future. However, evidence that could be included in NMA was not available for some regimens of interest, namely: DCV24 + SOF24 for genotype 1 infection; DCV + ASU + PR for treatment-naive patients with genotype 1 infection; DCV12 + SOF12 for treatment-experienced patients with genotype 1 infection; DCV + SOF for genotype 2 infection; SOF12 + PR 12 for treatment-naive patients with genotype 3 infection (although the sensitivity analysis incorporating results from BOSON mitigated this evidence gap); SOF12 + LDV12 + RBV12 and DCV24 + SOF24 ± RBV24 for genotype 3 infection regardless of treatment experience; SOF12 + LDV12 and DCV12 + ASU12 + PR12 for patients with genotype 4 infection; and SOF12 + PR12 for treatment-experienced patients with genotype 4 infection. Trial data for some of these regimens may be available in conference abstracts, which were not included in the systematic review. Furthermore, given the rapid and ongoing developments in the field, and because changes to review scope could only be made up to a certain point (February 2015) without compromising methodological quality and timeliness, it is possible that some regimens currently considered relevant may not have been captured in the review.

Conclusions and Implications for Decision- or Policy-Making

For SVR:

- For treatment-naive and -experienced patients with genotype 1 infection, Harvoni, Holkira Pak and daclatasvir were superior to PR-based treatments. Harvoni and Holkira Pak were better than daclatasvir-based regimens in some patient subgroups. There was limited evidence for patients with cirrhosis.
- The data available for genotype 2 to 4 were limited. For patients with genotype 2 infection, SOF12 + RBV12 significantly improved SVR rates over PR24 in treatment-naive patients, but SOF12 + PR12 did not. In treatment-experienced patients, neither SOF16 + RBV16 nor SOF12 + PR12 were significantly different from SOF12+ RBV12.
- For patients with genotype 3 infection and regardless of treatment experience, SOF24 + RBV24, DCV12 + SOF12, and SOF12 + PR12 significantly improved SVR compared with PR48, and there were no significant differences between these three regimens.
- For genotype 4 patients, DCV24 + ASU24 + PR24 and SOF12 + PR12 were superior to SOF12 + RBV12 in treatment-experienced and naive patients respectively.
- The data for genotype 5 and 6 infection were insufficient for analysis.
- Data were limited to evaluate patients with HIV coinfection, however Harvoni and SOF24 + RBV24 significantly improved SVR compared to PR48 in treatment-naive patients with genotype 1 infection. NMA could not be performed for patients infected with other Genotypes and coinfected with HIV, although the following regimens demonstrated high rates of SVR in treatment-naive patients in individual trials: SOF12 + RBV12 in genotype 2;

SOF24 + RBV24 in genotype 3; SOF24 + RBV24 and SOF12 + PR12 in genotype 4. There were no data for treatment-experienced patients with HIV coinfection.

- No evidence was available to allow analysis of efficacy for the following regimens: DCV24 + SOF24 for genotype 1 infection; DCV + ASU + PR for treatment-naive patients with genotype 1 infection; DCV12 + SOF12 for treatment-experienced patients with genotype 1 infection; DCV + SOF for genotype 2 infection; SOF12 + LDV12 + RBV12 and DCV24 + SOF24 ± RBV24 for genotype 3 infection regardless of treatment experience; SOF12 + LDV12 and DCV12 + ASU12 + PR12 for patients with genotype 4 infection; and SOF12 + PR12 for treatment-experienced patients with genotype 4 infection.

For rash, anemia, depression:

- For treatment-naive and -experienced patients, Harvoni, Holkira Pak and daclatasvir-based regimens were associated with lower risks for rash and anemia than PR-based treatments, but only Harvoni and daclatasvir-based regimens were associated with less depression compared to PR-based treatments. In particular, Holkira Pak with RBV was less favourable than Harvoni.
- For treatment-experienced patients, Harvoni, Holkira Pak and daclatasvir-based regimens were associated with less rash and anemia than PR-based treatments, but evidence was sparse for depression. For rash, daclatasvir with PR was less favourable than Harvoni, Holkira Pak and daclatasvir without PR. For anemia, Holkira Pak with RBV was less favourable than Harvoni and Holkira Pak without RBV.

1 CONTEXT AND POLICY ISSUES

1.1 Background

Approximately 242 000 Canadians are infected with chronic hepatitis C virus (HCV) and the number grows by an estimated 7 900 new infections each year.(3) It is difficult to accurately estimate the prevalence of HCV cases as limited population-level surveillance has been carried out in Canada. Prevalence and incidence may be underestimated, as 30% to 70% of patients are unaware that they are infected.(4) Chronic hepatitis C (CHC)-infected persons progress through various stages of disease and in due course may develop critical illnesses resulting from associated sequelae.(4, 5) It is estimated that 15% to 25% of patients with CHC infection will develop hepatocellular carcinoma or progressive liver disease within 20 years of infection, resulting in liver transplantation for some, and decreased life expectancy and quality of life for many. The lifetime risk of developing complications of CHC infection may be higher than 25% because many individuals are infected for much longer than 20 years.(6, 7)

HCV can be divided into six unique Genotypes, each with one or more subtypes. Genotype 1 is the most common in Canada (55% to 65%) and historically the most difficult to cure.(8, 9) Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada, respectively. Genotypes 4, 5, and 6 are less common in Canada and account for less than 5% of HCV cases.(9, 10) The goal of therapy for patients with CHC infection is to achieve sustained virologic response (SVR), i.e., undetectable HCV at 12 or 24 weeks after completion of anti-HCV treatment. The vast majority of patients that achieve SVR remain free of detectable HCV over the long-term (unless reinfected), hence SVR is considered to represent virologic cure. Furthermore, achievement of SVR is associated with reduced risks for the hepatic sequelae of CHC infection such as cirrhosis and hepatocellular carcinoma. Treatment of CHC infection is guided by genotype, the presence and degree of liver fibrosis or cirrhosis, prior treatment experience, and patient factors such as the presence of co-morbidities. Until 2011, the standard of care for CHC infection was pegylated interferon alfa combined with ribavirin (PR).(11) Following regulatory approvals beginning in 2011, combinations of the direct-acting antiviral agents (DAAs) boceprevir, telaprevir, simeprevir, and sofosbuvir with PR demonstrated substantially greater efficacy in terms of SVR than PR alone in clinical studies, resulting in a changed paradigm for management of patients with chronic CHC genotype 1 infection.(12, 13)

In 2014, CADTH completed a Therapeutic Review evaluating the clinical and cost-effectiveness of treatments for CHC genotype 1 infection that included the DAA-based regimens available in Canada at the time.(14) Based on this review, the Canadian Drug Expert Committee (CDEC) recommended that (15):

- DAA plus PR treatment should be offered only to persons with CHC infection who have fibrosis stages F2, F3, or F4.
- Simeprevir daily for 12 weeks, in combination with PR for 24 to 48 weeks, should be used as the protease inhibitor of choice for treatment-naive patients or for treatment-experienced patients with prior relapse.
- Persons in whom a DAA plus PR regimen has failed should not be re-treated with another DAA plus PR regimen.

At the time, CDEC could make no definitive recommendations regarding the place in therapy for sofosbuvir relative to other available protease inhibitors.

Despite the improved efficacy of these new treatment regimens compared with PR alone, they may be associated with significant side effects, long treatment schedules, and limited success in specific HCV Genotypes.(16) Rapid developments have occurred in HCV treatment since the introduction of the first DAAs, with considerable focus placed on the development of interferon-free regimens due to the significant toxicities associated with interferon therapy. A number of interferon-free treatment regimens have recently entered the market or are in late-stage development. Apart from better tolerability, potential benefits of some or all of these regimens are shorter treatment durations, higher efficacy in terms of SVR rates, efficacy against HCV Genotypes other than genotype 1, and all-oral dosing. The FDA and Health Canada have approved Harvoni (an interferon-free combination of ledipasvir and sofosbuvir) and Holkira Pak, a combination of a dasabuvir tablet and an ombitasvir, paritaprevir, and ritonavir tablet, which may also be combined with ribavirin (Table 3).(17, 18) Interferon-free regimens containing daclatasvir and asunaprevir have been submitted to the CADTH Common Drug Review (CDR) as pre-Notice of Compliance (NOC) submissions, suggesting that they may be approved by Health Canada in the near future.(19, 20) A number of other treatment regimens are in phase 3 clinical trial programs that span multiple Genotypes and address more specific subgroups of HCV patients that have previously been difficult to treat, including those with HIV coinfection, decompensated liver disease, and liver transplant.(21)

1.2 Treatment of Chronic Hepatitis C Infection

The Canadian Association of Gastroenterology along with the Canadian Association for the Study of the Liver recently updated their Consensus Guidelines citing the need to adjust their recommendations based on the rapidly changing treatment landscape and the dramatically improved rates of virological clearance found in studies of the new DAA agents.(1) The guidelines suggest that the interferon-free DAA regimens (Harvoni and Holkira Pak) should be considered first-line treatment for patients with CHC genotype 1 infection. PR, boceprevir (Victrelis) and teleprevir (Incivek) were listed as regimens not recommended for this genotype. As of January 1, 2015 Vertex Pharmaceuticals has discontinued sales of Incivek in Canada and both Incivek and Victrelis are no longer available in the United States, having been rendered essentially obsolete by the market entry of the newer DAA regimens.

Regulatory approvals of newer regimens (Table 1) have given way to discussions of affordability and accessibility, which pose a challenge for both publicly and privately funded drug programs in Canada, given the prevalence of CHC infection and the higher cost of new treatments compared with PR-based regimens.

In anticipation of the need and demand for supporting evidence and information regarding the comparative effectiveness of new regimens for CHC infection, MAGIC, in collaboration with CADTH, updated CADTHs previous Therapeutic Review to include recently approved and emerging regimens for the treatment of CHC infection (Genotypes 1 through 6).

Table 1: Health Canada–Approved Therapies for the Treatment of Chronic Hepatitis C Infection

Product	Treatment indication	Mechanism of Action
Pegylated Interferon-Containing Products		
Peginterferon-alfa 2a (PEGASYS), Peginterferon-alfa 2a plus ribavirin (PEGASYS RBV)	For the treatment of CHC in adult patients without cirrhosis and adult patients with compensated cirrhosis, including HCV/HIV coinfection patients with stable HIV disease with or without antiretroviral therapy.	Interferons bind to specific receptors on the cell surface, initiating a complex intracellular signalling pathway and rapid activation of gene transcription.

Table 1: Health Canada–Approved Therapies for the Treatment of Chronic Hepatitis C Infection		
Product	**Treatment indication**	**Mechanism of Action**
Peginterferon-alfa 2b plus ribavirin (PEGETRON)	Treatment of adult patients (18 years or older) with CHC who have compensated liver disease and are positive for HCV RNA, including patients who have not received previous treatment or who failed prior treatment with interferon alfa (pegylated or non-pegylated) and ribavirin combination therapy.	Interferon-stimulated genes modulate many biological effects, including the inhibition of viral replication in infected cells, inhibition of cell proliferation, and immunomodulation. The mechanism of action of ribavirin is not known.
Protease Inhibitors		
Boceprevir (VICTRELIS) (VICTRELIS TRIPLE)	Treatment of CHC genotype 1 infection, in combination with peginterferon-alfa and ribavirin, in adult patients (18 years or older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous therapy	DAA against the HCV that is a specific inhibitor of the HCV NS3/4A protease, covalently, yet reversibly, binds to the NS3/4A protease active-site serine (Ser139) through an α-ketoamide functional group to inhibit viral replication in HCV-infected host cells
Telaprevir (INCIVEK) *Note: telaprevir has been discontinued in Canada as of January 1st, 2015.	Treatment of CHC genotype 1 infection, in combination with peginterferon-alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are treatment-naive or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers	DAA against the HCV that is a specific inhibitor of the HCV NS3/4A protease, which is essential for viral replication
Simeprevir (GALEXOS)	Treatment of CHC genotype 1 infection, in combination with peginterferon-alfa and ribavirin in adults with compensated liver disease, including cirrhosis, who are treatment-naive or who have failed previous interferon therapy (pegylated or non-pegylated) with ribavirin	DAA against the HCV that is a specific inhibitor of the HCV NS3/4A protease through a non-covalent, induced-fit binding into the active site of the NS3 protease
Nucleotide Polymerase Inhibitor		
Sofosbuvir (SOVALDI)	Treatment of CHC infection in adult patients with compensated liver disease, including cirrhosis, as follows: • for the treatment of genotype 1 and genotype 4 CHC infection in combination with pegylated interferon and ribavirin • for the treatment of genotype 2 and genotype 3 CHC infection in combination with ribavirin	DAA against the HCV that is mediated by a membrane-associated multiprotein replication complex. The HCV polymerase (NS5B protein) is an RNA-dependent RNA polymerase and is the essential initiating and catalytic subunit of this replication complex and is critical for the viral replication cycle
Ledipasvir/Sofosbuvir (Harvoni fixed-dose single tablet)	Treatment of CHC infection genotype 1 infection in adults, including: • Treatment-naive patients with and without cirrhosis • Treatment-experienced patients with or without cirrhosis. The product monograph states that the safety and efficacy of Harvoni have not been studied in patients infected with HCV genotype 2, 4, 5 or 6 and has not been fully	Both sofosbuvir and ledipasvir exhibit high potency and specificity as individual agents against HCV that target the HCV NS5B and NS5A proteins, respectively. Ledipasvir is a direct-acting antiviral agent that inhibits HCV RNA replication and virion production by targeting the HCV NS5A protein. The NS5A protein is thought to play multiple roles in

Table 1: Health Canada–Approved Therapies for the Treatment of Chronic Hepatitis C Infection		
Product	**Treatment indication**	**Mechanism of Action**
	established in patients infected with genotype 3.	mediating viral replication, host-cell interactions, and viral pathogenesis.
ombitasvir/paritaprevir/ ritonavir (fixed dose single tablet) and dasabuvir (HOLKIRA PAK)	Indicated for the treatment of adults with genotype 1 CHC, including those with compensated cirrhosis: • with ribavirin in non-cirrhotic patients with genotype 1a infection • without ribavirin in non-cirrhotic patients with genotype 1b infection • with ribavirin in patients with compensated cirrhosis. Safety and efficacy has not been established in other Genotypes.	HOLKIRA PAK combines three direct-acting HCV antiviral agents with distinct mechanisms of action, and non-overlapping resistance profiles, to target HCV at multiple steps in the viral lifecycle. Paritaprevir is an inhibitor of HCV NS3/4A protease, ombitasvir is an inhibitor of HCV NS5A which is essential for viral replication, and dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene, which is essential for replication of the viral genome. Inhibition of viral replication leads to a rapid decline of HCV viral load and clearing of HCV levels in the body. Ritonavir is not active against HCV rather it is a pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure (i.e., area under the curve).

CHC = chronic hepatitis C; DAA = direct-acting antiviral agent; HCV = hepatitis C virus; NS = non-structural protein; RNA = ribonucleic acid.

1.3 Policy Questions

There are three policy questions for this project, reflecting the information needs of federal, provincial and territorial public drug plans across Canada related to the treatments for CHC infection:

1. How should interferon-free DAA regimens be listed for reimbursement for CHC infection (Genotypes 1 to 6)?
2. Should reimbursement of regimens for CHC infection be guided by fibrosis staging and limited to fibrosis stages ≥ F2?
3. Should re-treatment with a DAA regimen be reimbursed for patients with CHC infection who fail to achieve SVR on another DAA regimen?

1.4 Research Questions

Five research questions were developed to address the aforementioned policy issues:

1. What is the comparative efficacy and safety of treatment regimens for patients with CHC infection (Genotypes 1 to 6) who are treatment-naive?

2. What is the comparative cost-effectiveness of treatment regimens for patients with CHC infection (Genotypes 1 to 4) who are treatment-naive?

3. What is the comparative efficacy and safety of treatment regimens for patients with CHC infection (Genotypes 1 to 6) who have relapsed or had a partial or null response to prior PR or DAA + PR or DAA-only therapy?
4. What is the comparative cost-effectiveness of treatment regimens for patients with CHC infection (Genotypes 1 to 4) who have relapsed or had a partial or null response to prior PR or DAA + PR or DAA-only therapy?[1]
5. For questions 1 to 4, how do the comparative efficacy, safety, and cost-effectiveness of treatment regimens vary across population subgroups based on fibrosis level (METAVIR score ≤ F1, F2, F3, or F4), cirrhosis stage (e.g., compensated versus decompensated), genotype subtype, post-liver transplant, baseline viral load, HIV/HCV coinfection, hepatitis B (HBV)/HCV coinfection, and tuberculosis (TB)/HCV coinfection?

This review report addresses the questions related to comparative efficacy and safety. Questions related to cost effectiveness are addressed in the accompanying Cost Effectiveness Analysis Report.

2 METHODS

This report is an update to CADTH's previous Therapeutic Review (14) on DAA agents for CHC genotype 1 infection published in October 2014, which addressed policy questions put forward to CADTH by publicly-funded drug plans. This review specifically expands the scope of the previous review to include HCV genotypes 2 to 6, as well as recently approved and emerging regimens.

A protocol and list of included studies was posted in April 2015, with stakeholder feedback sought on the latter. Both were vetted by clinical experts and methodologists.

The strategy for building and analyzing the evidence base for the treatment of CHC infection consisted of two fundamental steps. First, a broad systematic review of the available evidence in the published literature for the outcomes specified in the protocol was undertaken to update the previous Therapeutic Review literature search for genotype 1, and to identify all studies for genotypes 2 to 6. The systematic review followed a protocol written a priori and was conducted in line with the Cochrane Handbook for Systematic Reviews of Interventions.(22) Second, an network meta-analysis (NMA) was conducted comparing the available treatment regimens reporting outcomes of interest.

2.1 Population, Intervention, Comparator, Outcomes, Study Design (PICOs) Statement

The main regimens of interest for this review were those:

- Currently approved by Health Canada for the populations of interest in this review

[1] The decision to model cost-effectiveness only for HCV genotypes 1 to 4 was based on the anticipated availability of sufficient clinical data to inform the analysis. Results for cost-effectiveness research questions are reported elsewhere.

- Considered of clinical relevance based on inclusion in Canadian (1) or US clinical practice guidelines (2), or
- Considered to have a high likelihood of regulatory approval in Canada in the near future (i.e., within approximately 12 months) based upon information available to CADTH as of February 2015.

Some regimens other than those meeting the above criteria were also included in the review and NMA, either because they were felt to be of potential clinical importance during scoping, or because they were potentially beneficial for constructing more robust networks.

The population, intervention, comparator, outcome, and study design (PICOS) statement is outlined below in Table 2. Further details on regimens eligible for inclusion in this review, such as doses and treatment duration, are presented in Appendix A.

Table 2: PICOS and Study Eligibility Criteria

Population	Adult patients with confirmed:
	CHC infection (Genotypes 1 through 6)
Interventions and Comparators	Currently available:
	• pegylated interferon alfa combined with ribavirin (PR[a]) • boceprevir in combination with PR[a] • telaprevir in combination with PR[a] • simeprevir in combination with PR • sofosbuvir in combination with PR • sofosbuvir/ledipasvir with or without ribavirin • paritaprevir/ritonavir/ombitasvir in combination with dasabuvir, with or without ribavirin • sofosbuvir in combination with ribavirin • simeprevir in combination with sofosbuvir, with or without ribavirin • daclatasvir in combination with asunaprevir, with or without PR • daclatasvir in combination with sofosbuvir
	Emerging Treatments
	• daclatasvir in combination with asunaprevir and beclabuvir • grazoprevir in combination with elbasvir • sofosbuvir in combination with GS-5816 • paritaprevir/ritonavir in combination with ABT-530
Outcomes	Sustained virological response, relapse, quality of life, hepatic cirrhosis, hepatocellular carcinoma, liver transplants, mortality (all-cause, liver-related), serious adverse events, withdrawals due to adverse events, rash, fatigue, anemia, thrombocytopenia, pruritus, neutropenia, depression, suicidal ideation, flu-like symptoms.
Study Design	Published, randomized or non-randomized, controlled or uncontrolled, prospective interventional studies.
Exclusion Criteria	Studies will be excluded if they: are in languages other than English; are presented in abstract format; do not meet the aforementioned selection criteria; provide results of a qualitative study; are follow-up, extension, or observational studies. Duplicate publications, narrative reviews, conference abstracts, and editorials will also be excluded.

PR = pegylated interferon alfa combined with ribavirin
[a] Included in the analysis primarily as a comparator for other regimens

Note that some regimens containing PR require a lead-in period or are eligible for changes in the duration of PR therapy based on viral response (i.e., response-guided therapy [RGT]); the

rules for inclusion of such regimens were the same as in the original CADTH Therapeutic Review.(14) For patients with HIV coinfection or those who are treated following liver transplantation, dosing regimens other than those described in Appendix A were eligible for inclusion, given that potential drug interactions between antiretroviral and immunosuppressant agents may require dosage adjustments of HCV medications.
Older regimens for CHC infection (PR alone, boceprevir, telaprevir) may be of limited clinical significance, given the availability of newer regimens; telaprevir has in fact been discontinued from the Canadian market by the manufacturer. However, Health Canada–approved regimens containing these agents have been retained in the review and network meta-analyses for comparative purposes. Only randomized controlled trials (RCTs) of such regimens were eligible for inclusion. For all other regimens listed in Table 2, both RCTs and non-randomized interventional studies (including single-arm trials) were eligible for inclusion in the review. Observational studies such as cohort studies or reports describing experience from compassionate use programs were excluded. Uncontrolled trials of telaprevir or boceprevir plus PR regimens were also excluded from the review.

When a study met the inclusion criteria but included an intervention arm(s) with regimens that were not eligible for inclusion in the review, that arm(s) was excluded from the review and only arm(s) that included regimens eligible for inclusion were included in the review. Additional details regarding the eligible dosing inclusion criteria are listed in Appendix A. A detailed list of excluded study arms is presented in Appendix D.

It is important to note that this review updates a 2014 CADTH Therapeutic Review on DAAs for CHC genotype 1 infection.(14) Clinical reviewers re-screened the original literature search results for studies involving study populations in genotypes 2 to 6. The updated search results were screened for all genotypes (1 through 6).

2.2 Systematic Review

A systematic review of all available evidence in the published literature for the clinical outcomes specified in the protocol was conducted, following the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews of Interventions. (22)

2.2.1 Electronic Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy (Appendix B). This search updated a previous search from the 2014 CADTH Therapeutic Review on DAAs for CHC genotype 1 infection originally conducted on January 9, 2014.(14) The updated search incorporates several additional DAAs that were not included in the original report.

Published literature was identified by searching the following bibliographic databases on February 4, 2015: MEDLINE (1946-) with in-process records and daily updates via Ovid; Embase (1974-) via Ovid; Cochrane Central Register of Controlled Trials via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were telaprevir, boceprevir, sofosbuvir, simeprevir, ledipasvir, paritaprevir, ombitasvir, dasabuvir, daclatasvir, asunaprevir, grazoprevir, elbasvir, beclabuvir, GS-5816, ABT-530, Incivek, Incivo, Victrelis, SOVALDI, GALEXOS, Olysio, Daklinza, Sunvepra, Viekira, Viekirax, Exviera, Holkira and Harvoni.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not to be limited by publication date but was limited to English language results. Conference abstracts were excluded from the search results. Alerts were run monthly and regular search updates were performed on databases not providing alert services. The last alert from which studies were selected for inclusion in the review was run on May 1, 2015.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters: A Practical Search Tool for Evidence-Based Medicine checklist (23): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews and databases. Google and other Internet search engines were used to search for additional web-based materials. Searches were supplemented by reviewing the bibliographies of key papers and through contacting appropriate experts.

2.2.2 Eligibility/Study Selection

Studies were included if the PICOS criteria were satisfied. Selection eligibility criteria (Table 3) were applied to each title and abstract identified in the literature search by two independent review authors in a standardized manner. Any uncertainties were resolved by discussion and consensus with a third review author. Any study passing the selection criteria was obtained in full-text format. The eligibility criteria were then applied and a final decision made for inclusion.

2.2.3 Data Extraction and Management

All information was extracted using a standardized data abstraction form, which was developed, piloted and modified in advance for the purposes of this systematic review. Data extracted included:

- Study characteristics, key inclusion and exclusion criteria, and definitions where required
- Baseline patient characteristics, demographics, and treatment history
- Interventions evaluated, including dose and duration
- Efficacy and safety results for specified outcomes, and specifically: SVR at 12 and 24 weeks and safety outcomes for the longest reported treatment and follow-up period
- Type of analysis (intention-to-treat or per-protocol)
- Study withdrawals, and
- Study-level definitions of SVR, prior relapse, partial or null response (if standard definitions were not employed), and cirrhosis.

Data were extracted by a single review author and checked in their entirety for accuracy by a second independent reviewer. Any disagreements were resolved through discussion with a third study author until consensus was reached.

2.2.4 Risk of Bias Assessment

Quality assessment was performed by a single review author and checked by a second reviewer. Assessment of bias in comparative randomized studies was completed using the Cochrane Risk of Bias tool (Appendix H).(22)

When data were sufficient for appraisal, we evaluated the single-arm studies using criteria applicable for the evaluation of case series.(24)

When studies with single-arm study data were insufficient for appraisal with this tool, we extracted and investigated attrition rates to provide a rudimentary assessment of the risk of bias.

2.2.5 Definitions

The following definitions were applied in this review:

Cirrhosis: progressive scarring of liver tissue that may affect performance of treatment for CHC infection. Cirrhosis is typically biopsy-proven in clinical trials of therapies for CHC infection.

Decompensated cirrhosis: the presence of cirrhosis plus one or more complications including esophageal varices, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, or hepatocellular carcinoma.

Genotype: a classification of HCV based on genetic material in the RNA strands of the virus. There are six main genotypes, which are further divided into subtypes in some cases.

Interferon-ineligible: patients in whom interferon therapy is contraindicated due to such conditions as anemia, alcohol abuse, advanced or decompensated cirrhosis, or severe psychiatric disorder.

Interferon-intolerant: patients who discontinue interferon therapy prematurely due to side effects.

Sustained virologic response: absence of detectable HCV RNA, measured 12 to 24 weeks following the completion of treatment.

Relapse: recurrence of detectable viral RNA at some point after achieving an undetectable HCV viral load during treatment.

Null response: no reduction of at least 1 $\log_{10}$ in HCV RNA during prior treatment.

Partial response: greater than a 1 $\log_{10}$ reduction in HCV RNA during prior treatment, but never achieving undetectable viral RNA.

Treatment-naive: not previously treated for CHC infection.

Treatment-experienced: one or more previous attempts at treatment of CHC infection. This group may contain a mix of patients who relapsed, those with a partial response, and those with a null response to prior treatment.

METAVIR score: standardized measure of inflammation and fibrosis seen on liver biopsy. The fibrosis score ranges from 0 to 4. Patients with higher fibrosis scores are more likely to progress to cirrhosis and hepatocellular carcinoma and may warrant earlier treatment.

Fibrosis score:[2]

- F0 = no fibrosis
- F1 = portal fibrosis without septa
- F2 = portal fibrosis with few septa
- F3 = numerous septa without cirrhosis
- F4 = cirrhosis.

2.3 Data Synthesis

Included studies were classified based on study populations and relevant comparisons. Prior to quantitative pooling of study-specific outcomes, a thorough qualitative analysis was undertaken to assess clinical and methodological heterogeneity. Studies that were judged to be sufficiently similar in terms of patients, interventions, and study designs were pooled using indirect treatment comparisons. Where substantial heterogeneity was detected (in certain comparisons or subsets of studies) then narrative summaries of findings were reported.

The primary efficacy outcome is SVR at 12 weeks (SVR12; undetectable HCV RNA levels 12 weeks after the end of therapy). We considered SVR12 to be an acceptable surrogate for SVR24 (undetectable HCV RNA levels 24 weeks after the end of treatment).(25) If both SVR12 and SVR24 were reported, SVR24 was used in the analyses to incorporate the longest follow-up data. Where only SVR24 was reported (and not SVR12), it was used in the SVR12 week outcome. Separate analyses were performed for each genotype for SVR, and within each genotype, analyses were separated by subpopulations based on prior treatment experience with PR (with or without DAA) or DAA alone, as follows:

- Treatment-naive
- Treatment-experienced
- Treatment-experienced with prior relapse
- Treatment-experienced with prior partial response
- Treatment-experienced with prior null response.

Within each of these 5 subpopulations, analyses were further separated by the presence or absence of cirrhosis. The analyses for genotype 1 were further separated by genotype subtype 1a and 1b.

Additonal analyses were carried out within each subpopulation, as data permitted, to include emerging treatments. Data were sufficient to conduct supplemental analyses that included emerging treatments in the following subgroups:

- SVR12 — genotype 1 treatment-naive: all patients, genotype 1a, genotype 1b, patients with cirrhosis, patients without cirrhosis
- SVR12 — genotype 1 treatment-experienced: all patients, genotype 1a, genotype 1b, patients with cirrhosis, patients without cirrhosis
- SVR12 — genotype 4 treatment-naive: all patients
- Anemia, rash — all genotypes treatment-naive: all patients
- Anemia, rash — all genotypes, treatment-experienced: all patients.

[2] For the purposes of classifying patients into categories of cirrhotic or non-cirrhotic for data analyses where no other information on cirrhosis status was available, METAVIR scores were applied as follows: F0 to F3 = no cirrhosis and F4 = cirrhosis.

The following sensitivity analyses were also conducted:

- Genotype 1 treatment-naive patients without cirrhosis: Inclusion of the SOF8 + LDV8 treatment regimen which is indicated only for the patient group with a pre-treatment HCV RNA of less than 6 million IU/mL.
- Genotype 1 treatment-naive and -experienced patients with cirrhosis: Inclusion of the TURQUOISE II study data (26) for treatment regimen PAR/RIT12 + OMB12 + DAS12 + RBV12. This study was not included in the primary analyses as baseline characteristics were not reported separately by previous treatment experience. Inclusion of this study in the sensitivity analyses assumes equivalent baseline characteristics for treatment-naive and -experienced patients.

Genotype 3 treatment-naive, all patients, patients with cirrhosis and patients without cirrhosis: Inclusion of data from the BOSON study for SOF12 + PR12 and SOF24 + RBV24 treatment regimens.(27) he BOSON study was used in sensitivity analyses despite being reported only in abstract (Microsoft PowerPoint Presentation) format and presented in oral sessions at the 50th Annual Meeting of the European Association for the Study of the Liver (The International Liver Congress™ 2015) in Vienna, Austria. This decision was made in consultation with clinical experts who advised that this study presented data for a relatively large group (n = 592) of patients with genotype 2 and 3 CHC infection for the SOF + RBV for 16 or 24 weeks and SOF 12 + PR12 treatment regimens which had the potential to impact results from the NMA.No clinical differences in harms across genotypes were anticipated, hence data were pooled across all genotypes for depression, rash and anemia. Subpopulations based on treatment experience were considered in the analyses where data were sufficient.

For studies that enrolled mixed populations (i.e., treatment-naive and experienced patients or multiple genotypes), the analysis utilized specific subpopulations rather than the entire study population, where data permitted and were adequately reported.

Studies in liver transplant patients were analyzed separately due to the unique characteristics of this population with respect to disease prognosis.(28)

2.3.1 Assessment of Heterogeneity

Studies were assessed for both clinical and methodological diversity. Clinical diversity was assessed by checking that the patients, exposures, and settings were not so different across studies that combining them would be inappropriate. Methodological diversity was assessed by checking that the studies were similar in terms of study design and risk of bias.

Once satisfied that the studies were minimally diverse and that it made sense to pool them, an assessment of statistical heterogeneity was undertaken (e.g., by examining forest plots providing a visual sense of heterogeneity and the I^2 statistic indicating the presence of statistical heterogeneity). If the effects observed across studies were heterogeneous, and varied to a large extent (i.e., $I^2 > 50\%$), the results were again explored to assess whether the differences could be explained by some clinical or methodological feature.

2.3.2 Assessment of Reporting Biases

Reporting bias was assessed by constructing funnel plots, as well as using bias indicators (e.g., Egger, Harbold-Egger) for each outcome.

2.4 Bayesian Indirect Treatment Comparisons

As there were no head-to-head RCTs comparing the DAA regimens, we undertook indirect treatment comparisons to provide evidence to inform the research questions on comparative efficacy and safety of DAA treatments for CHC infection.

Bayesian NMAs were conducted for SVR12 and specific adverse events (i.e., rash, anemia, and depression) for both treatment-naive and treatment-experienced patients and for the key subgroups of interest. The choice of outcomes for NMA was based on the sufficiency of the data available to derive robust and consistent network models.(29-31) Treatment-experienced patients were further analyzed based on their response to prior PR treatment, specifically whether they experienced relapse, partial response, or null response.

A hierarchical approach was taken for data synthesis, with the base-case analyses limited to Health Canada–approved regimens, pre-NOC regimens submitted to CDR, and off-label included regimens consisting of drugs for which cost information was available at the time of the associated economic analysis (Table 3 'Currently Available' interventions). Other regimens for which there were the appropriate clinical data, but cost information was lacking for one or more constituent drugs, were included in secondary scenario analyses of all in-scope regimens (Table 2). All analyses of interventions involving peginterferon assume that 2a and 2b provide comparable efficacy.(22)

WinBUGS software version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) was used to conduct Bayesian NMA using a binomial likelihood model, which allows for the incorporation of multi-arm trials.(32) Pegylated interferon 2a or 2b plus ribavirin dual therapy administered for 48 weeks (PR48) was chosen as the reference group in the model for genotype 1. The reference groups for the comparisons involving genotypes 2 to 4 were defined based on consultation with clinical experts and availability of data and are shown in Table 3.

Table 3: Reference Group Treatments and Sources for PR (or Other Treatment) Used in the NMA

Genotype	Naive	Study	Experienced	Study
Genotype 1	PR48	—	PR48	—
Genotype 2	PR24	—	SOF12+RBV12	Included Study: Jacobson 2013 (33)
Genotype 3	PR48	Meta-analysis: Andruilli 2008 (34)	PR48	Observational Study: Poynard 2009 (35)
Genotype 4	PR48	Meta-analysis: Yee 2014 (36)	SOF12+RBV12	Included Study: Ruane 2014 (37)
Genotype 5 and 6	Data were insufficient for pooling			

Both fixed and random effects NMAs were conducted; assessment of model fit and choice of model was based on the assessment of the deviance information criterion (DIC) and comparison of residual deviance to number of unconstrained data points.(38)

Point estimates and 95% credible intervals for odds ratios (OR) were derived using Markov Chain Monte Carlo methods.(39) Relative risk and absolute risk for an outcome of interest were estimated based on the ORs and the mean proportion of patients that experienced the outcome in the reference group among included studies. The standard conversion of OR to relative risk was used (i.e., relative risk = $OR/[1+I_c (OR-1)]$) where I_c is the incidence of the event in the control group. Ideally, I_c is the "real" population event rate. Often this event rate is difficult to

determine and, indeed, our clinical experts were directly asked this question and could not provide this estimate. An alternative choice is to base this estimate on the "control event rate" that is determined as part of the estimation process of the NMA. The estimate and its credible intervals were discussed with the clinical experts in order to assess whether the estimates are in alignment with their clinical experience.

Vague priors, $N(0, 100^2)$, were assigned for basic parameters of the treatment effects in the model.(40) For the random-effect model, informative priors for the variance parameter were considered based on Turner et al.(41) Informative priors were deemed appropriate given that the networks had an insufficient number of studies to produce robust estimates of between-study variance and, thus, estimates would be dominated by a null prior. Continuity correction was also applied to adjust the zero events for safety outcome. For studies that reported 100% for SVR12, the SVR rate was reduced by one event for sample size (≥ 10) or 0.5 event for sample size (< 10) to avoid the computational issues, as suggested by clinical experts. To ensure convergence was reached, trace plots and the Brooks–Gelman–Rubin statistic were assessed.(32) Three chains were fit in WinBUGS for each analysis, with at least 20,000 iterations, and a burn-in of at least 20,000 iterations.(32, 42)

2.4.1 Special Consideration — Single-Arm Studies

Although it is ideal to use RCTs to evaluate treatment effects in study populations, CHC infection is a unique area in which other study designs have been permitted by regulators for the newer regimens. In this review, we considered interventional, single-arm studies (i.e., where there was no formal comparative control group included in the design and possibly an historical control cohort was used) or studies where only a single arm of the study fits the eligibility criteria. The NMA methodology was adjusted in order to incorporate the effect estimates from such single-arm evidence into the networks of treatments.

For single-arm studies, detailed patient baseline characteristics and comprehensive descriptions on the use of historical control cohorts were captured along with any patient characteristics provided for the historical cohort. No individual patient data were available for analyses, so it was not possible to use comparative effectiveness methods, such as the propensity scores weighting method. Instead, single-arm studies were incorporated into the NMA by creating a "virtual" study where a comparator arm matched for baseline patient characteristics was identified for the single arm.

Based on clinical experts' advice, comprehensive baseline characteristics including previous treatment experience, previous response type, METAVIR score, cirrhosis status, baseline viral load, liver transplant, IL28B, genotype, HIV, renal function, age and male sex were considered when matching a comparator arm from the randomized studies to an arm from single-arm studies. A summary score of baseline characteristics was derived for treatment-experienced and naive patients separately using a scoring scheme (Table 4). Based on discussions with the clinical experts, weights of 100%, 50%, and 10% were assigned to each baseline variable in the summary score according to the high, moderate and low clinical importance for matching on the baseline variable.

For each subgroup network analysis, a comparator arm from the included randomized studies with the closest summary score of baseline characteristics was selected for an arm from single-arm studies to create a virtual study.

The matching of comparator studies to single-arm studies was performed within each genotype, by treatment experience (i.e., naive/experienced) and by cirrhosis status (i.e., absent/present) where appropriate.

Table 4: Scoring Scheme for Baseline Characteristics

Importance	Variables	Treatment-Experienced	Treatment-Naive
HIGH (weight 100%)	**Previous treatment experience**	% of PR	--
	Previous response type	% null responders	--
	METAVIR score	[(%F0*0) + (%F1*1) + (%F2*2) + (%F3*3) + (%F4*4)]/4	[(%F0*0) + (%F1*1) + (%F2*2) + (%F3*3) + (%F4*4)]/4
	Cirrhotic	% cirrhotic	% cirrhotic
	Baseline viral load (log_{10})	Mean/7†	Mean/7†
	Liver transplant	Yes = 1, No = 0	Yes = 1, No = 0
	IL28B	[(%CC*0) + (%CT*1) + (%TT*2)]/2	[(%CC*0) + (%CT*1) + (%TT*2)]/2
	Genotype	% genotype 1a§	% genotype 1a§
MODERATE (weight 50%)	**HIV**	Yes = 1, No = 0	Yes = 1, No = 0
	Renal function*	Yes = 1, No = 0	Yes = 1, No = 0
LOW (weight 10%)	**Age**	Mean/standard deviation	Mean/standard deviation
	Sex	% male	% male

† Cut-off of 7 was used as ≥ 8 treated for hepatitis C.
§ For genotype 1, % of genotype 1a was considered in the summary score.
* Yes/No determination of whether renal function was good was based on the study reported renal function measures and cut-offs.

2.4.2 Heterogeneity

NMA requires studies to be sufficiently similar in order to pool their results. As a result, heterogeneity across trials in terms of patient characteristics, trial methodologies, and treatment protocols was carefully assessed and described narratively.

To further investigate heterogeneity, where warranted, subgroup analyses were considered, although limited data precluded some analyses specified *a priori* (e.g., stratifying network by METAVIR fibrosis scores of F4).

Subgroups were selected in advance to compare the treatment effect across subpopulations for which a plausible difference in efficacy or safety could be expected. Subgroup analyses were conducted within each genotype and for each treatment experience category, where appropriate. The following subpopulations of interest were specified a priori:

- genotype subtypes (e.g., genotype1a versus 1b)
- baseline viral load (using study-defined thresholds; data for the study-specified thresholds of 800,000 or 1,000,000 UI/mL were pooled for analyses)
- presence or absence of cirrhosis (if defined differently from METAVIR score F4)
- compensated cirrhosis, advanced compensated cirrhosis, and decompensated cirrhosis in patients with cirrhosis
- liver transplant recipients
- HIV, TB, or HBV coinfection.

There were discrepancies in the reporting of adverse events among the studies of treatment-naive patients. In some studies, adverse events were reported for the full treatment period, and for other studies, events were reported for only part of this period (first 12 weeks). In the previous Therapeutic Review (14), we explored the impact of these reporting differences through regression analysis and determined that there was no significant interaction between follow-up duration and adverse events. Thus, the NMA analyses of adverse events in the current Therapeutic Review included data from all studies, regardless of the reporting period.

2.4.3 Consistency

Inconsistency is a conflict between direct evidence and indirect evidence on a comparison between two treatments. Inconsistency was formally assessed by comparing the deviance and DIC statistics of the consistency and inconsistency models.(30, 31) To help identify the loops in which inconsistency was present, the posterior mean deviance of the individual data points in the inconsistency model was plotted against their posterior mean deviance in the consistency model.(30) Using the plots, loops in which inconsistency was present could be identified.

2.4.4 Model Diagnostics

Model diagnostics including trace plots and the Brooks–Gelman–Rubin statistic were examined to assess model convergence.(32, 40)

2.5 Calculation of Relative Risks

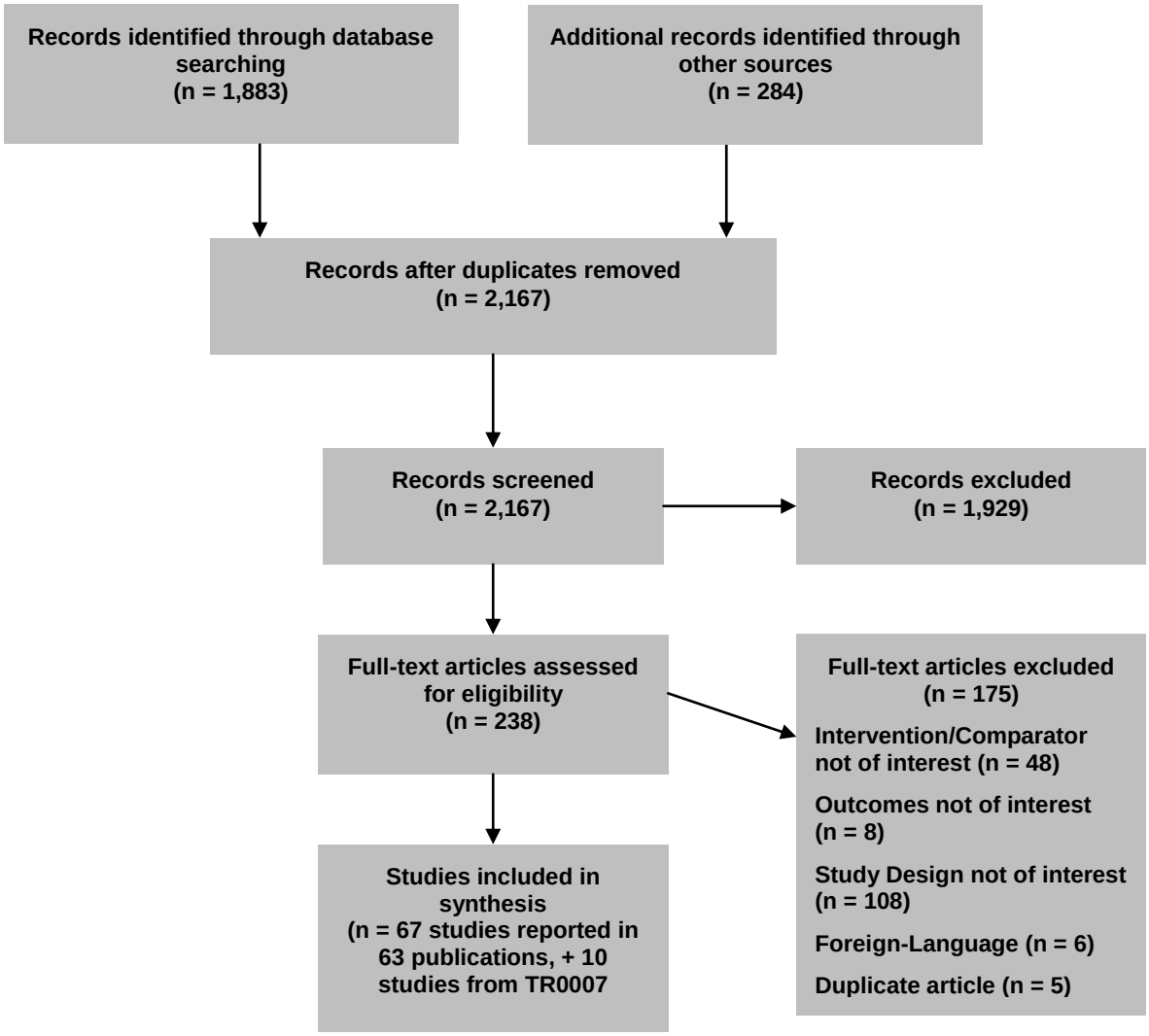
The probabilities of achieving SVR in the reference arms identified in Table 3 were generated directly from the NMA model. They were calculated by using the mean logarithmic (log) odds of the SVR rate in the reference arm averaged over all trials in which the reference treatment was used. Given this assumed baseline (log odds of SVR rate in the reference arm), the NMA model added the logarithmic odds ratios (LORs) to the baseline to estimate the absolute probability of achieving SVR in the DAA treatment arms. The relative risks between treatments were further calculated based on the absolute probability of achieving SVR in each treatment arm.

3 RESULTS: SYSTEMATIC REVIEW

3.1 Selection of Primary Studies

A total of 1,883 references were identified through the updated lerature search, including 1,078 references from the original CADTH Therapeutic Review retrieved for re-screening for genotypes 2 to 6. Following a detailed review of titles and abstracts, 240 potentially relevant articles were retrieved in full-text for further review. Of the 240 potentially relevant articles, a total of 67 publications describing 63 unique studies (26, 33, 37, 43-102) were selected for inclusion. The study selection process is described in detail in the PRISMA flowchart presented in Figure 1. Included studies are presented in Appendix C and excluded studies (with reasons) are presented in Appendix D. Ten studies were carried forward from a previous Therapeutic Review.(14)

Figure 1: PRISMA Flow Diagram



3.2 Characteristics of Included Studies

3.2.1 Trial Characteristics

Included studies predominantly reported on patients with CHC genotype 1 infection (26, 43-46, 49-53, 56, 58, 59, 61-64, 68-70, 72-74, 76, 77, 81-87, 89-92, 95-97, 102), or a mix of patients with genotype 1 and other genotypes (57, 60, 65, 66, 75, 88, 93, 94, 101) (Table 5). Eleven studies (33, 54, 65-67, 75, 80, 88, 93, 94, 100) reported on patients with CHC genotype 2 infection, 11 on genotype 3 (33, 54, 65-67, 75, 78, 88, 93, 94, 100), and eight on genotype 4 (37, 55, 57, 60, 66, 75, 88, 101), 2 on genotype 5 (60, 66), and three on genotype 6 (60, 66, 101). Only two studies included patients with CHC genotypes 5 (NEUTRINO (66)) and 6 (C-EDGE (101)) infection (among others). The ATOMIC study aimed to enroll patients with genotype infection 5 but no patients infected with this genotype were ultimately included (Table 6).(60)

Table 5: Summary of Study Availability by Genotype

Genotype	Studies Reporting (n)	References
Single Genotype Studies		
1	40	(26, 43-46, 49-53, 56, 58, 59, 61-64, 68-70, 72-74, 76, 77, 81-87, 89-92, 95-97, 102)
2	1	(80)
3	1	(78)
4	2	(37, 55)
5	0	--
6	0	--
Mixed Genotype Studies		
1 to 3	3	(65, 93, 94)
1 or 4	1	(57)
1,4,6	1	(101)
1,4 to 6	2	(60, 66)
2, 3	5	(33, 54, 66, 67, 100)
Additional Studies (Outcomes not Reported by Genotype)		
Mixed Genotype	8	(48, 71, 77, 79, 89, 97-99)

The included studies stratified by previous treatment experience and subgroups of patients with and without cirrhosis are described in Highlight Box 1.

Highlight Box 1: Number of Studies by Genotype, Treatment Experience and Cirrhosis Status

Genotype 1 treatment-naive = 35 studies (additional 5 emerging), treatment experienced = 26 studies (additional 2 emerging)
- Treatment-naive with cirrhosis = 14 studies, without cirrhosis = 29 studies
- Treatment-experienced with cirrhosis = 16 studies, without cirrhosis = 18 studies

Genotype 2 treatment-naive = 5 studies, treatment experienced = 5 studies
- Treatment-naive with cirrhosis = 5 studies, without cirrhosis = 6 studies
- Treatment-experienced with cirrhosis = 4 studies, without cirrhosis = 4 studies

Genotype 3 treatment-naive = 3 studies, treatment experienced = 6 studies
- Treatment-naive with cirrhosis = 3 studies, without cirrhosis = 3 studies
- Treatment-experienced with cirrhosis = 4 studies, without cirrhosis = 6 studies

Genotype 4 treatment-naive = 3 studies, treatment experienced = 2 studies
- Treatment-naive with cirrhosis = 2 studies, without cirrhosis = 2 studies
- Treatment-experienced with cirrhosis = 2 studies, without cirrhosis = 2 studies

Genotype 5 treatment-naive = 1 study, no studies in treatment experienced patients
- Treatment-naive with cirrhosis = 1 study, without cirrhosis = 1 study

Genotype 6 treatment-naive = 2 studies, treatment experienced = 1 study
- Treatment-naive with cirrhosis = unclear, without cirrhosis = unclear
- Treatment-experienced with cirrhosis = unclear, without cirrhosis = unclear

Post-liver transplant patients = 2 studies

A detailed description of the dosage regimens reported in the included studies has been included in Appendix G. A summary of studies reporting key interferon-regimens of interest is provided below in Table 6. All interferon-free regimens of interest, with the exception of DCV24 + SOF24 were represented in the included studies by at least one treatment population.

All included studies were conducted between 2013 and 2015 Table 7. Sample size ranged from 14 to 870 participants. Included study characteristics for regimens of interest for this Therapeutic Review are reported in Appendix E.

Fourteen of the 21 studies in treatment-naive patients were randomized studies as were 6 of 12 treatment-experienced studies and 14 of the 24 combined treatment-naive and -experienced studies (Appendix E). One study (HALLMARK-DUAL) randomized the treatment-naive arm of the study, but did not randomize the non-responders or treatment ineligible or intolerant arms.(73) None of the studies reporting patients post-liver transplant randomized patients to treatment.(47, 62) The remaining studies reported single-arm cohorts of the treatment interventions. Four studies of treatment-naive patients (44, 58, 66, 80) and four studies of treatment-experienced patients (33, 45, 80, 102) used historical controls in the study design.

Table 6: Summary of Studies Reporting Approved Interferon-Free Regimens				
Treatment	Studies Reporting (N)			
	Treatment-Naive	Treatment-Experienced	Combined Treatment Experience	Post-liver Transplant
SOF8 + LDV8	1	0	1	0
SOF12 + LDV12	4	2	2	0
SOF24 + LDV24	1	2	0	0
PAR/RIT12 + OMB12 + DAS12	1	0	0	0
PAR/RIT12 + OMB12 + DAS12 + RBV12	0	1	1	0
PAR/RIT24 + OMB24 + DAS24 + RBV24	0	0	1	0
DCV24 + ASU24	0	1	2	0
DCV24 + ASU24 + PR24	0	1	0	0
DCV12 + SOF12	0	2	0	0
DCV24 + SOF24	0	0	0	0

Studies were predominantly multinational, however 22 studies were conducted by single nation study groups (USA = 15 (44, 52, 55, 58, 59, 63, 65-68, 81-84, 93, 96), Japan = 3 (61, 74, 80), New Zealand = 2 (53, 54), France = 1 (46), Puerto Rico = 1 (88). Eleven studies specifically stated that they included Canadian centres.(26, 33, 51, 56, 57, 64, 66, 76, 86, 87, 90, 91) Four studies stated they were carried out in North America but did not specify Canadian centre involvement.(49, 50, 73, 102)

Table 7: Summary of Interventions Evaluated					
Intervention	Publications (n)	Individual Trials (n)	DB RCT (n)	Patients (n)	Publication Year
Included in the NMA					
Treatment-Naive					
PR48	6	6	4	342	2013–2014
SOF24 + RBV24	1	1	0	25	2013
SOF12 + LDV12	4	4	0	500	2014–2015
SOF24 + LDV24	1	1	0	217	2014
SOF8 + LDV8	1	1	0	215	2014
SOF8 + LDV8 + RBV8	1	1	0	216	2014
SOF12 + LDV12 + RBV12	1	1	0	217	2014
SOF24 + LDV24 + RBV24	1	1	0	217	2014
PAR/RIT12 + OMB12 + DAS12	1	1	0	209	2014
PAR/RIT12 + OMB12 + DAS12 + RBV12	2	2	1	577	2014
SOF12 + PR12	2	2	0	379	2013
SIM12 + PR24-48 RGT	2	2	2	521	2014
SOF12 + RBV12	1	1	0	256	2013
PR24	1	1	0	243	2013
Studies From TR0007					
BOCEPREVIR 800 MG EVERY 8 HOURS	1	1	1	1,097	2011
TELAPREVIR 750 MG EVERY 8 HOURS OR 1,125 MG EVERY 12 HOURS	3	3	1	1,989	2011–2014

Table 7: Summary of Interventions Evaluated					
Intervention	**Publications (n)**	**Individual Trials (n)**	**DB RCT (n)**	**Patients (n)**	**Publication Year**
SIMEPREVIR 150 MG DAILY	**1**	**1**	**1**	**386**	**2013**
Treatment-Experienced					
SOF12 + LDV12	2	2	0	123	2014
SOF24 + LDV24	2	2	0	187	2014–2015
SOF12 + LDV12 + RBV12[a]	3	3	0	239	2014–2015
SOF24 + LDV24 + RBV24[a]	1	1	0	111	2014
PAR/RIT12 + OMB12 + DAS12	1	1	0	91	2014
PAR/RIT12 + OMB12 + DAS12 + RBV12	1	1	1	297	2014
DCV24 + ASU24	1	1	0	20	2014
DCV24 + ASU24 + PR24	2	2	0	419	2014–2015
SOF12 + PR12	2	2	0	127	2014–2015
SIM12 + PR48	1	1	0	379	2015
STUDIES FROM TR0007					
BOCEPREVIR 800 MG EVERY 8 HOURS	1	1	1	403	2011
TELAPREVIR 750 MG EVERY 8 HOURS	1	1	1	662	2011
SIMEPREVIR 150 MG DAILY	2	2	2	855	2014
TREATMENT-Combined					
SOF24 + RBV24	4	4	0	689	2014–2015
SIM12 + SOF12	2	2	0	76	2014–2015
SOF12 + LDV12	2	2	0	209	2014–2015
SOF8 + LDV8	1	1	0	20	2014
SOF8 + LDV8 + RBV8[a]	1	1	0	21	2014
SOF12 + LDV12 + RBV12[a]	3	3	0	234	2014–2015
PAR/RIT12 + OMB12 + DAS12 + RBV12	1	1	0	38	2015
DCV24 + ASU24	2	2	1	867	2014
DCV12 + SOF12	2	2	0	193	2014–2015
SOF12 + PR12	2	2	0	42	2013–2015
SIM12 + PR24-48 RGT	1	1	0	68	2014
SIM12 + PR48	1	1	0	38	2014
SOF12 + RBV12	7	7	1	457	2013–2015
Not Included in the NMA[b]					
Treatment-Naive					
SOF12 + PR12	2	2	0	48	2013–2015
GRA12 + ELB12	1	1	1	316	2015
DCV12 + ASU12 + BEC12 (75mg BID)	1	1	0	11	2015
DCV12 + ASU12 + BEC12 (150mg BID)	1	1	0	10	2015
Studies FROM TR0007					
TELAPREVIR 750 MG EVERY 8 HOURS	1	1	0	540	2011
Treatment-Combined					
PAR/RIT12 + OMB12 + DAS12 + RBV12	2	2	0	239	2014–2015
PAR/RIT24 + OMB24 + DAS24 + RBV24	1	1	0	172	2014

Table 7: Summary of Interventions Evaluated					
Intervention	**Publications (n)**	**Individual Trials (n)**	**DB RCT (n)**	**Patients (n)**	**Publication Year**
SOF12 + RBV12	**1**	**1**	**1**	**207**	**2013**
Post-Liver Transplant					
SOF24 + RBV24	1[c]	1	0	40	2015
PAR/RIT24 + OMB24 + DAS24 + RBV24	1	1	0	34	2014

DB = double blind, NMA = network meta-analysis, PR = pegylated interferon plus ribavirin.
[a]Total number of publications does not include the US Food and Drug Administration or European Medicines Agency reports (three on boceprevir, three on telaprevir, three on simeprevir, and three on sofosbuvir).
[b]Includes all patients enrolled in the included studies, including regimens with duration or dose not aligned with the study protocol. Not all patients were included in the NMA.
[c]Data not provided by treatment status.
Note: Interventions listed in this table were selected based on prioritized reporting of regimens by CADTH.

The following studies were not included in the base-case analysis for SVR12 because they involved emerging treatments:

Table 8: Studies Not Included in the Base-Case Analysis
Treatment-Naive
Hassanein et al. 2015 (55)
Lawitz et al. 2014 C-WORTHY (64)
Muir et al. 2015 UNITY-2 (76)
Poordad et al. 2015 UNITY-1 (87)
Sulkowski et al. 2014 C-WORTHY (90)
Zeuzem et al., 2015 C-EDGE (101)
Treatment-Experienced
Forns et al. 2015 C-SALVAGE (52)
Lawitz et al. 2014 C-WORTHY (64)
Muir et al. 2015 UNITY-2 (76)
Poordad et al. et al. 2015 UNITY-1 (87)

3.2.2 Patient Characteristics

Patient characteristics are described in detail in Appendix E.

Enrolled patients were adults aged 18 and over and the proportion of male participants was generally much higher than 50% (range 28% to 100%).

Patients enrolled in the studies of treatment-naive patients were mostly non-cirrhotic (range 78% to 100%) when reported. In the studies of treatment-experienced populations, patients with cirrhosis were included in proportions ranging from 0% to 100%. SIRIUS (experienced only)(46), UNITY-2 (naive and experienced)(76), Pearlman (naive and experienced)(84), C-WORTHY (naive and experienced)(64, 90) and TURQUOISE II (naive and experienced)(26) were the only studies to report close to 100% of included patients had cirrhosis. In patients with cirrhosis, data was generally limited to the presence or absence of cirrhosis either as specified by study authors, or as reported in METAVIR scores of F0 to F3 (non-cirrhotic) and F4 (cirrhotic). Studies reporting combined fibrosis scores of F3/F4 were excluded from the analyses.(49, 95) In

patients with cirrhosis, data were not reported by advanced compensated cirrhosis or early compensated cirrhosis. All studies excluded patients with decompensated cirrhosis.

Baseline viral load, when reported, ranged from 5.6 to 6.8 international units per millilitre (IU/mL) on average.

No studies of patients with hepatitis B virus (HBV) or tuberculosis (TB) coinfection met the inclusion criteria for the systematic review. In general, coinfection with HBV or TB was an exclusion criteria in many of the included studies. Patients with HIV coinfection were included in four studies of treatment-naive patients and three with combined treatment-naive and -experienced patients.(75, 83, 88, 90, 91, 94, 95) No patients with HIV coinfection were included in solely treatment-experienced studies, or in those reporting outcomes for patients post-liver transplant.

Previous treatment experience in the included study populations was predominantly with PR, with few studies reporting treatment experience with a DAA plus PR (43, 46, 83, 85, 96) or with a DAA alone (96). Fifteen studies reported mixed previous treatment experience for enrolled patients, including PR, PR plus DAA and/or DAA alone; however, proportions were not reported individually by genotype.(33, 37, 47, 53, 73, 76, 85, 86, 96, 100) Only one study reported on patients with interferon-free DAA experience (2%).(96)

3.3 Quality Assessment of Included Studies

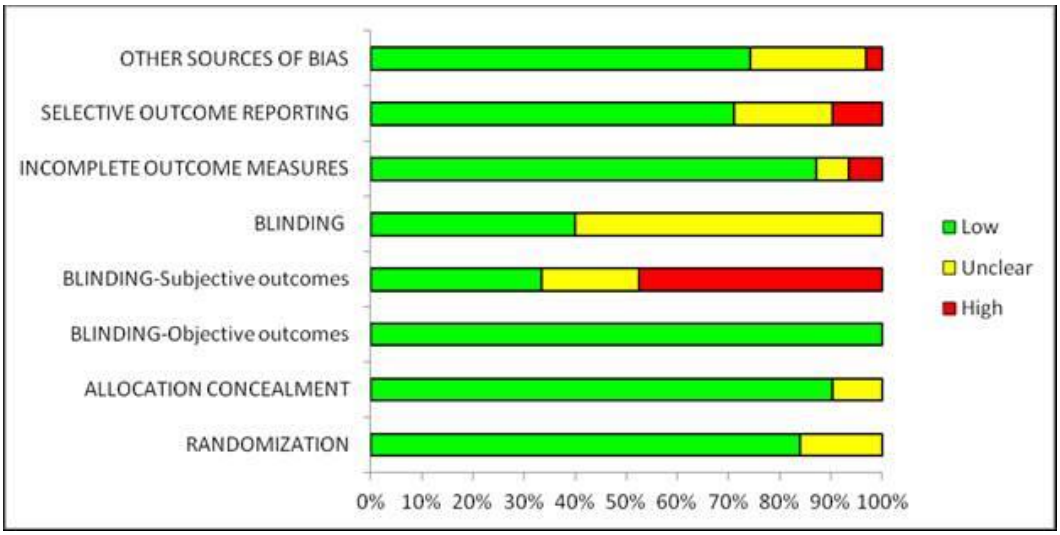
The details of the quality assessment for the 77 included studies are provided in Appendix H.(26, 33, 37, 43-112)

3.3.1 Randomized Studies

Among the 77 included studies, there were 31 randomized and comparative studies (26, 33, 37, 43-46, 50, 51, 53-56, 64, 65, 69, 70, 72-74, 76, 82, 84, 87, 90-93, 101, 102), including 10 RCTs carried forward from the previous review.(103-112) The remaining studies involved single treatment arms. There were 14, 8, and 9 treatment-naive, treatment-experienced, and combined treatment-naive and experienced studies, respectively.

In general, the included randomized studies were of adequate quality with respect to all domains of quality assessment (Figure 2). Most of the studies used an interactive web- or voice-response system or central randomization to perform randomization and allocation concealment, although eight trials claimed to be a RCT but did not provide the approach. In the current review, we assessed the risk of bias in blinding domain for newly identified studies separately for objective and subjective outcomes. Regardless of the method of blinding, 21 studies were considered to be of low risk of bias for the objective outcomes, 7 of which also provided the blinding approach for subjective outcomes. For the 10 studies carried forward from the previous review, 4 were judged to have a low risk of bias in the blinding domain as a whole. Twenty-seven trials were of low risk of bias in the domain of incomplete outcome measures, given that the overall completion rate exceeded 80% and that the number and reasons of early discontinuation were balanced across trial arms. When comparing the reported outcomes of the published article and those in the corresponding protocol, 22 trials were likely free of selective outcome reporting bias; 9 studies which either did not report certain outcomes or wrongly reported primary or secondary outcomes were considered at unclear and high risk of bias, respectively. Except for the above assessment domains, 8 studies were judged to respectively have unclear and high risk of bias given the other concerns rooted in study design or statistical issues.

Figure 2: Summary of the Risk of Bias Assessments for the Randomized Controlled Trials



3.3.2 Single-Arm/Cohort Studies

In an RCT, a key purpose of randomization is to ensure that the populations in the treatment arms being compared are as similar as possible on a number of baseline characteristics, so that any differences in response between groups at the end of study can be attributed solely to the interventions being compared. Many of the included studies (n = 30) evaluated interventions of interest in single groups, or cohorts, of study participants with either no comparative control, or employed comparisons to historical control populations (n = 12). When there is no randomization, and no control, there is little information available to confirm assessment of how similar the populations being compared truly are comparable. When the control population was enrolled at a different time, for a different purpose from that of the study drug, further comparability issues are raised and there is potential for confounding by variables we are unable to control for post-hoc. Therefore, many potential confounding variables have not been controlled for in the study design, and rarely were they controlled for in the analysis through statistical means.

For the current review, the quality assessment for single-armed studies was conducted on the attrition rates. Three important sources of bias are allocation, blinding and attrition. As allocation and blinding in these studies could not be evaluated because of their design, we chose to evaluate attrition following consultation with clinical experts. Patient attrition can bias outcomes if patients with missing outcome data are excluded from the analysis and have less favourable results than others. Further, attrition is the only criteria that be could consistently identified and evaluated across studies. We examined rates of attrition by study, across treatment regimens and examined these rates in context with the results to identify areas of concern.

Among the 30 included single-armed studies, there were 10, 7 and 13 treatment-naive, treatment-experienced, and treatment-naive and -experienced studies, respectively. In the 10 treatment-naive studies, the attrition rates of 0 to 17.4% were reported for 6 designed single-armed studies; and 0 to 7.7% for 4 single arms created from RCTs. In the seven treatment-experienced studies, the attrition rates of 0 to 2.5% were reported for five designed single-armed. The remaining two single arms created from RCTs reported 0% or no related information. In the 13 combined studies, the attrition rates of 0 to 24.3% were reported for 9

designed single-armed studies and 0 to 47.6% for 4 single arms created from RCTs. Please refer to Table 9 for details.

Table 9: Summary of Attrition Rates for the Single-Arm Studies	
Author, Year, Study Name (if Applicable)	**Attrition Rate**
Treatment-Naive (N = 10)	
Feld et al., 2014 SAPPHIRE-I (50)	2.7%
Ferenci et al., 2014 PEARL-III (51)	0.5%
Ferenci et al., 2014 PEARL-IV (51)	0.0%
Kohli et al., 2015 (58)	0.0%
Kowdley et al., 2013 ATOMIC (60)	7.7%
Lawitz et al., 2013 NEUTRINO(66)	11.0%
Lawitz et al., 2013 (65)	4.0%
Osinusi et al., 2013 SPARE-1(82)	10.0%
Osinusi et al., 2015 (83)	2.0%
Rodriguez-Torres et al., 2015 (88)	17.4%
Treatment-Experienced (N = 7)	
Andreone et al., 2014 PEARL-II (45)	0.0%
Jensen et al., 2015 HALLMARK-QUAD (57)	0.3%
Lawitz et al., 2014 (67)	NR
Lok et al., 2014 (70)	DUAL A2: NR DUAL B2: NR
Osinusi et al., 2014 SYNERGY (81)	0.0%
Pol S et al., 2015 (85)	0.0%
Wyles et al., 2015 (96)	0.0%
Combined Treatment-Experienced (N = 13)	
Dieterich et al., 2014 (49)	8.5%
Gane et al., 2013 ELECTRON (54)	0.0%
Gane et al., 2014 ELECTRON (53)	0.0%
Jacobson et al., 2013 FUSION (33)	47.6%
Kumada et al., 2014 (61)	14.3%
Lalezari et al. et al., 2015 (63)	2.6%
Manns et al., 2014 HALLMARK-DUAL (73)	1.7% for IFN ineligible/intolerant patients; 0.5% for naive patients: 0.0% for exp. Patients
Molina et al., 2015 PHOTON-2 (75)	1.5%
Nelson D. et al., Accepted 2015 ALLY-3 (AI444-218) (78)	NR
Omata M et al., 2014 (80)	0.0%
Sulkowski et al., 2015 TURQUOISE-I-1a (92)	3.2%
Sulkowski et al., 2014 (93)	24.3% for naive pts with G1 with 24-wk trt; 11.8% for exp pts with G3 with 24-wk trt; 19.2% for naive pts with G2 with 12-wk trt
Sulkowski et al., 2014 (94)	0.0%
TREATMENT EMEREGENT (N = 3)	
Zeuzem et al., 2015 C-EDGE (101)	0.90%
Forns et al., 2015 C-SALVAGE (52)	2.5%
Poordad et al. et al., 2015 UNITY-1 (86)	NR

4 RESULTS: EFFICACY — SUSTAINED VIROLOGIC RESPONSE AT 12 WEEKS

4.1 Genotype 1

NMAs were conducted for a single efficacy outcome, SVR at 12 weeks. The choice of this outcome for NMA was based on clinical relevance, and the sufficiency of the data available to derive robust and consistent network models. Patient populations were analyzed according to treatment experience (naive or experienced) and then by subgroups within each (e.g., cirrhotic, non-cirrhotic). For each patient group, the relative risks based on the odds ratios from the NMA are provided comparing each DAA treatment to PR48. Results for select head-to-head comparisons of the DAA treatment regimens are also presented. A full listing of the random effects model results, as well as model diagnostics for the fixed and random effects models,is available in Appendix I along with estimated relative risks and absolute risks. Results from additional sensitivity analyses are also discussed in context with the relevant patient populations. Full NMA results for the sensitivity analyses are available in Appendix K.

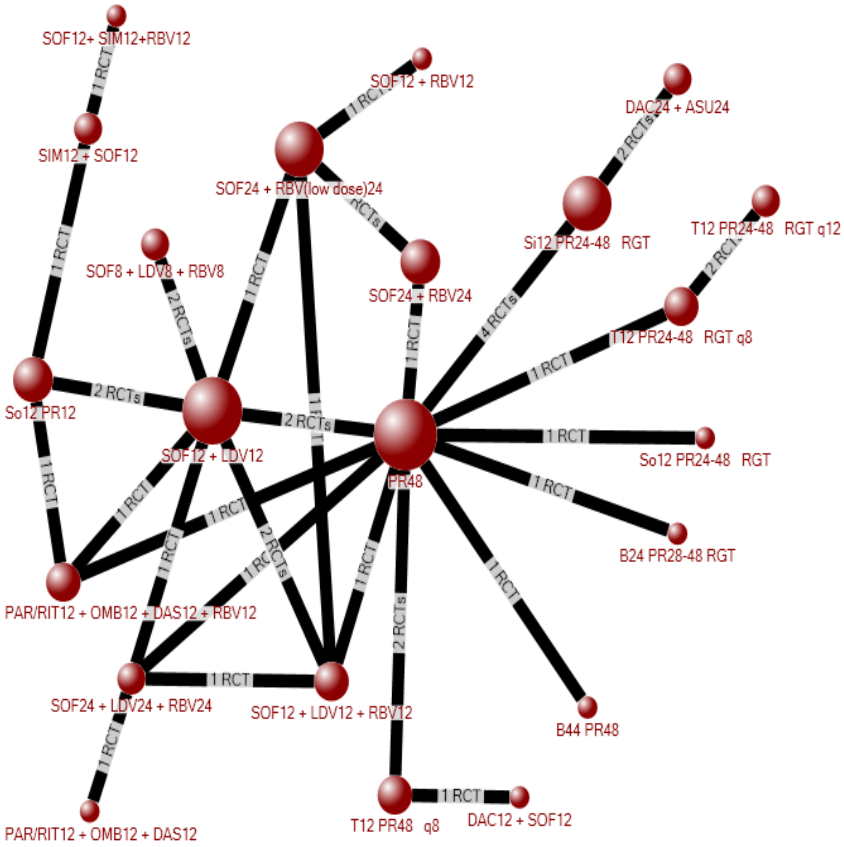
4.1.1 Treatment-Naive Patients

a) All Patients

The evidence network for SVR12 in treatment-naive genotype 1 patients included 35 studies (44, 49-51, 53, 54, 56, 58-61, 63, 65, 66, 68, 69, 72-75, 82-84, 91, 93-95) and a total of 6,766 participants (Figure 3). Overall, 22 different treatment regimens were considered, providing for 20 direct treatment comparisons (based on one 3-arm study and 17 2-arm studies), and 17 treatment estimates (based on 17 single-arm studies). Evidence that could be incorporated in the NMA was available for all regimens of interest for treatment-naive patients with genotype 1 infection except for DCV + ASU + PR and DCV24 + SOF24. It should be noted that PAR/RIT12 + OMB12 + DAS12 is only indicated in Canada, and recommended by treatment guidelines, for patients with genotype 1b infection without cirrhosis (i.e., addition of RBV is recommended for all other genotype 1 populations using PAR/RIT12 + OMB12 + DAS 12). SOF8 + LDV8 was not included in the base-case analysis of treatment-naive patients as it is only indicated in Canada for patients with baseline HCV RNA < 6 million IU/mL, based on post-hoc subgroup analyses showing higher relapse rates among patients with higher viral loads.

The NMA based on this evidence network was consistent (Appendix I).The rate of SVR12 for the reference treatment PR48 was 0.52 (95% CrI 0.47 to 0.57).

Figure 3: SVR Genotype 1 Patients Treatment-Naive: Evidence Network



The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in Table 10. Compared with PR48, all of the DAA treatment strategies currently approved in Canada or recommended by North American guidelines, with the exception of SIM12 + SOF12, significantly improved SVR in genotype 1 treatment-naive patients (RR range 1.48 to 1.86).

When the individual DAA treatment strategies were compared head-to-head:

- SOF12 + LDV12 and PAR/RIT12 + OMB12 + DAS12 ± RBV12 significantly improved SVR compared to SOF24 + RBV24 (which is only recommended by the product monograph in genotype 1 for interferon-ineligible patients undergoing treatment with SOF).
- SOF12 + LDV12 significantly improved SVR compared to SOF12 + PR12, SIM12 + PR24-48 RGT and DCV24 + ASU24.
- PAR/RIT12 + OMB12 + DAS12 + RBV12 significantly improved SVR over SOF12 + PR12, SIM12 + PR24-48 RGT and DCV24 + ASU24.
- DCV24 + ASU24 significantly improved SVR over SIM12 + PR24-48 RGT.

Table 10: SVR Genotype 1 Patients Treatment-Naive: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF24 + RBV24	PR48	1.48 (1.01,1.82)
SIM12 + SOF12		1.74 (0.98,2.01)
SOF12 + LDV12		1.86 (1.69,2.05)

Table 10: SVR Genotype 1 Patients Treatment-Naive: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF12 + PR12		1.59 (1.19,1.86)
SIM12 + PR24-48 RGT		1.51 (1.34,1.69)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.85 (1.68,2.05)
DCV24 + ASU24		1.65 (1.44,1.86)
DCV12 + SOF12		1.85 (1.38,2.08)
PAR/RIT12 + OMB12 + DAS12		1.86 (1.55,2.07)
SIM12 + SOF12	SOF24 + RBV24	1.15 (0.66,1.73)
SOF12 + LDV12		1.25 (1.05,1.83)
SOF12 + PR12		1.06 (0.80,1.55)
SIM12 + PR24-48 RGT		1.02 (0.83,1.51)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.24 (1.05,1.83)
DCV24 + ASU24		1.11 (0.90,1.65)
DCV12 + SOF12		1.24 (0.90,1.84)
PAR/RIT12 + OMB12 + DAS12		1.25 (1.00,1.83)
SOF12 + LDV12	SIM12 + SOF12	1.06 (0.96,1.89)
SOF12 + PR12		0.92 (0.70,1.52)
SIM12 + PR24-48 RGT		0.87 (0.75,1.56)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.06 (0.95,1.88)
DCV24 + ASU24		0.95 (0.81,1.71)
DCV12 + SOF12		1.05 (0.80,1.88)
PAR/RIT12 + OMB12 + DAS12		1.06 (0.88,1.93)
SOF12 + PR12	SOF12 + LDV12	0.86 (0.66,0.95)
SIM12 + PR24-48 RGT		0.82 (0.74,0.88)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.00 (0.96,1.03)
DCV24 + ASU24		0.89 (0.79,0.96)
DCV12 + SOF12		1.00 (0.77,1.06)
PAR/RIT12 + OMB12 + DAS12		1.01 (0.83,1.06)
SIM12 + PR24-48 RGT	SOF12 + PR12	0.95 (0.81,1.28)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.16 (1.05,1.51)
DCV24 + ASU24		1.04 (0.87,1.39)
DCV12 + SOF12		1.15 (0.90,1.55)
PAR/RIT12 + OMB12 + DAS12		1.16 (0.96,1.55)
PAR/RIT12 + OMB12 + DAS12 + RBV12	SIM12 + PR24-48 RGT	1.22 (1.12,1.36)
DCV24 + ASU24		1.09 (1.01,1.18)
DCV12 + SOF12		1.22 (0.92,1.37)
PAR/RIT12 + OMB12 + DAS12		1.23 (1.01,1.37)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.90 (0.79,0.98)
DCV12 + SOF12		1.00 (0.77,1.07)

Table 10: SVR Genotype 1 Patients Treatment-Naive: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
PAR/RIT12 + OMB12 + DAS12		1.01 (0.83,1.07)
DCV12 + SOF12	DCV24 + ASU24	1.12 (0.85,1.27)
PAR/RIT12 + OMB12 + DAS12		1.12 (0.92,1.27)
PAR/RIT12 + OMB12 + DAS12	DCV12 + SOF12	1.00 (0.84,1.31)
Random-Effect Model	Residual Deviance	62.51 vs. 72 data points
	Deviance Information Criteria	385.205
Fixed-Effect Model	Residual Deviance	63.06 vs. 72 data points
	Deviance Information Criteria	384.588

Emerging Treatments

When emerging treatments were added to the network of genotype 1 treatment-naive patients, a total of 1053 additional patients reported in 6 studies (64, 76, 86, 90, 101) were included in the NMA. Nine new treatments were added to the evidence network. The rate of SVR12 for the reference treatment PR48 was 0.53 (95% CrI 0.48 to 0.58).

The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix K.

Compared with PR48, the emerging treatments GRA12+ELB12, GRA12+ELB12+RBV12, DCV12 + ASU12 + BEC12 + RBV12, DCV12 + ASU12 + BEC12, GRA12 + ELB12 (50mg QD), GRA12 + ELB12 (50mg QD) + RBV12, and GRA18 + ELB18 (50mg QD) + RBV18 signficantly improved SVR12. There was no significant difference in SVR12 compared with PR48 for the emerging treatments GRA18 + ELB18 (50mg QD) or GRA8 + ELB8 (50mg QD) + RBV8.

b) Genotype 1a

The evidence network for SVR12 in treatment-naive genotype 1a patients included 18 studies (44, 49-51, 56, 59, 66, 72, 75, 82, 84, 91, 94, 95, 104, 107, 109) and a total of 3,594 participants. Overall, 16 treatment regimens were considered, providing for 17 direct treatment comparisons (based on one four-arm study and 11 two-arm studies), and six treatment estimates (based on six single-arm studies). The NMA based on this evidence network was consistent (Appendix I). The rate of SVR12 for the reference treatment PR48 was 0.39 (95% CrI 0.31 to 0.47).

The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in Table 11. Compared with PR48, three treatment strategies significantly improved SVR in genotype 1a treatment-naive patients (SOF12 + LDV12 and PAR/RIT12 + OMB12 + DAS12 + RBV12, as well as SIM12 + PR24-48 RGT).

When the individual DAA treatment strategies were compared head-to-head:

- SOF12 + LDV12 significantly improved SVR compared to SOF12 + PR12 and SIM12 + PR24-48 RGT.
- PAR/RIT12 + OMB12 + DAS12 + RBV12 significantly improved SVR compared to SOF12 + PR12.

Table 11: SVR Genotype 1a Patients Treatment-Naive: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	PR48	2.05 (0.89,2.95)
SIM12 + SOF12		2.06 (0.38,2.93)
SOF12 + LDV12		2.48 (1.96,3.12)
SOF12 + PR12		1.70 (0.36,2.64)
SIM12 + PR24-48 RGT		1.83 (1.35,2.40)
PAR/RIT12 + OMB12 + DAS12 + RBV12		2.47 (1.87,3.13)
SIM12 + SOF12	SOF24 + RBV24	1.01 (0.19,2.20)
SOF12 + LDV12		1.20 (0.95,2.57)
SOF12 + PR12		0.84 (0.18,1.88)
SIM12 + PR24-48 RGT		0.89 (0.62,1.99)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.19 (0.92,2.55)
SOF12 + LDV12	SIM12 + SOF12	1.18 (0.97,6.26)
SOF12 + PR12		0.87 (0.29,2.56)
SIM12 + PR24-48 RGT		0.88 (0.62,4.89)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.17 (0.94,6.16)
SOF12 + PR12	SOF12 + LDV12	0.69 (0.16,0.95)
SIM12 + PR24-48 RGT		0.74 (0.56,0.96)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.00 (0.86,1.08)
SIM12 + PR24-48 RGT	SOF12 + PR12	1.07 (0.69,5.20)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.44 (1.03,6.37)
PAR/RIT12 + OMB12 + DAS12 + RBV12	SIM12 + PR24-48 RGT	1.35 (0.99,1.77)
Random-Effect Model	Residual Deviance	38.18 vs. 38 data points
	Deviance Information Criteria	209.769
Fixed-Effect Model	Residual Deviance	38.94 vs. 38 data points
	Deviance Information Criteria	209.12

Emerging Treatments

When emerging treatments were added to the network of genotype 1a treatment-naive patients, a total of 1053 additional patients reported in 5 studies (76, 86, 90, 101) were included in the NMA. Nine new treatments were added to the evidence network. The rate of SVR12 for the reference treatment PR48 was 0.37 (95% CrI 0.30 to 0.45).

The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix I. Compared with PR48, the emerging treatments GRA12 + ELB12, DCV12 + ASU12 + BEC12 + RBV1, DCV12 + ASU12 + BEC12, and GRA12 + ELB12 (50mg QD) significantly improved SVR.

c) Genotype 1b

The evidence network for SVR12 in treatment-naive genotype 1b patients included 20 studies (44, 49-51, 56, 59, 61, 66, 72, 74, 75, 82, 84, 91, 94, 95, 104, 107, 109) and a total of 2,379 participants. Overall, 16 different treatment regimens were considered, providing for 14 direct treatment comparisons (based on one 4-arm study and eight 2-arm studies), and 11 treatment estimates (based on 11 single-arm studies). The NMA based on this evidence network was consistent (Appendix I). The rate of SVR12 for the reference treatment PR48 was 0.52 (95% CrI 0.42 to 0.63).

The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented Table 12. Compared with PR48, three treatment strategies significantly improved SVR in genotype 1b treatment-naive patients (SOF12 + LDV12, PAR/RIT12 + OMB12 + DAS12 and DCV24 +ASU24). There was no statistically significant difference between SOF24 + RBV24, SOF12+PR12 or SIM12 + PR24-48RGT and PR48.

When the individual DAA treatment strategies were compared head-to-head:

- SOF12 + LDV12 significantly improved SVR compared to SOF12+PR12, SIM12 + PR24-48 RGT and DCV24 +ASU24.
- No differences were found when SOF12 + LDV12 was compared to PAR/RIT12 + OMB12 + DAS12.
- DCV24 + ASU24 significantly improved SVR compared to SIM12 + PR24-48 RGT.

Table 12: SVR Genotype 1b Patients Treatment-Naive: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF24 + RBV24	PR48	1.61 (0.45,2.21)
SOF12 + LDV12		1.89 (1.58,2.34)
SIM12 + PR24-48 RGT		1.63 (1.39,1.96)
PAR/RIT12 + OMB12 + DAS12		1.86 (1.43,2.33)
DCV24 + ASU24		1.76 (1.48,2.13)
SOF12 + PR12		1.56 (0.56,2.09)
SOF12 + LDV12	SOF24 + RBV24	1.16 (0.99,3.89)
SIM12 + PR24-48 RGT		1.00 (0.80,3.42)
PAR/RIT12 + OMB12 + DAS12		1.14 (0.90,3.79)
DCV24 + ASU24		1.08 (0.89,3.67)
SOF12 + PR12		0.99 (0.37,3.00)
SIM12 + PR24-48 RGT	SOF12 + LDV12	0.86 (0.76,0.93)
PAR/RIT12 + OMB12 + DAS12		1.00 (0.78,1.04)
DCV24 + ASU24		0.93 (0.85,0.98)
SOF12 + PR12		0.84 (0.30,0.99)
PAR/RIT12 + OMB12 + DAS12	SIM12 + PR24-48 RGT	1.15 (0.91,1.30)
DCV24 + ASU24		1.08 (1.00,1.19)
SOF12 + PR12		0.97 (0.34,1.20)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12	0.94 (0.85,1.18)
SOF12 + PR12		0.85 (0.31,1.06)
SOF12 + PR12	DCV24 + ASU24	0.90 (0.32,1.09)

Table 12: SVR Genotype 1b Patients Treatment-Naive: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% Crl)**
Random-Effect Model	Residual Deviance	39.64 vs. 42 data points
	Deviance Information Criteria	209.409
Fixed-Effect Model	Residual Deviance	39.56 vs. 42 data points
	Deviance Information Criteria	208.133

Emerging Treatments

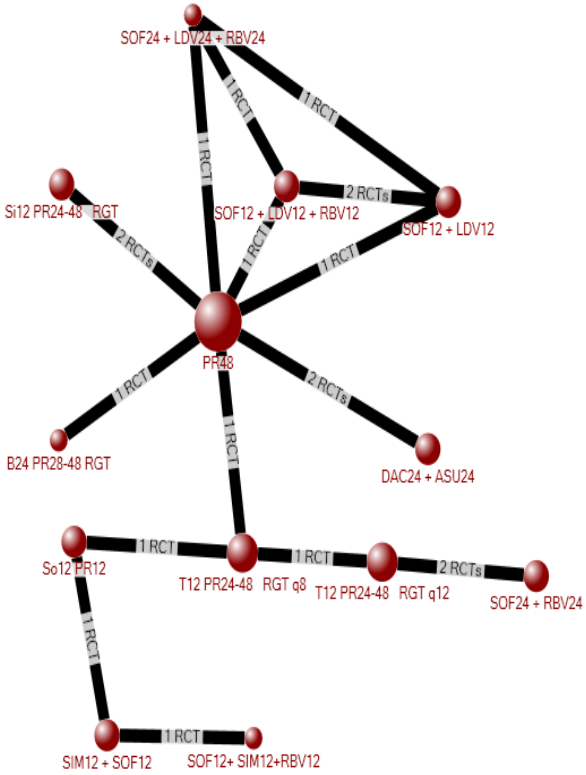
When emerging treatments were added to the network of genotype 1b treatment-naive patients, a total of 268 additional patients reported in 4 studies (64, 76, 86, 90) were included in the NMA. Four new treatments were added to the evidence network. The rate of SVR12 for the reference treatment PR48 was 0.54 (95% CrI 0.45 to 0.63).

The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix K. Compared with PR48, GRA12 + ELB12 and DCV12 + ASU12 + BEC12 significantly improved SVR. There was no significant difference for DCV12 + ASU12 + BEC12 + RBV12 or GRA12 + ELB12 (50mg QD) compared with PR48.

d) Patients With Cirrhosis

The evidence network for SVR12 in treatment-naive genotype 1 patients with cirrhosis included 14 studies (44, 56, 61, 66, 67, 72-75, 84, 94, 104, 107, 109) and a total of 539 participants (Figure 4). Overall, 13 different treatment regimens were considered, providing for 11 direct treatment comparisons (based on one 3-arm study and eight 2-arm studies), and 5 treatment estimates (based on 5 single-arm studies). The rate of SVR12 for the reference treatment PR4 was 0.40 (95% CrI 0.31 to 0.49).

Figure 4: SVR Genotype 1 Patients with Cirrhosis Treatment-Naive: Evidence Network



The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in Table 13. Compared with PR48, all of the DAA treatment strategies shown (i.e., SOF12 + LDV12, DCV24 + ASU24, SOF12 + PR12 and SIM12 + PR24-48 RGT12) with the exception of SIM12 + SOF12 and SOF24 + RBV24, significantly improved SVR in genotype 1 treatment-naive patients with cirrhosis. When the individual DAA treatment strategies were compared head-to-head:

- SOF12 + LDV12 significantly improved SVR compared to SIM12 + PR24-48 RGT and SOF24 + RBV24.

Table 13: SVR Genotype 1 Patients with Cirrhosis Treatment-Naive: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SIM12 + SOF12	PR48	2.18 (0.93,2.95)
SOF12 + PR12		2.04 (1.13,2.75)
SIM12 + PR24-48 RGT		1.70 (1.06,2.39)
SOF24 + RBV24		1.76 (0.62,2.57)
DCV24 + ASU24		2.25 (1.66,2.96)
SOF12 + LDV12		2.41 (1.89,3.09)
SOF12 + PR12	SIM12 + SOF12	0.94 (0.60,1.89)
SIM12 + PR24-48 RGT		0.78 (0.49,1.85)
SOF24 + RBV24		0.82 (0.31,1.83)

Table 13: SVR Genotype 1 Patients with Cirrhosis Treatment-Naive: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
DCV24 + ASU24		1.01 (0.79,2.41)
SOF12 + LDV12		1.08 (0.90,2.58)
SIM12 + PR24-48 RGT	SOF12 + PR12	0.84 (0.52,1.52)
SOF24 + RBV24		0.86 (0.37,1.32)
DCV24 + ASU24		1.09 (0.84,1.98)
SOF12 + LDV12		1.16 (0.94,2.10)
SOF24 + RBV24	SIM12 + PR24-48 RGT	1.03 (0.36,1.77)
DCV24 + ASU24		1.32 (0.95,2.10)
SOF12 + LDV12		1.41 (1.08,2.20)
DCV24 + ASU24	SOF24 + RBV24	1.27 (0.90,3.67)
SOF12 + LDV12		1.36 (1.00,3.88)
SOF12 + LDV12	DCV24 + ASU24	1.07 (0.90,1.35)
Random-Effect Model	Residual Deviance	26.88 vs. 30 data points
	Deviance Information Criteria	141.592
Fixed-Effect Model	Residual Deviance	26.53 vs. 30 data points
	Deviance Information Criteria	140.778

Emerging Treatments

When emerging treatments were added to the network of genotype 1 treatment- naive patients with cirrhosis, a total of 305 additional patients reported in 3 studies (64, 76, 101) were included in the NMA. Seven new treatments were added to the evidence network. The rate of SVR12 for the reference treatment PR48 was 0.39 (95% CrI 0.32 to 0.46).

The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix K. Compared to PR48 all emerging treatments (i.e., GRA12 + ELB12, DCV12 + ASU12 +BEC12 + RBV12, GRA12 + ELB12 (50mg QD), GRA18 + ELB18 (50mg QD), GRA12 + ELB12 (50mg QD) + RBV12, GRA18 + ELB18 (50mg QD) + RBV18) except for DCV12 + ASU12 + BEC12 significantly improved SVR.

Sensitivity Analysis

PAR/RIT12 + OMB12 + DAS12 + RBV12 could not be included in the base-case analyses of patients with cirrhosis because the only trial evaluating this regimen in this population was the TURQUOISE II study,(26) which did not present separate baseline patient characteristics for treatment-naive and experienced patients. As described above under Methods, such data were required for the matching procedure used to incorporate data from single-arm trials. Baseline characteristics data by previous treatment experience were made available to the reviewers by the manufactuer but could not be utilized as permission was not granted to report these data in the review. To permit inclusion of PAR/RIT12 + OMB12 + DAS12 + RBV12 in the analysis of patients with cirrhosis, an assumption was made in consultation with clinical experts that the combined baseline characteristics reported for experienced and naive patients in TURQUOISE II could be applied to each of these groups. Addition of this treatment to the

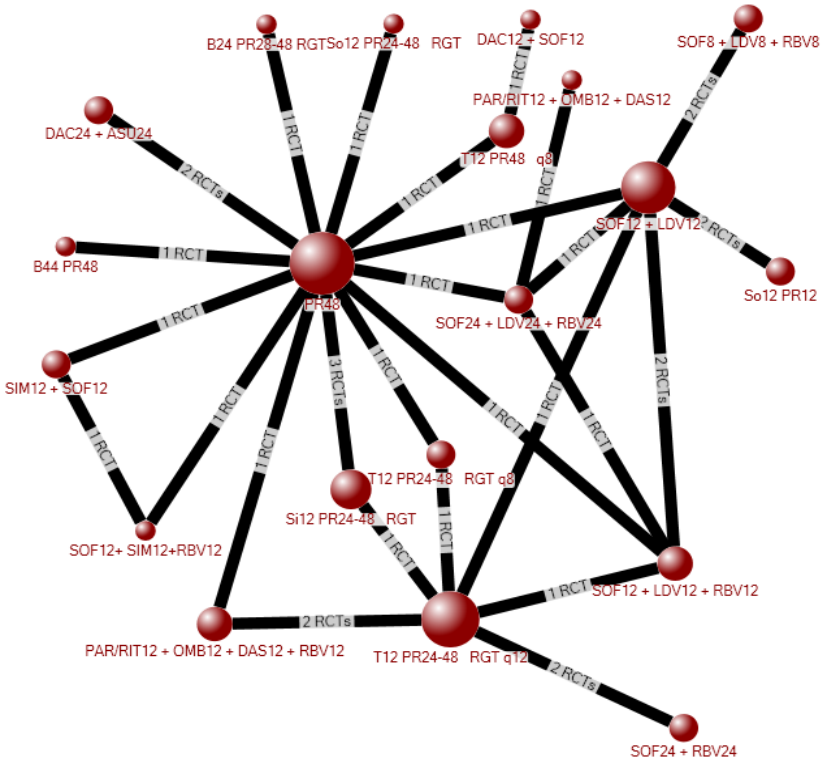
network extended the treatment network by one treatment node and added 1 study. The rate of SVR12 for the reference treatment PR48 was 0.38 (95% CrI 0.31 to 0.48).

Compared with PR48, PAR/RIT12 + OMB12 + DAS12 + RBV12 significantly improved SVR among treatment-naive patients with cirrhosis (RR 2.42 (1.94 to 3.06) (Appendix K). PAR/RIT12 + OMB12 + DAS12 + RBV12 did not signifcantly improved SVR compared to SOF12 + LDV12 ± RBV12, DCV24 + ASU24 or SOF12 + PR12, but did significantly improve SVR compared to SIM12 + PR24-48 RGT (RR 1.422, 95% CrI 1.09, 2.17).

e) Patients Without Cirrhosis

The evidence network for SVR12 in treatment-naive genotype 1 patients without cirrhosis included 29 studies (44, 49-51, 53, 54, 56, 58-61, 63, 65, 66, 68, 69, 72-75, 82-84, 91, 93-95) and a total of 6,018 participants (Figure 5). Overall, 20 different treatment regimens were considered, providing for 25 direct treatment comparisons (based on one four-arm study and 14 two-arm studies), and 14 treament estimates (based on 14 single-arm studies. The NMA based on this evidence network was consistent (Appendix I). The rate of SVR12 for the reference treatment PR48 was 0.49 (95% CrI 0.44 to 0.55).

Figure 5: SVR Genotype 1 Patients Without Cirrhosis Treatment-Naive: Evidence Network



The results of the random effects NMA model of selected treatments compared to PR48 and each other are presented in Table 14. Compared with PR48, all of the DAA treatment strategies (i.e., SOF12 + LDV12, PAR/RIT12 + OMB12 + DAS12 ± RBV12, DCV24 + ASU24, DCV12 + SOF12, SIM12 + PR24-48 RGT, SOF24 + RBV24, and SOF12 + PR12) except SIM12 + SOF12 significantly improved SVR in genotype 1 treatment-naive patients without cirrhosis.

When the individual DAA treatment strategies were compared head-to-head:

- SOF12 + LDV12 significantly improved SVR compared to SOF12 + PR12, SIM12 + PR24-48 RGT, SOF24 + RBV24 and DCV24 + ASU24.
- PAR/RIT12 + OMB12 + DAS12 + RBV12 significantly improved SVR compared to SIM12 + PR24-48 RGT and SOF24 + RBV24.
- DCV24 + ASU24 significantly improved SVR compared to SIM12 + PR24-48 RGT.

Table 14: SVR Genotype 1 Patients Without Cirrhosis Treatment-Naive: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF12 + LDV12	PR48	1.98 (1.78,2.23)
SIM12 + PR24-48 RGT		1.59 (1.41,1.78)
SOF24 + RBV24		1.63 (1.29,1.90)
PAR/RIT12 + OMB12 + DAS12		1.93 (1.34,2.21)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.94 (1.75,2.18)
DCV24 + ASU24		1.94 (1.75,2.18)
DCV12 + SOF12		1.90 (1.28,2.21)
SOF12 + PR12		1.77 (1.28,2.07)
SIM12 + SOF12		1.80 (0.80,2.19)
SIM12 + PR24-48 RGT	SOF12 + LDV12	0.80 (0.72,0.88)
SOF24 + RBV24		0.83 (0.65,0.93)
PAR/RIT12 + OMB12 + DAS12		0.99 (0.67,1.04)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.98 (0.93,1.03)
DCV24 + ASU24		0.92 (0.85,0.98)
DCV12 + SOF12		0.97 (0.66,1.04)
SOF12 + PR12		0.90 (0.67,0.98)
SIM12 + SOF12		0.92 (0.41,1.04)
SOF24 + RBV24	SIM12 + PR24-48 RGT	1.03 (0.81,1.19)
PAR/RIT12 + OMB12 + DAS12		1.22 (0.83,1.38)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.22 (1.12,1.37)
DCV24 + ASU24		1.14 (1.03,1.29)
DCV12 + SOF12		1.19 (0.81,1.38)
SOF12 + PR12		1.12 (0.80,1.30)
SIM12 + SOF12		1.14 (0.50,1.37)
PAR/RIT12 + OMB12 + DAS12	SOF24 + RBV24	1.18 (0.83,1.50)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.19 (1.07,1.48)
DCV24 + ASU24		1.11 (0.97,1.42)
DCV12 + SOF12		1.16 (0.79,1.49)
SOF12 + PR12		1.08 (0.79,1.37)
SIM12 + SOF12		1.10 (0.49,1.46)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PAR/RIT12 + OMB12 + DAS12	1.00 (0.93,1.45)
DCV24 + ASU24		0.94 (0.85,1.37)

Table 14: SVR Genotype 1 Patients Without Cirrhosis Treatment-Naive: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
DCV12 + SOF12		0.98 (0.68,1.44)
SOF12 + PR12		0.92 (0.67,1.29)
SIM12 + SOF12		0.94 (0.42,1.33)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.94 (0.86,1.00)
DCV12 + SOF12		0.99 (0.67,1.07)
SOF12 + PR12		0.92 (0.66,1.02)
SIM12 + SOF12		0.93 (0.41,1.07)
DCV12 + SOF12	DCV24 + ASU24	1.05 (0.72,1.16)
SOF12 + PR12		0.98 (0.70,1.11)
SIM12 + SOF12		1.00 (0.45,1.16)
SOF12 + PR12	DCV12 + SOF12	0.94 (0.67,1.38)
SIM12 + SOF12		0.96 (0.44,1.37)
SIM12 + SOF12	SOF12 + PR12	1.02 (0.46,1.45)
Random-Effect Model	Residual Deviance	57.81 vs. 61 data points
	Deviance Information Criteria	346.783
Fixed-Effect Model	Residual Deviance	60.76 vs. 61 data points
	Deviance Information Criteria	346.998

Emerging Treatments

When emerging treatments were added to the network of genotype 1 treatment-naive non-cirrhotic patients, a total of 776 additional patients reported in 4 additional studies (86, 90, 101) were included in the NMA. Four new treatments were added to the evidence network. The rate of SVR12 for the reference treatment PR48 was 0.50 (95% CrI 0.44 to 0.54).

The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix K.

Compared to PR48, GRA12 + ELB12, DCV12 + ASU12 + BEC12, and GRA12 + ELB12 (50mg QD) significantly improved SVR. There was no significant difference between PR48 and GRA12 + ELB12 + RBV12, GRA8 + ELB8 (50mg QD) + RBV8, or GRA12 + ELB12 (50mg QD) + RBV12.

Sensitivity Analysis

Sensitivity analyses were conducted to include the SOF8 + LDV8 treatment regimen for the analysis of treatment-naive patients without cirrhosis. This treatment regimen was not included in the base-case analyses as the current Health Canada–approved use is in treatment-naive patients without cirrhosis who have a pre-treatment HCV RNA of less than 6 million IU/mL. Many of the studies of SOF8 + LDV8 did not specify the pre-treatment HCV RNA levels of the included participants. Since clinical input indicated that a large proportion of genotype 1 treatment-naive patients are likely to have HCV RNA levels of less than 6 million IU/mL, a sensitivity analysis was conducted to incorporate SOF8 + LDV8 trial arms into the NMA for treatment-naive patients without cirrhosis. Addition of this treatment extended the network by

one treatment node from one study (LONESTAR).(68) The rate of SVR12 for the reference treatment PR48 was 0.49 (95% CrI 0.44 to 0.55).

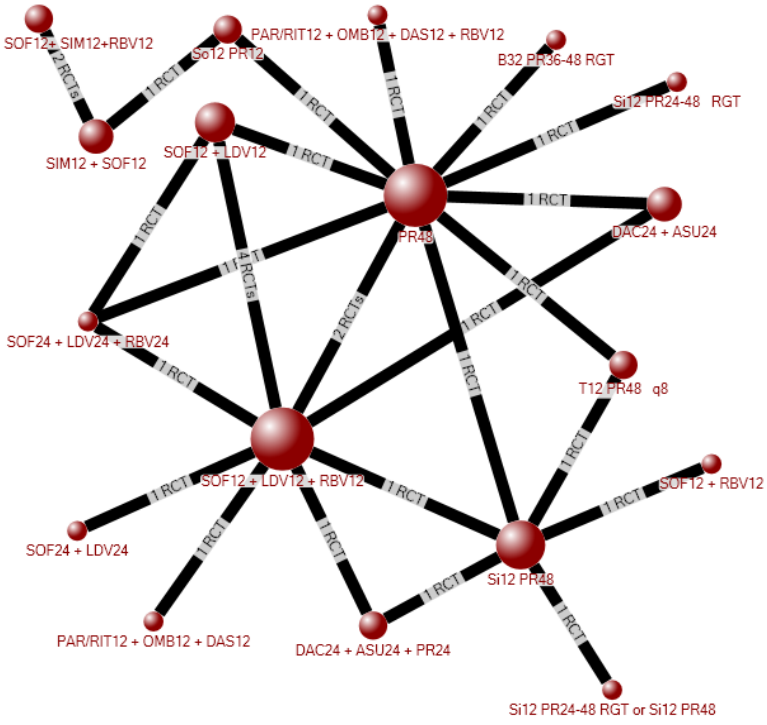
Compared with PR48, SOF8+LDV8 signficantly increased SVR (RR 1.93, 95% CrI 1.66 to 2.19) (Appendix K). Compared with SOF12 + LDV12, no significant improvements in SVR were found. Compared to PAR/RIT12 + OMB12 + DAS12 ± RBV, DCV24 + ASU24 and DCV12 + SOF12 there were no significant improvements in SVR with SOF8 + LDV8. There was a significant improvement in SVR when SOF8 + LDV8 was compared to SIM12 + PR24-48 RGT, and a marginally significant improvement in SVR when compared to SOF12 + PR12.

4.1.2 Treatment-Experienced Patients

a) All Patients

The evidence network for SVR12 in treatment-experienced genotype 1 patients included 26 studies (45, 46, 49, 53, 54, 57, 61, 68-70, 73, 74, 81, 84, 85, 96, 102, 103, 105, 111) and a total of 4,146 participants (Figure 6). Overall, 18 different treatment regimens were considered, providing for 17 direct treatment comparisons (based on one four-arm study and 11 two-arm studies), and 14 treatment estimates (based on 14 single-arm studies). Evidence that could be incorporated in the NMA was available for all regimens of interest for treatment-experienced patients with genotype 1 infection except DCV + SOF for either 12 or 24 weeks. It should be noted that PAR/RIT12 + OMB12 + DAS12 is only indicated in Canada, and recommended by treatment guidelines, for patients with genotype 1b infection without cirrhosis (i.e., addition of RBV is recommended for all other genotype 1 populations using PAR/RIT12 + OMB12 + DAS 12). The NMA based on this evidence network was consistent (Appendix I). The rate of SVR12 for the reference treatment PR48 was 0.26 (95% CrI 0.23 to 0.28).

Figure 6: SVR Genotype 1 Patients Treatment-Experienced: Evidence Network



The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in Table 15. Compared with PR48, all of the DAA treatment strategies

significantly improved SVR in genotype 1 treatment-experienced patients (RR ranged from 2.72 to 3.75).

When the individual DAA treatment strategies were compared head-to-head:

- SOF12 + LDV12 and PAR/RIT12 + OMB12 + DAS12 + RBV12 significantly improved SVR compared to SOF12 + PR12, SIM12 + PR24-48 RGT, SIM12 + PR48 and DCV24 + ASU24.
- DCV24 + ASU24 significantly improved SVR when compared to SIM12 + PR48.
- DCV24 + ASU24 + PR24 significantly improved SVR compared to SIM12 + PR48 and SIM12 + PR24-48 RGT.

Table 15: SVR Genotype 1 Patients Treatment-Experienced: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF12 + LDV12	PR48	3.69 (3.28,4.14)
SOF24 + LDV24		3.63 (2.72,4.15)
SIM12 + PR24-48 RGT		2.72 (2.05,3.28)
SIM12 + PR48		2.85 (2.28,3.36)
PAR/RIT12 + OMB12 + DAS12		3.67 (2.31,4.17)
PAR/RIT12 + OMB12 + DAS12 + RBV12		3.75 (3.35,4.20)
DCV24 + ASU24		3.07 (2.50,3.59)
DCV24 + ASU24 + PR24		3.53 (3.03,4.01)
SOF12 + PR12		3.10 (2.30,3.70)
SIM12 + SOF12		3.52 (2.25,4.10)
SOF24 + LDV24	SOF12 + LDV12	0.99 (0.75,1.08)
SIM12 + PR24-48 RGT		0.74 (0.56,0.88)
SIM12 + PR48		0.77 (0.63,0.89)
PAR/RIT12 + OMB12 + DAS12		1.00 (0.63,1.09)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.01 (0.95,1.10)
DCV24 + ASU24		0.83 (0.70,0.93)
DCV24 + ASU24 + PR24		0.96 (0.85,1.05)
SOF12 + PR12		0.84 (0.63,0.97)
SIM12 + SOF12		0.96 (0.61,1.07)
SIM12 + PR24-48 RGT	SOF24 + LDV24	0.75 (0.57,1.02)
SIM12 + PR48		0.78 (0.64,1.04)
PAR/RIT12 + OMB12 + DAS12		1.01 (0.65,1.32)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.02 (0.95,1.37)
DCV24 + ASU24		0.85 (0.70,1.12)
DCV24 + ASU24 + PR24		0.97 (0.85,1.28)
SOF12 + PR12		0.86 (0.64,1.15)
SIM12 + SOF12		0.98 (0.62,1.29)
SIM12 + PR48	SIM12 + PR24-48 RGT	1.05 (0.81,1.42)
PAR/RIT12 + OMB12 + DAS12		1.34 (0.84,1.79)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.38 (1.16,1.82)

Table 15: SVR Genotype 1 Patients Treatment-Experienced: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
DCV24 + ASU24		1.13 (0.88,1.50)
DCV24 + ASU24 + PR24		1.30 (1.06,1.72)
SOF12 + PR12		1.14 (0.83,1.54)
SIM12 + SOF12		1.29 (0.83,1.72)
PAR/RIT12 + OMB12 + DAS12	SIM12 + PR48	1.28 (0.83,1.60)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.32 (1.15,1.60)
DCV24 + ASU24		1.08 (0.87,1.33)
DCV24 + ASU24 + PR24		1.24 (1.11,1.46)
SOF12 + PR12		1.09 (0.79,1.37)
SIM12 + SOF12		1.24 (0.80,1.52)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PAR/RIT12 + OMB12 + DAS12	1.01 (0.94,1.61)
DCV24 + ASU24		0.84 (0.69,1.32)
DCV24 + ASU24 + PR24		0.96 (0.84,1.50)
SOF12 + PR12		0.85 (0.63,1.34)
SIM12 + SOF12		0.96 (0.62,1.49)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.82 (0.68,0.92)
DCV24 + ASU24 + PR24		0.95 (0.83,1.02)
SOF12 + PR12		0.83 (0.62,0.95)
SIM12 + SOF12		0.95 (0.61,1.04)
DCV24 + ASU24 + PR24	DCV24 + ASU24	1.15 (0.99,1.38)
SOF12 + PR12		1.01 (0.76,1.26)
SIM12 + SOF12		1.15 (0.73,1.39)
SOF12 + PR12	DCV24 + ASU24 + PR24	0.88 (0.66,1.04)
SIM12 + SOF12		1.01 (0.64,1.15)
SIM12 + SOF12	SOF12 + PR12	1.13 (0.78,1.42)
Random-Effect Model	Residual Deviance	49.23 vs. 54 data points
	Deviance Information Criteria	285.992
Fixed-Effect Model	Residual Deviance	49.08 vs. 54 data points
	Deviance Information Criteria	284.484

Emerging Treatments

When emerging treatments were added to the network of genotype 1 treatment-experienced patients, a total of 680 additional patients reported in 4 additional studies (52, 64, 76, 86) were included in the NMA. Seven new treatments were added to the evidence network. The rate of SVR12 for the reference treatment PR48 was 2.3 (95% CrI 0.21 to 0.26).

The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix K. Compared with PR48, all seven significantly increased SVR (RR ranged from 3.80 to 4.20)

b) Genotype 1a

The evidence network for SVR12 in treatment-experienced genotype 1a patients included 12 studies (43, 46, 49, 57, 84, 87, 102, 103, 105, 111) and a total of 1,683 participants. Overall, 14 different treatment regimens were considered, providing for 9 direct treatment comparisons (based on one three-arm study and six two-arm studies), and 5 treatment estimates (based on five single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.26 (95% CrI 0.21 to 0.32).

The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in Table 16. Compared with PR48 dual therapy, all of the DAA treatment strategies significantly improved SVR in genotype 1 treatment-experienced patients (RR ranged from 2.52 to 3.72), except for Si12+PR48 and SOF24 + LDV24.

When the individual DAA treatment strategies were compared head-to-head:

- SOF12 + LDV12 and PAR/RIT12 + OMB12 + DAS12 + RBV12 significantly improved SVR compared to SIM12 + PR24-48 RGT and SIM12 + PR48.
- PAR/RIT12 + OMB12 + DAS12 + RBV12 also significantly improved SVR compared to SOF12 + PR12.

Table 16: SVR Genotype 1a Patients Treatment-Experienced: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SIM12 + PR24-48 RGT	PR48	2.52 (1.38,3.49)
SIM12 + PR48		2.14 (0.71,3.26)
PAR/RIT12 + OMB12 + DAS12 + RBV12		3.72 (2.97,4.62)
DCV24 + ASU24 + PR24		3.18 (1.85,4.12)
SOF12 + PR12		3.02 (1.80,3.97)
SIM12 + SOF12		3.51 (2.08,4.46)
SOF12 + LDV12		3.56 (2.79,4.46)
SOF24 + LDV24		3.21 (0.62,4.34)
SIM12 + PR48	SIM12 + PR24-48 RGT	0.85 (0.30,1.55)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.47 (1.12,2.60)
DCV24 + ASU24 + PR24		1.25 (0.94,1.77)
SOF12 + PR12		1.19 (0.73,2.10)
SIM12 + SOF12		1.38 (0.85,2.39)
SOF12 + LDV12		1.41 (1.05,2.49)
SOF24 + LDV24		1.26 (0.25,2.28)
PAR/RIT12 + OMB12 + DAS12 + RBV12	SIM12 + PR48	1.73 (1.22,4.79)
DCV24 + ASU24 + PR24		1.48 (0.86,4.04)
SOF12 + PR12		1.40 (0.83,3.87)
SIM12 + SOF12		1.62 (0.97,4.44)

Table 16: SVR Genotype 1a Patients Treatment-Experienced: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF12 + LDV12		1.66 (1.14,4.78)
SOF24 + LDV24		1.46 (0.30,4.11)
DCV24 + ASU24 + PR24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.86 (0.52,1.01)
SOF12 + PR12		0.82 (0.51,0.98)
SIM12 + SOF12		0.96 (0.59,1.07)
SOF12 + LDV12		0.96 (0.82,1.08)
SOF24 + LDV24		0.88 (0.17,1.05)
SOF12 + PR12	DCV24 + ASU24 + PR24	0.95 (0.61,1.56)
SIM12 + SOF12		1.10 (0.69,1.77)
SOF12 + LDV12		1.11 (0.91,1.85)
SOF24 + LDV24		1.02 (0.20,1.70)
SIM12 + SOF12	SOF12 + PR12	1.15 (0.84,1.61)
SOF12 + LDV12		1.17 (0.95,1.88)
SOF24 + LDV24		1.07 (0.21,1.70)
SOF12 + LDV12	SIM12 + SOF12	1.01 (0.84,1.64)
SOF24 + LDV24		0.93 (0.18,1.49)
SOF24 + LDV24	SOF12 + LDV12	0.92 (0.18,1.14)
Random-Effect Model	Residual Deviance	25.34 vs. 26 data points
	Deviance Information Criteria	152.687
Fixed-Effect Model	Residual Deviance	25.33 vs. 26 data points
	Deviance Information Criteria	152.52

Emerging Treatments

When emerging treatments were added to the network of genotype 1a treatment-experienced patients, a total of 175 additional patients reported in 3 additional studies (52, 76, 86) were included in the NMA. Three new treatments were added to the evidence network. The rate of SVR12 for the reference treatment PR48 was 0.26 (95% CrI 0.21 to 30).

The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix K.

Compared with PR48, all emerging treatments (i.e., GRA12 + ELB12 + RBV12, DCV12 + ASU12 + BEC12 + RBV12 and DCV12 + ASU12 + BEC12) significantly increased SVR.

c) Genotype 1b

The evidence network for SVR12 in treatment-experienced genotype 1b patients included 17 studies (43, 45, 46, 49, 57, 61, 70, 73, 74, 85, 87, 96, 102, 103, 105, 111) and a total of 2,135 participants. Overall, 14 different treatment regimens were considered, providing for 12 direct treatment comparisons (based on one 4-arm study and six 2-arm studies), and 10 treatment estimates (based on 10 single-arm studies). The NMA based on this evidence network was

consistent (Appendix I). The rate of SVR12 for the reference treatment PR48 was 0.21 (95% CrI 0.18 to 0.26).

The results of the random effects NMA model of selected treatments compared to PR48 and each other are presented in Table 17. Compared with PR48, all of the DAA treatment strategies significantly improved SVR in genotype 1b treatment-experienced patients (RR ranged from 3.02 to 4.52).

When the individual DAA treatment strategies were compared head-to-head:

- DCV24 + ASU24 + PR24 significantly improved SVR compared to SOF12 + LDV12, SOF24 + LDV24, SIM12 + PR24-48 RGT, SIM12 + PR48, SOF12 + PR12 and DCV24 + ASU24
- PAR/RIT12 + OMB12 + DAS12 + RBV12 significantly improved SVR compared to SOF12 + LDV12, SIM12 + PR24-48 RGT, SIM12 + PR48, SOF12 + PR12 and DCV24 + ASU24
- PAR/RIT12 + OMB12 + DAS12 significantly improved SVR compared to SIM12 + PR24-48 RGT

Table 17: SVR Genotype 1b Patients Treatment-Experienced: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF12 + LDV12	PR48	3.18 (1.81,4.34)
SOF24 + LDV24		3.90 (1.55,4.99)
SIM12 + PR24-48 RGT		3.02 (1.84,3.90)
SIM12 + PR48		3.63 (2.15,4.63)
PAR/RIT12 + OMB12 + DAS12		4.29 (3.27,5.20)
PAR/RIT12 + OMB12 + DAS12 + RBV12		4.46 (3.75,5.36)
DCV24 + ASU24		3.46 (2.59,4.39)
DCV24 + ASU24 + PR24		4.52 (3.82,5.43)
SOF12 + PR12		3.20 (1.58,4.52)
SOF24 + LDV24	SOF12 + LDV12	1.21 (0.52,2.13)
SIM12 + PR24-48 RGT		0.95 (0.56,1.68)
SIM12 + PR48		1.13 (0.68,2.00)
PAR/RIT12 + OMB12 + DAS12		1.34 (0.98,2.35)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.40 (1.08,2.45)
DCV24 + ASU24		1.09 (0.77,1.93)
DCV24 + ASU24 + PR24		1.42 (1.10,2.50)
SOF12 + PR12		1.01 (0.49,1.89)
SIM12 + PR24-48 RGT	SOF24 + LDV24	0.78 (0.48,1.88)
SIM12 + PR48		0.93 (0.58,2.27)
PAR/RIT12 + OMB12 + DAS12		1.09 (0.86,2.65)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.13 (0.98,2.81)
DCV24 + ASU24		0.89 (0.68,2.10)
DCV24 + ASU24 + PR24		1.14 (1.00,2.86)
SOF12 + PR12		0.84 (0.41,2.09)
SIM12 + PR48	SIM12 + PR24-48 RGT	1.19 (0.74,1.95)

Table 17: SVR Genotype 1b Patients Treatment-Experienced: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
PAR/RIT12 + OMB12 + DAS12		1.41 (1.15,2.14)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.47 (1.18,2.42)
DCV24 + ASU24		1.15 (0.84,1.88)
DCV24 + ASU24 + PR24		1.49 (1.21,2.46)
SOF12 + PR12		1.07 (0.53,1.85)
PAR/RIT12 + OMB12 + DAS12	SIM12 + PR48	1.18 (0.91,1.89)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.22 (1.05,1.99)
DCV24 + ASU24		0.95 (0.71,1.56)
DCV24 + ASU24 + PR24		1.24 (1.07,2.03)
SOF12 + PR12		0.89 (0.45,1.54)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PAR/RIT12 + OMB12 + DAS12	1.03 (0.96,1.32)
DCV24 + ASU24		0.81 (0.63,1.05)
DCV24 + ASU24 + PR24		1.04 (0.99,1.35)
SOF12 + PR12		0.75 (0.38,1.06)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.78 (0.61,0.90)
DCV24 + ASU24 + PR24		1.01 (0.98,1.07)
SOF12 + PR12		0.72 (0.37,0.96)
DCV24 + ASU24 + PR24	DCV24 + ASU24	1.30 (1.14,1.67)
SOF12 + PR12		0.93 (0.46,1.35)
SOF12 + PR12	DCV24 + ASU24 + PR24	0.71 (0.36,0.94)
Random-Effect Model	Residual Deviance	32.73 vs. 36 data points
	Deviance Information Criteria	185.675
Fixed-Effect Model	Residual Deviance	31.68 vs. 36 data points
	Deviance Information Criteria	184.506

Emerging Treatments

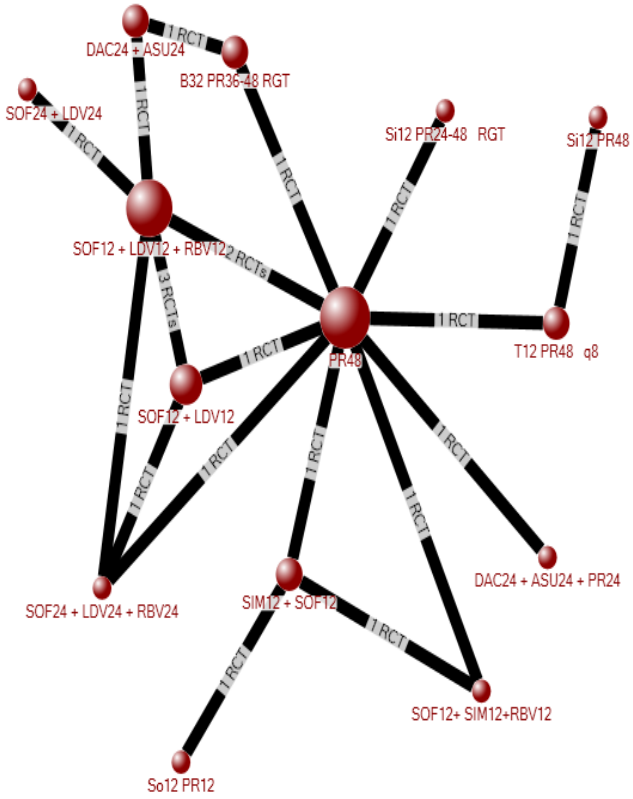
When emerging treatments were added to the network of genotype 1b treatment-experienced patients, a total of 97 additional patients reported in 3 additional studies (52, 76, 86) were included in the NMA. Three new treatments were added to the evidence network (GRA12 + ELB12 + RBV12; DCV12 + ASU12 + BEC12 ± RBV12). The rate of SVR12 for the reference treatment PR48 was 0.21 (95% CrI 0.17 to 0.24).

The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix K. Relative to PR48, GRA12 + ELB12 + RBV12 and DCV12 + ASU12 + BEC12 both significantly improved SVR (Appendix K).

d) Patients With Cirrhosis

The evidence network for SVR12 in treatment-experienced genotype 1 patients with cirrhosis included 14 studies (43, 46, 54, 57, 61, 69, 73, 74, 84, 87, 96, 103, 105, 111) and a total of 850 participants (Figure 7). Overall, 14 different treatment regimens were considered, providing for 11 direct treatment comparisons (based on one 3-arm study and eight 2-arm studies), and five treatment estimates (based on five single-arm studies). The NMA based on this evidence network was consistent (Appendix I). The rate of SVR12 for the reference treatment PR48 was 0.17 (95% CrI 0.12 to 0.23).

Figure 7: SVR Genotype 1 Treatment-Experienced Patients with Cirrhosis Treatment-Experienced: Evidence Network



The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in Table 18. Compared with PR48, all of the DAA treatment strategies (i.e., SOF12 + LDV12, SOF24 + LDV24, DCV24 + ASU24 ± PR24, SIM12 + PR24-48 RGT and SIM12 + SOF12) except SIM12 + PR48 and SOF12 + PR12 significantly improved SVR in genotype 1 treatment-experienced patients with cirrhosis.

When the individual DAA treatment strategies were compared head-to-head, only DCV24 + ASU24 + PR24 significantly improved SVR compared to SIM12 + PR48.

Table 18: SVR Genotype 1 Patients with Cirrhosis Treatment-Experienced: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF12 + LDV12	PR48	4.31 (2.45,6.85)
SOF24 + LDV24		4.50 (1.60,7.22)
SIM12 + PR24-48 RGT		3.56 (1.61,6.09)
SIM12 + PR48		2.71 (0.89,5.32)
DCV24 + ASU24		5.06 (3.12,7.65)
DCV24 + ASU24 + PR24		5.35 (3.73,7.80)
SIM12 + SOF12		4.67 (1.80,7.16)
SOF12 + PR12		2.94 (0.32,6.24)
SOF24 + LDV24	SOF12 + LDV12	1.04 (0.42,1.71)
SIM12 + PR24-48 RGT		0.83 (0.36,1.58)
SIM12 + PR48		0.63 (0.20,1.37)
DCV24 + ASU24		1.15 (0.83,1.91)
DCV24 + ASU24 + PR24		1.22 (0.90,2.10)
SIM12 + SOF12		1.09 (0.41,1.92)
SOF12 + PR12		0.70 (0.07,1.60)
SIM12 + PR24-48 RGT	SOF24 + LDV24	0.81 (0.35,2.28)
SIM12 + PR48		0.62 (0.19,1.93)
DCV24 + ASU24		1.10 (0.77,2.93)
DCV24 + ASU24 + PR24		1.16 (0.85,3.27)
SIM12 + SOF12		1.03 (0.41,2.85)
SOF12 + PR12		0.68 (0.07,2.11)
SIM12 + PR48	SIM12 + PR24-48 RGT	0.77 (0.24,2.05)
DCV24 + ASU24		1.39 (0.84,3.14)
DCV24 + ASU24 + PR24		1.48 (0.99,3.26)
SIM12 + SOF12		1.29 (0.48,2.98)
SOF12 + PR12		0.84 (0.09,2.38)
DCV24 + ASU24	SIM12 + PR48	1.84 (0.95,5.80)
DCV24 + ASU24 + PR24		1.95 (1.09,5.94)
SIM12 + SOF12		1.67 (0.59,5.41)
SOF12 + PR12		1.06 (0.11,4.05)
DCV24 + ASU24 + PR24	DCV24 + ASU24	1.05 (0.81,1.56)
SIM12 + SOF12		0.95 (0.36,1.44)
SOF12 + PR12		0.59 (0.06,1.19)
SIM12 + SOF12	DCV24 + ASU24 + PR24	0.90 (0.34,1.19)
SOF12 + PR12		0.56 (0.06,1.08)
SOF12 + PR12	SIM12 + SOF12	0.65 (0.12,1.03)
Random-Effect Model	Residual Deviance	29.34 vs. 31 data points
	Deviance Information Criteria	145.523

Table 18: SVR Genotype 1 Patients with Cirrhosis Treatment-Experienced: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
Fixed-Effect Model	Residual Deviance	29.3 vs. 31 data points
	Deviance Information Criteria	145.001

Emerging Treatments

When emerging treatments were added to the network of genotype 1 treatment-experienced patients with cirrhosis, a total of 124 additional patients reported in two additional studies (52, 76) were included in the NMA. Three new treatments were added to the evidence network. The rate of SVR12 for the reference treatment PR48 was 0.16 (95% CrI 0.11 to 0.22).

The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix K. Compared with PR48, all three emerging treatments (i.e., GRA12 + ELB12 + RBV12, DCV12 + ASU12 + BEC12 + RBV12 and DCV12 + ASU12 + BEC12) significantly increased SVR (RR ranged from 5.65 to 5.94).

Sensitivity Analysis

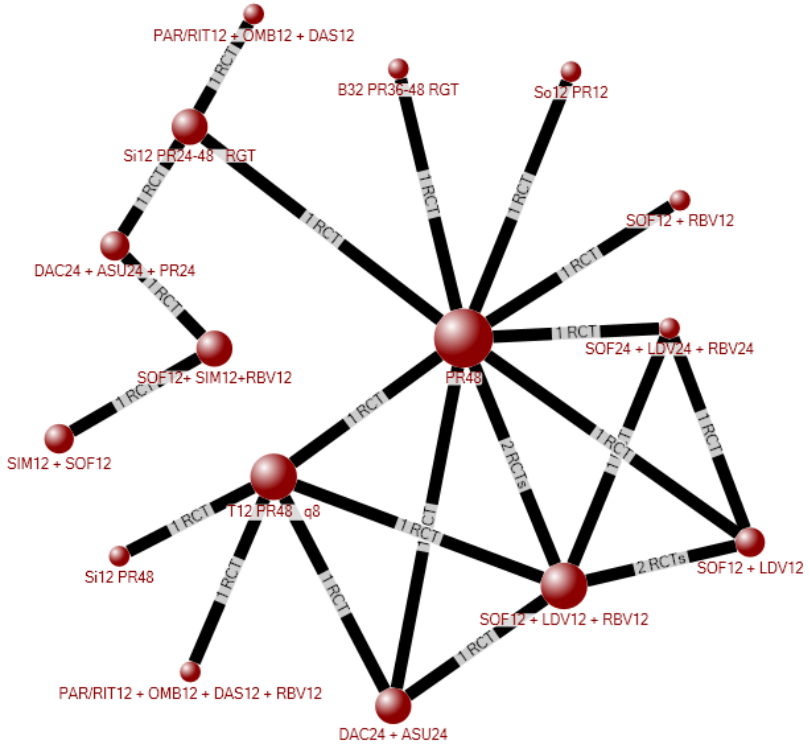
Similar to the analysis of treatment-naive patients with cirrhosis, PAR/RIT12 + OMB12 + DAS12 + RBV12 could not be included in the base-case analysis of treatment-experienced patients with cirrhosis due to the lack of separately reported data on patient baseline characteristics in the TURQUOISE II study.(26) Hence, sensitivity analyses were conducted to include the PAR/RIT12 + OMB12 + DAS12 + RBV12 treatment regimen from the TURQUOISE II study by applying the combined baseline characteristics to the naive and experienced subgroups. Addition of this treatment to the network extended the treatment network by one treatment node and added 1 study. The rate of SVR12 for the reference treatment PR48 was 0.16 (95% CrI 0.11 to 0.22).

Compared with PR48, PAR/RIT12 + OMB12 + DAS12 + RBV12 resulted in a significant increase in SVR (RR 5.49, 95% CrI 3.86 to 7.99). There were no significant differences between PAR/RIT12 + OMB12 + DAS12 + RBV12 and SOF12 + LDV12 ± RBV12, SOF24 + LDV24, DCV24 + ASU24, DCV24 + ASU24 + PR24, SIM12 + SOF12, or SOF12 PR12.

e) Patients Without Cirrhosis

The evidence network for SVR12 in treatment-experienced genotype 1 patients without cirrhosis included 19 studies (43, 45, 53, 54, 57, 61, 69, 70, 73, 74, 85, 87, 96, 102, 103, 105, 111) and a total of 3,038 participants (Figure 8). Overall, 16 different treatment regimens were considered, providing for 10 direct treatment comparisons (based on one 3-arm study and seven 2-arm studies), and 11 treatment estimates (based on 11 single-arm studies). The NMA based on this evidence network was consistent (Appendix I). The rate of SVR12 for the reference treatment PR48 was 0.26 (95% CrI 0.22 to 0.29).

Figure 8: SVR Genotype 1 Non-Cirrhotic-Treatment-Experienced Evidenced Network



The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in Table 19. Compared with PR48, all of the DAA treatment strategies (i.e., SOF12 + LDV12, PAR/RIT12 + OMB12 + DAS12 ± RBV12, DCV24 + ASU24 ± PR24, SIM12 + PR24-48 RGT, SIM12 + PR48 and SOF12 + PR12) except SIM12 + SOF12 significantly improved SVR in genotype 1 treatment-experienced patients without cirrhosis.

When the individual DAA treatment strategies were compared head-to-head:

- PAR/RIT12 + OMB12 + DAS12 ± RBV12 significantly improved SVR compared to SIM12 + PR24-48 RGT, SIM12 + PR48, SOF12 + PR12, DCV24 + ASU24 and SIM12 + SOF12.
- PAR/RIT12 + OMB12 + DAS12 + RBV12 also significantly improved SVR compared to, SOF12 + LDV12 and DCV24 + ASU24 + PR24.
- SOF12 + LDV12 and DCV24 + ASU24 + PR24 significantly improved SVR compared to SIM12 + PR24-48 RGT.

Table 19: SVR Genotype 1 Patients Without Cirrhosis Treatment-Experienced: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SIM12 + SOF12	PR48	1.02 (0.05,3.64)
SOF12 + LDV12		3.56 (2.99,4.15)
SIM12 + PR24-48 RGT		2.59 (1.76,3.21)
SIM12 + PR48		3.05 (2.15,3.72)
PAR/RIT12 + OMB12 + DAS12		3.75 (3.20,4.33)
PAR/RIT12 + OMB12 + DAS12 + RBV12		3.82 (3.35,4.39)

Table 19: SVR Genotype 1 Patients Without Cirrhosis Treatment-Experienced: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
DCV24 + ASU24		3.07 (2.42,3.69)
DCV24 + ASU24 + PR24		3.37 (2.56,3.97)
SOF12+PR12		3.10 (2.28,3.77)
SOF12 + LDV12	SIM12 + SOF12	3.45 (0.97,73.05)
SIM12 + PR24-48 RGT		2.50 (0.70,49.78)
SIM12 + PR48		2.95 (0.82,61.51)
PAR/RIT12 + OMB12 + DAS12		3.68 (1.04,75.47)
PAR/RIT12 + OMB12 + DAS12 + RBV12		3.73 (1.06,77.60)
DCV24 + ASU24		2.99 (0.85,60.85)
DCV24 + ASU24 + PR24		3.25 (0.94,65.47)
SOF12+PR12		3.03 (0.84,64.10)
SIM12 + PR24-48 RGT	SOF12 + LDV12	0.73 (0.50,0.90)
SIM12 + PR48		0.86 (0.62,1.03)
PAR/RIT12 + OMB12 + DAS12		1.05 (0.93,1.21)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.07 (1.00,1.23)
DCV24 + ASU24		0.86 (0.70,1.02)
DCV24 + ASU24 + PR24		0.95 (0.73,1.11)
SOF12+PR12		0.87 (0.66,1.05)
SIM12 + PR48	SIM12 + PR24-48 RGT	1.17 (0.84,1.71)
PAR/RIT12 + OMB12 + DAS12		1.45 (1.22,2.06)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.47 (1.23,2.15)
DCV24 + ASU24		1.18 (0.91,1.73)
DCV24 + ASU24 + PR24		1.30 (1.10,1.67)
SOF12+PR12		1.19 (0.87,1.78)
PAR/RIT12 + OMB12 + DAS12	SIM12 + PR48	1.23 (1.04,1.69)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.25 (1.10,1.71)
DCV24 + ASU24		1.01 (0.82,1.35)
DCV24 + ASU24 + PR24		1.11 (0.85,1.51)
SOF12+PR12		1.02 (0.76,1.44)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PAR/RIT12 + OMB12 + DAS12	1.01 (0.97,1.13)
DCV24 + ASU24		0.82 (0.66,0.95)
DCV24 + ASU24 + PR24		0.90 (0.70,1.01)
SOF12+PR12		0.83 (0.63,0.97)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.81 (0.66,0.90)
DCV24 + ASU24 + PR24		0.89 (0.68,0.97)

Table 19: SVR Genotype 1 Patients Without Cirrhosis Treatment-Experienced: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF12+PR12		0.81 (0.62,0.93)
DCV24 + ASU24 + PR24	DCV24 + ASU24	1.10 (0.84,1.37)
SOF12+PR12		1.01 (0.75,1.31)
SOF12+PR12	DCV24 + ASU24 + PR24	0.92 (0.69,1.22)
Random-Effect Model	Residual Deviance	35.49 vs. 40 data points
	Deviance Information Criteria	220.783
Fixed-Effect Model	Residual Deviance	35.38 vs. 40 data points
	Deviance Information Criteria	220.182

Emerging Treatments

When emerging treatments were added to the network of genotype 1 treatment-experienced non-cirrhotic patients, a total of 148 additional patients reported in two additional studies (52, 86) were added to the NMA. Two new treatments were added to the evidence network. The rate of SVR12 for the reference treatment PR48 was 0.25 (95% CrI 0.21 to 0.28).

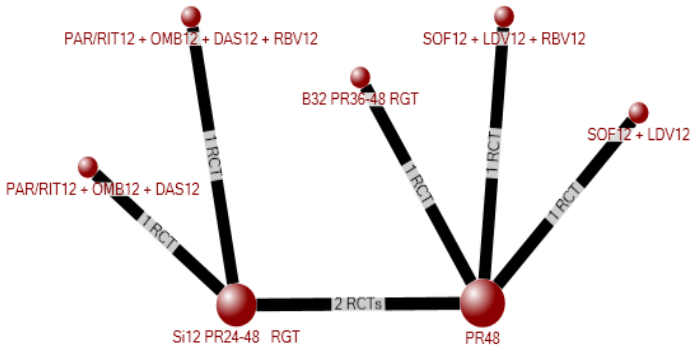
The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix K. Compared to PR48, both emerging treatments (GRA12 + ELB12 + RBV12 and DCV12 + ASU12 + BEC12) significantly increased SVR.

4.1.3 Treatment-Experienced Patients With Prior Relapse

a) All Patients

The evidence network for SVR12 in treatment-experienced patients with genotype 1 with prior relapse included seven studies (45, 49, 74, 81, 102, 103, 105) and a total of 741 participants (Figure 9). Overall, 7 different treatment regimens were considered, providing for two diect treatment comparisons (based on two 2-arm studies) and five treatment estimates (based on five single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.30 (95% CrI 0.25 to 0.36).

Figure 9: SVR Genotype 1 Patients Treatment-Experienced With Prior Relapse: Evidence Network



The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in Table 20. Compared with PR48, all of the DAA treatment strategies (i.e., SOF12 + LDV12, PAR/RIT12 + OMB12 + DAS12 ± RBV12 and SIM12 + PR24-48 RGT) showed significant improvement in SVR (RR ranged from 2.49 to 3.13).

When the individual DAA treatment strategies were compared head-to-head, PAR/RIT12 + OMB12 + DAS12 ± RBV12 significantly improved SVR compared to SIM12 + PR24-48 RGT.

Table 20: SVR Genotype 1 Patients Treatment-Experienced With Prior Relapse: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SIM12 + PR24-48 RGT	PR48	2.49 (1.87,3.10)
SOF12 + LDV12		2.91 (1.99,3.71)
PAR/RIT12 + OMB12 + DAS12		3.13 (2.43,3.83)
PAR/RIT12 + OMB12 + DAS12 + RBV12		3.08 (2.46,3.77)
SOF12 + LDV12	SIM12 + PR24-48 RGT	1.18 (0.79,1.54)
PAR/RIT12 + OMB12 + DAS12		1.25 (1.05,1.55)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.24 (1.07,1.50)
PAR/RIT12 + OMB12 + DAS12	SOF12 + LDV12	1.06 (0.85,1.55)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.04 (0.86,1.54)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PAR/RIT12 + OMB12 + DAS12	0.98 (0.84,1.19)
Random-Effect Model	Residual Deviance	13.67 vs. 14 data points
	Deviance Information Criteria	84.089
Fixed-Effect Model	Residual Deviance	13.66 vs. 14 data points
	Deviance Information Criteria	83.718

b) Genotype 1a

The evidence network for SVR12 in treatment-experienced patients with genotype 1a infection and prior relapse included three studies (49, 102, 105) and a total of 227 participants. Overall, three different treatment regimens were considered, providing for a single direct treatment comparisons (based on one two-arm study), and two treatment estimates (based on two single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.28 (95% CrI 0.21 to 0.35).

The results of the random effects NMA model of selected treatments compared to PR48 and each other are presented in Table 21. Compared with PR48, both DAA treatment strategies (i.e., PAR/RIT12 + OMB12 + DAS12 + RBV12 and SIM12 + PR24-48 RGT) showed significant improvement in SVR (RR of 3.30 and 2.62 respectively). There were no statistically significant differences in SVR when the two DAA treatment strategies were compared to each other.

Table 21: SVR Genotype 1a Patients Treatment-Experienced With Prior Relapse: Relative Risk for All Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SIM12 + PR24-48 RGT	PR48	2.62 (1.85,3.60)
PAR/RIT12 + OMB12 + DAS12 + RBV12		3.30 (2.51,4.36)
PAR/RIT12 + OMB12 + DAS12 + RBV12	SIM12 + PR24-48 RGT	1.26 (0.98,1.66)

Table 21: SVR Genotype 1a Patients Treatment-Experienced With Prior Relapse: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
Random-Effect Model	Residual Deviance	5.624 vs. 6 data points
	Deviance Information Criteria	33.823
Fixed-Effect Model	Residual Deviance	5.68 vs. 6 data points
	Deviance Information Criteria	33.668

c) Genotype 1b

The evidence network for SVR12 in treatment-experienced patients with genotype 1b infection and prior relapse included three studies (49, 102, 105) and a total of 267 participants. Overall, three different treatment regimens were considered, providing a single direct treatment comparison (based on one two-arm study), and two treatment estimates (based on two single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.43 (95% CrI 0.37 to 0.50).

The results of the random effects NMA model of selected treatments compared to PR48 and each other are presented in Table 22. Compared with PR48, both DAA treatment strategies (i.e., PAR/RIT12 + OMB12 + DAS12 + RBV12 and SIM12 + PR24-48 RGT) showed significant improvement in SVR (RR of 2.21 and 1.99 respectively). There were no statistically significant differences in SVR when the DAA treatment strategies were compared to each other.

Table 22: SVR Genotype 1b Patients Treatment-Experienced With Prior Relapse: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SIM12 + PR24-48 RGT	PR48	1.99 (1.62,2.39)
PAR/RIT12 + OMB12 + DAS12 + RBV12		2.21 (1.84,2.61)
PAR/RIT12 + OMB12 + DAS12 + RBV12	SIM12 + PR24-48 RGT	1.11 (0.94,1.31)
Random-Effect Model	Residual Deviance	5.741 vs. 6 data points
	Deviance Information Criteria	31.796
Fixed-Effect Model	Residual Deviance	5.75 vs. 6 data points
	Deviance Information Criteria	31.74

d) Patients With Cirrhosis

The analysis of SVR12 in treatment-experienced patients with cirrhosis and prior relapse included two studies (87, 111) and a total of 58 participants. Overall, two different treatment regimens were considered, providing for a single direct treatment comparison (based on one two-arm study). The rate of SVR12 for the reference treatment PR48 was 0.27 (95% CrI 0.11 to 0.49).

The results of the random effects NMA model of selected treatments compared to PR48 are presented in Table 22. Only one DAA treatment strategy was considered, and compared with PR48, SIM12 + PR24-48 RGT significantly improved SVR.

Table 23: SVR Genotype 1 Patients with Cirrhosis Treatment-Experienced With Prior Relapse: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SIM12 + PR24-48 RGT	PR48	2.68 (1.28,6.70)
Random-Effect Model	Residual Deviance	2.015 vs. 2 data points
	Deviance Information Criteria	11.069
Fixed-Effect Model	Residual Deviance	1.97 vs. 2 data points
	Deviance Information Criteria	10.976

e) Patients Without Cirrhosis

The evidence diagram for SVR12 in treatment-experienced patients without cirrhosis and prior relapse included five studies (45, 49, 102, 103, 105) and a total of 569 participants. Overall, five different treatment regimens were considered, providing two direct treatment comparisons (based on two two-arm studies), and three treatment estimates (based on three single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.37 (95% CrI 0.31 to 0.42).

The results of the random effects NMA model of DAA treatments compared to PR48 and each other are presented in Table 22. Compared with PR48, all three of the treatment strategies (i.e., PAR/RIT12 + OMB12 + DAS12 ± RBV12 and SIM12 + PR24-48 RGT) significantly improved SVR (RR ranged from 2.12 to 2.56).

When the individual DAA treatment strategies were compared head-to-head:

- PAR/RIT12 + OMB12 + DAS12 ± RBV12 significantly improved SVR compared to SIM12 + PR24-48 RGT
- No significant difference in SVR was found when PAR/RIT12 + OMB12 + DAS12 + RBV12 was compared to PAR/RIT12 + OMB12 + DAS12

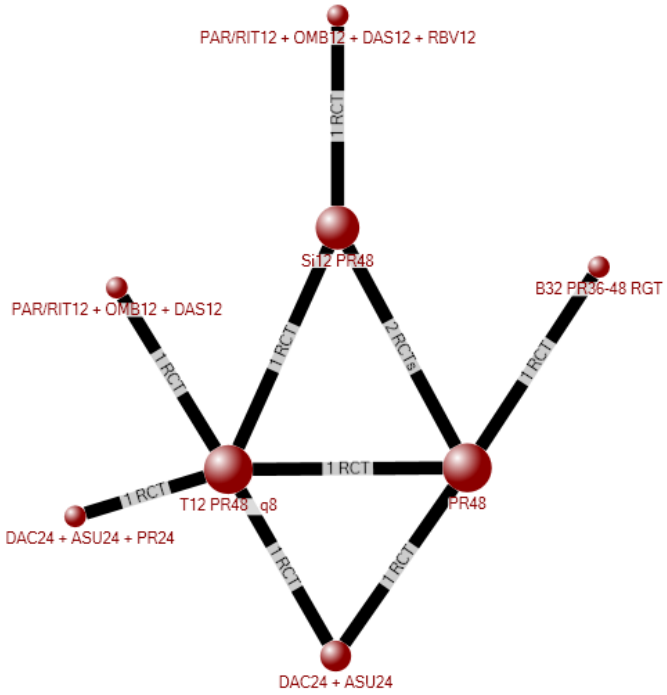
Table 24: SVR Genotype 1 Patients Without Cirrhosis Treatment-Experienced With Prior Relapse: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SIM12 + PR24-48 RGT	PR48	2.12 (1.64,2.57)
PAR/RIT12 + OMB12 + DAS12		2.61 (2.16,3.09)
PAR/RIT12 + OMB12 + DAS12 + RBV12		2.56 (2.09,3.04)
PAR/RIT12 + OMB12 + DAS12	SIM12 + PR24-48 RGT	1.23 (1.02,1.56)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.20 (1.06,1.45)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PAR/RIT12 + OMB12 + DAS12	0.98 (0.83,1.14)
Random-Effect Model	Residual Deviance	8.881 vs. 10 data points
	Deviance Information Criteria	59.882
Fixed-Effect Model	Residual Deviance	8.843 vs. 10 data points
	Deviance Information Criteria	59.796

4.1.4 Treatment-Experienced Patients With Prior Partial Response

a) All Patients

The evidence network for SVR12 in treatment-experienced genotype 1 patients with prior partial response included 10 studies (45, 49, 57, 61, 73, 87, 102, 103, 111, 112) and a total of 840 participants (Figure 10). Overall, eight different treatment regimens were considered, providing for four direct treatment comparisons (based on four two-arm studies), and six treatment estimates (based on six single-arm studies). The NMA based on this evidence network was consistent (Appendix I). The rate of SVR12 for the reference treatment PR48 was 0.13 (95% CrI 0.08 to 0.19).

Figure 10: SVR Genotype 1 Patients Treatment-Experienced With Prior Partial Response: Evidence Network



The results of the random effects NMA model of DAA treatments compared to PR48 and each other are presented in Table 22. Compared with PR48, all treatments (i.e., PAR/RIT12 + OMB12 + DAS12 ± RBV12, DCV24 + ASU24 ± PR24 and SIM12 + PR48) showed significant improvement in SVR.

When the individual DAA treatment strategies were compared head-to-head, PAR/RIT12 + OMB12 + DAS12 + RBV12 significantly improved SVR compared to SIM12 + PR48

Table 25: SVR Genotype 1 Patients Treatment-Experienced With Prior Partial Response: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SIM12 + PR48	PR48	4.25 (1.85,7.08)
PAR/RIT12 + OMB12 + DAS12		6.52 (2.35,10.53)
PAR/RIT12 + OMB12 + DAS12 + RBV12		7.19 (4.05,11.41)

Table 25: SVR Genotype 1 Patients Treatment-Experienced With Prior Partial Response: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
DCV24 + ASU24		5.43 (2.59,8.80)
DCV24 + ASU24 + PR24		6.17 (1.72,9.90)
PAR/RIT12 + OMB12 + DAS12	SIM12 + PR48	1.53 (0.72,2.81)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.67 (1.23,3.10)
DCV24 + ASU24		1.27 (0.74,2.47)
DCV24 + ASU24 + PR24		1.45 (0.56,2.45)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PAR/RIT12 + OMB12 + DAS12	1.08 (0.76,2.56)
DCV24 + ASU24		0.83 (0.50,1.83)
DCV24 + ASU24 + PR24		0.95 (0.38,1.72)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.76 (0.42,1.16)
DCV24 + ASU24 + PR24		0.88 (0.30,1.17)
DCV24 + ASU24 + PR24	DCV24 + ASU24	1.14 (0.42,1.77)
Random-Effect Model	Residual Deviance	20.56 vs. 20 data points
	Deviance Information Criteria	113.704
Fixed-Effect Model	Residual Deviance	20.84 vs. 20 data points
	Deviance Information Criteria	113.016

b) Genotype 1a

The evidence network for SVR12 in treatment-experienced genotype 1a patients with prior partial response included four studies (49, 87, 102, 111) and a total of 202 participants. Overall, four different treatment regimens were considered, providing for two direct treatment comparisons (based on two two-arm studies), and two treatment estimates (based on two single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.21 (95% CrI 0.08 to 0.44).

The results of the random effects NMA model of DAA treatments compared to PR48 and each other are presented in Table 22. Compared with PR48, PAR/RIT12 + OMB12 + DAS12 + RBV12 was the only treatment to significantly increase SVR and, in particular, SIM12 + PR48 did not significantly improve SVR.

When the individual DAA treatment strategies were compared head-to-head, PAR/RIT12 + OMB12 + DAS12 + RBV12 significantly improved SVR compared to SIM12 + PR48.

Table 26: SVR Genotype 1a Patients Treatment-Experienced With Prior Partial Response: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SIM12 + PR48	PR48	1.82 (0.58,5.78)
PAR/RIT12 + OMB12 + DAS12 + RBV12		4.14 (1.97,11.79)
PAR/RIT12 + OMB12 + DAS12 + RBV12	SIM12 PR48	2.24 (1.30,5.65)
Random-Effect Model	Residual Deviance	7.191 vs. 8 data points
	Deviance Information Criteria	42.855
Fixed-Effect Model	Residual Deviance	7.265 vs. 8 data points
	Deviance Information Criteria	42.87

c) Genotype 1b

The evidence network for SVR12 in treatment-experienced genotype 1b patients with prior partial response included four studies (49, 87, 102, 111) and a total of 238 participants. Overall, four different treatment regimens were considered, providing for two direct treatment comparisons (based on two two-arm studies), and two treatment estimates (based on two single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.22 (95% CrI 0.06 to 0.49).

The results of the random effects NMA model of DAA treatments compared to PR48 and each other are presented in Table 22. Compared with PR48, PAR/RIT12 + OMB12 + DAS12 + RBV12 was the only treatment to significantly increase SVR and, in particular, SIM12 + PR48 did not significantly improve SVR.

When the individual DAA treatment strategies were compared head-to-head, no significant difference in SVR between PAR/RIT12 + OMB12 + DAS12 + RBV12 and SIM12 + PR48 was identified.

Table 27: SVR Genotype 1b Patients Treatment-Experienced With Prior Partial Response: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SIM12 + PR48	PR48	2.79 (0.81,9.87)
PAR/RIT12 + OMB12 + DAS12 + RBV12		3.91 (1.64,13.57)
PAR/RIT12 + OMB12 + DAS12 + RBV12	SIM12 PR48	1.34 (0.91,4.31)
Random-Effect Model	Residual Deviance	8.159 vs. 8 data points
	Deviance Information Criteria	41.779
Fixed-Effect Model	Residual Deviance	8.3 vs. 8 data points
	Deviance Information Criteria	41.847

`THE evidence network for SVR12 in treatment-experienced genotype 1 patients with cirrhosis and prior partial response included two studies (87, 111) and a total of 77 participants. Overall, 3 different treatment regimens were considered, providing for two direct comparisons (based on two two-arm studies), and two treatment estimates (based on two single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.22 (95% CrI 0.03 to 0.62).

The results of the random effects NMA model of DAA treatments compared to PR48 are presented in Table 22. Compared with PR48, none of the treatments (in particular, SIM12 + PR48) had a significant effect on SVR.

Table 28: SVR Genotype 1 Patients with Cirrhosis Treatment-Experienced With Prior Partial Response: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SIM12 + PR48	PR48	1.57 (0.26,10.81)
Random-Effect Model	Residual Deviance	3.785 vs. 4 data points
	Deviance Information Criteria	20.106
Fixed-Effect Model	Residual Deviance	3.758 vs. 4 data points
	Deviance Information Criteria	20.045

d) Patients Without Cirrhosis

The evidence network for SVR12 in treatment-experienced genotype 1 patients without cirrhosis and prior partial response included six studies (45, 49, 87, 102, 103, 111) and a total of 444 participants. Overall, four different treatment regimens were considered, providing for three direct treatment comparisons (based on three two-arm studies), and three treatment estimates (based on three single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.16 (95% CrI 0.09 to 0.26).

The results of the random effects NMA model of DAA treatments compared to PR48 are presented in Table 29. Compared to PR48, both PAR/RIT12 + OMB12 + DAS12 and PAR/RIT12 + OMB12 + DAS12 + RBV12 significantly increased SVR, but SIM12 + PR48 was not significantly different.

When the individual DAA treatment strategies were compared head-to-head, none of the treatments were significantly different from one another.

Table 29: SVR Genotype 1 Patients Without Cirrhosis Treatment-Experienced With Prior Partial Response: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SIM12 + PR48	PR48	3.06 (0.32,6.67)
PAR/RIT12 + OMB12 + DAS12		5.54 (2.54,10.25)
PAR/RIT12 + OMB12 + DAS12 + RBV12		5.54 (1.67,10.14)
PAR/RIT12 + OMB12 + DAS12	SIM12 + PR48	1.76 (0.93,15.18)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.76 (0.98,11.86)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PAR/RIT12 + OMB12 + DAS12	1.01 (0.34,1.74)

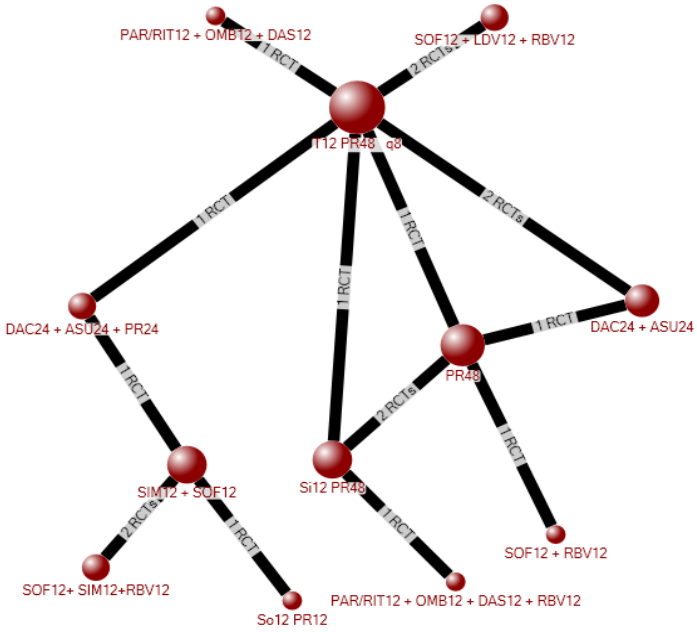
Table 29: SVR Genotype 1 Patients Without Cirrhosis Treatment-Experienced With Prior Partial Response: Relative Risk for Selected Treatment Comparisons		
Random-Effect Model	Residual Deviance	12.44 vs. 12 data points
	Deviance Information Criteria	64.345
Fixed-Effect Model	Residual Deviance	12.82 vs. 12 data points
	Deviance Information Criteria	64.298

4.1.5 Treatment-Experienced Patients With Prior Null Response

a) All Patients

The evidence network for SVR12 in treatment-experienced genotype 1 patients and prior null response included 17 studies (45, 49, 53, 54, 57, 61, 69, 70, 73, 84, 87, 102, 111, 112) and a total of 1,403 participants (Figure 11). Overall, 12 different treatment regimens were considered, providing for 6 direct treatment comparisons (based on six 2-arm studies), and 11 treatment estimates (based on 11 single-arm studies). The NMA based on this evidence network was consistent (Appendix I). The rate of SVR12 for the reference treatment PR48 was 0.18 (95% CrI 0.11 to 0.25).

Figure 11: SVR Genotype 1 Patients Treatment-Experienced With Prior Null Response: Evidence Network



The results of the random effects NMA model of DAA treatments compared to PR48 are presented in Table 30. Compared with PR48, PAR/RIT12 + OMB12 + DAS12 ± RBV12 and DCV24 + ASU24 ± PR24 significantly improved SVR, whereas SOF12 + PR12, SIM12 + PR48 and SIM12 + SOF12 were not significantly different from PR48.

When the individual DAA treatment strategies were compared head-to-head:

- PAR/RIT12 + OMB12 + DAS12 + RBV12 significantly improved SVR compared to SOF12 + PR12 and SIM12 + PR48.
- DCV24 + ASU24 ± PR24 significantly improved SVR compared to SOF12 + PR12.

Table 30: SVR Genotype 1 Patients Treatment-Experienced With Prior Null Response: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SIM12 + SOF12	PR48	1.21(0.19,3.58)
SOF12 + PR12		0.56(0.06,2.83)
SIM12 + PR48		1.67(0.46,3.10)
PAR/RIT12 + OMB12 + DAS12		4.33(1.09,6.86)
PAR/RIT12 + OMB12 + DAS12 + RBV12		4.51(1.33,7.00)
DCV24 + ASU24		3.67(1.32,5.78)
DCV24 + ASU24 + PR24		4.16(1.12,6.57)
SOF12 + PR12	SIM12 + SOF12	0.47(0.09,2.84)
SIM12 + PR48		1.31(0.31,8.75)
PAR/RIT12 + OMB12 + DAS12		3.35(0.83,21.80)
PAR/RIT12 + OMB12 + DAS12 + RBV12		3.53(0.98,22.23)
DCV24 + ASU24		2.91(0.86,18.25)
DCV24 + ASU24 + PR24		3.20(0.94,18.16)
SIM12 + PR48	SOF12+PR12	2.83(0.38,26.96)
PAR/RIT12 + OMB12 + DAS12		7.31(0.99,70.43)
PAR/RIT12 + OMB12 + DAS12 + RBV12		7.72(1.15,72.18)
DCV24 + ASU24		6.36(1.00,59.63)
DCV24 + ASU24 + PR24		6.93(1.05,63.00)
PAR/RIT12 + OMB12 + DAS12	SIM12 + PR48	2.51(0.80,7.79)
PAR/RIT12 + OMB12 + DAS12 + RBV12		2.62(1.17,7.01)
DCV24 + ASU24		2.15(0.88,6.74)
DCV24 + ASU24 + PR24		2.43(0.77,7.19)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PAR/RIT12 + OMB12 + DAS12	1.03(0.38,3.23)
DCV24 + ASU24		0.85(0.37,2.66)
DCV24 + ASU24 + PR24		0.98(0.32,2.78)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.82(0.34,2.29)
DCV24 + ASU24 + PR24		0.95(0.30,2.36)
DCV24 + ASU24 + PR24	DCV24 + ASU24	1.14(0.37,2.44)

Table 30: SVR Genotype 1 Patients Treatment-Experienced With Prior Null Response: Relative Risk for Selected Treatment Comparisons		
Random-Effect Model	Residual Deviance	35.61 vs. 34 data points
	Deviance Information Criteria	188.092
Fixed-Effect Model	Residual Deviance	32.86 vs. 34 data points
	Deviance Information Criteria	182.925

b) Genotype 1a

The evidence network for SVR12 in treatment-experienced genotype 1a patients and prior null response included five studies (26, 49, 87, 102, 111) and a total of 478 participants. Overall, four different treatment regimens were considered, providing for three direct treatment comparisons (based on three two-arm studies), and two treatment estimates (based on two single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.14 (95% CrI 0.04 to 0.34).

The results of the random effects NMA model of DAA treatments compared to PR48 are presented in Table 31. Compared with PR48, both PAR/RIT12 + OMB12 + DAS12 + RBV12 and PAR/RIT24 + OMB24 + DAS24 + RBV24 significantly improved SVR, whereas SIM12 + PR48 was not significantly different from PR48.

When the individual DAA treatment strategies were compared head-to-head:

- Both PAR/RIT12 + OMB12 + DAS12 + RBV12 and PAR/RIT24 + OMB24 + DAS24 + RBV24 significantly improved SVR compared to SIM12 + PR48.
- PAR/RIT12 + OMB12 + DAS12 + RBV12 and PAR/RIT24 + OMB24 + DAS24 + RBV24 were not significantly different from one another.

Table 31: SVR Genotype 1a Patients Treatment-Experienced With Prior Null Response: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
PAR/RIT12 + OMB12 + DAS12 + RBV12	PR48	5.51 (1.70,18.80)
PAR/RIT24 + OMB24 + DAS24 + RBV24		5.94 (1.73,20.49)
SIM12 + PR48		1.85 (0.33,7.33)
PAR/RIT24 + OMB24 + DAS24 + RBV24	PAR/RIT12 + OMB12 + DAS12 + RBV12	1.06 (0.57,2.14)
SIM12 + PR48		0.34 (0.08,0.91)
SIM12 + PR48	PAR/RIT24 + OMB24 + DAS24 + RBV24	0.32 (0.07,0.92)
Random-Effect Model	Residual Deviance	12.13 vs. 10 data points
	Deviance Information Criteria	60.688
Fixed-Effect Model	Residual Deviance	13.75 vs. 10 data points
	Deviance Information Criteria	61.415

c) Genotype 1b

The evidence network for SVR12 in treatment-experienced genotype 1b patients and prior null response included five studies (49, 70, 87, 102, 111) and a total of 63 participants. Overall, four different treatment regimens were considered, providing for two direct treatment comparisons (based on two two-arm studies), and three treatment estimates (based on three single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.09 (95% CrI 0.02 to 0.25).

The results of the random effects NMA model of DAA treatments compared to PR48 are presented in Table 32. Compared with PR48, PAR/RIT12 + OMB12 + DAS12 + RBV12 significantly improved SVR, whereas SIM12 + PR48 and DCV24 + ASU24 were not significantly different from PR48.

When the individual DAA treatment strategies were compared head-to-head:

- PAR/RIT12 + OMB12 + DAS12 + RBV12 significantly improved SVR compared to SIM12 + PR48 and DCV24 + ASU24

Table 32: SVR Genotype 1b Treatment-Experienced With Prior Null Response: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PR48	8.32(2.73,35.44)
SIM12 + PR48		2.64(0.65,12.05)
DCV24 + ASU24		3.54(0.67,16.80)
SIM12 + PR48	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.32(0.12,0.69)
DCV24 + ASU24		0.43(0.11,0.99)
DCV24 + ASU24	SIM12 + PR48	1.33(0.50,2.95)
Random-Effect Model	Residual Deviance	9.996 vs. 10 data points
	Deviance Information Criteria	58.923
Fixed-Effect Model	Residual Deviance	9.929 vs. 10 data points
	Deviance Information Criteria	58.649

d) Patients With Cirrhosis

The evidence network for SVR12 in treatment-experienced genotype 1 patients with cirrhosis and prior null response included five studies (53, 69, 84, 87, 111) and a total of 213 participants. Overall, four different treatment regimens were considered, providing for four direct treatment comparisons (based on four 2-arm studies), and one treatment estimate (based on one single-arm study). The rate of SVR12 for the reference treatment PR48 was 0.17 (95% CrI 0.04 to 0.44).

The results of the random effects NMA model of DAA treatments compared to PR48 are presented in Table 33. Compared with PR48, none of the treatments (i.e., SIM12 + PR48, SIM12 + SOF12 and SOF12 + PR12) had a significant effect on SVR.

When the individual DAA treatment strategies were compared head-to-head, SIM12 + SOF12 was significantly better than SIM12 + PR48.

Table 33: SVR Genotype 1 Patients with Cirrhosis Treatment-Experienced With Prior Null Response: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SIM12 + PR48	PR48	0.58 (0.10,2.47)
SIM12 + SOF12		3.36 (0.70,12.86)
SOF12 + PR12		1.64 (0.12,7.97)
SIM12 + SOF12	SIM12 + PR48	5.65 (1.60,24.60)
SOF12 + PR12		2.68 (0.28,15.78)
SOF12 + PR12	SIM12 + SOF12	0.49 (0.08,1.13)
Random-Effect Model	Residual Deviance	29.34 vs. 31 data points
	Deviance Information Criteria	145.523
Fixed-Effect Model	Residual Deviance	29.3 vs. 31 data points
	Deviance Information Criteria	145.001

e) Patients Without Cirrhosis

The evidence network for SVR12 in treatment-experienced patients without cirrhosis and prior null response included five studies (45, 49, 69, 70, 102) and a total of 735 participants. Overall, 7 different treatment regimens were considered, providing for four direct treatment comparisons (based on four 2-arm studies), and one treatment estimate (based on one single-arm study). The rate of SVR12 for the reference treatment PR48 was 0.08 (95% CrI 0.03 to 0.17).

The results of the random effects NMA model of DAA treatments compared to PR48 are presented in Table 34. Compared with PR48, PAR/RIT12 + OMB12 + DAS12 ± RBV12 significantly improved SVR, whereas SIM12 + PR48, DCV24 + ASU24 ± PR24 and SIM12 + SOF12 were not significantly different from PR48.

When the individual DAA treatment strategies were compared head-to-head, PAR/RIT12 + OMB12 + DAS12 ± RBV12 and DCV24 + ASU24 + PR24 were significantly better than SIM12 + PR48.

Table 34: SVR Genotype 1 Patients Without Cirrhosis Treatment-Experienced With Prior Null Response: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SIM12 + PR48	PR48	1.07 (0.10,3.70)
PAR/RIT12 + OMB12 + DAS12		8.00 (1.26,21.07)
PAR/RIT12 + OMB12 + DAS12 + RBV12		7.39 (1.01,18.58)
DCV24 + ASU24		2.10 (0.18,7.77)
DCV24 + ASU24 + PR24		6.58 (0.63,18.80)
SIM12 + SOF12		4.70 (0.33,14.66)
PAR/RIT12 + OMB12 + DAS12	SIM12 + PR48	7.09 (2.05,65.26)
PAR/RIT12 + OMB12 + DAS12 + RBV12		6.60 (1.94,48.81)
DCV24 + ASU24		1.87 (0.35,16.10)
DCV24 + ASU24 + PR24		5.73 (1.68,38.65)
SIM12 + SOF12		4.15 (0.90,22.96)
PAR/RIT12 + OMB12 + DAS12 +	PAR/RIT12 + OMB12 + DAS12	0.93 (0.17,3.96)

Table 34: SVR Genotype 1 Patients Without Cirrhosis Treatment-Experienced With Prior Null Response: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
RBV12		
DCV24 + ASU24		0.27 (0.03,1.32)
DCV24 + ASU24 + PR24		0.86 (0.09,4.13)
SIM12 + SOF12		0.63 (0.05,2.64)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.29 (0.04,1.46)
DCV24 + ASU24 + PR24		0.92 (0.12,4.86)
SIM12 + SOF12		0.68 (0.06,2.89)
DCV24 + ASU24 + PR24	DCV24 + ASU24	2.98 (0.39,29.47)
SIM12 + SOF12		2.19 (0.21,18.31)
SIM12 + SOF12	DCV24 + ASU24 + PR24	0.76 (0.07,4.13)
Random-Effect Model	Residual Deviance	24.31 vs. 23 data points
	Deviance Information Criteria	124.546
Fixed-Effect Model	Residual Deviance	25.71 vs. 23 data points
	Deviance Information Criteria	124.841

4.1.6 Subgroup Analyses — Treatment-Naive Patients

a) Viral Load at Baseline > 800,000 or 1,000,000 IU/mL

Studies that reported SVR results according to baseline viral load used one of two thresholds: >800,000 IU/mL or >1,000,000 IU/mL. Based on clinical expert input, it was considered appropriate to pool results across studies regardless of the threshold used. The evidence network for SVR12 in treatment-naive genotype 1 patients with viral load at baseline > 800,000 or 1,000,000 IU/mL included 13 studies (44, 50, 56, 59, 61, 66, 72-75, 82, 94, 95) and a total of 3,113 patients. Overall, the 14 treatment regimens considered provided for 14 direct treatment comparisons (based on one four-arm study, one three-arm study and five two-arm studies), and six treatment estimates (based on six single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.36 (95% CrI 0.31 to 0.4

The results of the random effects NMA model of treatments compared to PR48 are presented in Table 35. In particular, compared with PR48, SOF24 + RBV24, SOF12 + LDV12, SOF8 + LDV8, SIM12 + PR24-48 RGT, PAR/RIT12 + OMB12 + DAS12 + RBV12 and DCV24 + ASU24) significantly improved SVR, whereas SOF12 + PR12 was not significantly different from PR48.

When the individual treatment strategies were compared head-to-head:

- SOF12 + LDV12, SOF8 + LDV8, PAR/RIT12 + OMB12 + DAS12 + RBV12 and DCV24 + ASU24 were significantly better than SOF12 + PR12.

Table 35: Genotype 1 Patients with Viral Load > 800,000 or 1,000,000 IU/mL Treatment-Naive: Relative Risk for All Teatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	PR48	1.86 (1.33,2.30)
SOF12 + LDV12		2.40 (1.89,2.84)
SOF24 + LDV24		1.96 (0.60,2.76)
SOF8 + LDV8		2.23 (1.36,2.79)
SOF8 + LDV8 + RBV8		2.18 (1.26,2.75)
SOF12 + LDV12 + RBV12		2.20 (1.11,2.79)
SOF24 + LDV24 + RBV24		2.28 (0.85,2.88)
SIM12 + PR24-48 RGT		2.04 (1.70,2.41)
PAR/RIT12 + OMB12 + DAS12 + RBV12		2.38 (1.51,2.89)
DCV24 + ASU24		2.33 (2.01,2.71)
SOF12 + PR12		0.53 (0.04,2.16)
SOF12 + LDV12	SOF24 + RBV24	1.29 (1.08,1.66)
SOF24 + LDV24		1.06 (0.33,1.60)
SOF8 + LDV8		1.20 (0.78,1.57)
SOF8 + LDV8 + RBV8		1.17 (0.73,1.55)
SOF12 + LDV12 + RBV12		1.18 (0.63,1.62)
SOF24 + LDV24 + RBV24		1.22 (0.47,1.72)
SIM12 + PR24-48 RGT		1.10 (0.87,1.55)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.27 (0.86,1.69)
DCV24 + ASU24		1.26 (1.03,1.75)
SOF12 + PR12		0.29 (0.02,1.17)
SOF24 + LDV24	SOF12 + LDV12	0.82 (0.26,1.15)
SOF8 + LDV8		0.94 (0.64,1.06)
SOF8 + LDV8 + RBV8		0.92 (0.60,1.05)
SOF12 + LDV12 + RBV12		0.92 (0.50,1.11)
SOF24 + LDV24 + RBV24		0.96 (0.37,1.21)
SIM12 + PR24-48 RGT		0.85 (0.72,1.08)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.99 (0.70,1.15)
DCV24 + ASU24		0.97 (0.85,1.23)
SOF12 + PR12		0.22 (0.02,0.89)
SOF8 + LDV8	SOF24 + LDV24	1.13 (0.70,3.47)
SOF8 + LDV8 + RBV8		1.11 (0.65,3.44)
SOF12 + LDV12 + RBV12		1.11 (0.66,2.99)
SOF24 + LDV24 + RBV24		1.12 (0.62,2.93)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.19 (0.77,3.77)
DCV24 + ASU24		1.19 (0.86,4.03)

Table 35: Genotype 1 Patients with Viral Load > 800,000 or 1,000,000 IU/mL Treatment-Naive: Relative Risk for All Teatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF12 + PR12		0.29 (0.05,0.83)
SOF8 + LDV8 + RBV8	SOF8 + LDV8	0.98 (0.74,1.23)
SOF12 + LDV12 + RBV12		0.99 (0.53,1.51)
SOF24 + LDV24 + RBV24		1.02 (0.40,1.65)
SIM12 + PR24-48 RGT		0.91 (0.73,1.51)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.05 (0.89,1.35)
DCV24 + ASU24		1.04 (0.86,1.71)
SOF12 + PR12		0.24 (0.02,0.98)
SOF12 + LDV12 + RBV12	SOF8 + LDV8 + RBV8	1.01 (0.55,1.58)
SOF24 + LDV24 + RBV24		1.04 (0.42,1.75)
SIM12 + PR24-48 RGT		0.93 (0.74,1.62)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.08 (0.83,1.55)
DCV24 + ASU24		1.06 (0.87,1.84)
SOF12 + PR12		0.25 (0.02,1.02)
SOF24 + LDV24 + RBV24	SOF12 + LDV12 + RBV12	1.02 (0.47,1.90)
SIM12 + PR24-48 RGT		0.92 (0.73,1.84)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.07 (0.72,2.03)
DCV24 + ASU24		1.05 (0.86,2.10)
SOF12 + PR12		0.25 (0.02,0.94)
SIM12 + PR24-48 RGT	SOF24 + LDV24 + RBV24	0.89 (0.70,2.42)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.03 (0.68,2.68)
DCV24 + ASU24		1.02 (0.83,2.78)
SOF12 + PR12		0.25 (0.03,0.93)
PAR/RIT12 + OMB12 + DAS12 + RBV12	SIM12 + PR24-48 RGT	1.17 (0.73,1.42)
DCV24 + ASU24		1.14 (0.98,1.36)
SOF12 + PR12		0.26 (0.02,1.08)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.97 (0.83,1.55)
SOF12 + PR12		0.23 (0.02,0.91)
SOF12 + PR12	DCV24 + ASU24	0.23 (0.02,0.93)
Random-Effect Model	Residual Deviance	27.1 vs. 29 data points
	Deviance Information Criteria	167.03
Fixed-Effect Model	Residual Deviance	26.28 vs. 29 data points
	Deviance Information Criteria	165.097

b) Viral Load at Baseline < 800,000 or 1,000,000 IU/mL

The evidence network for SVR12 in treatment-naive genotype 1 patients with viral load at baseline <800,000 or 1,000,000 IU/mL included 13 studies (44, 50, 56, 59, 61, 66, 72-75, 82, 94, 95) and a total of 813 patients. Overall, the 14 treatment regimens considered, provided for 14 direct treatment comparisons (based on one 4-arm study, one 3-arm study and five 2-arm studies), and six treatment estimates (based on six single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.80 (95% CrI 0.72 to 0.88).

The results of the random effects NMA model of treatments compared to PR48 are presented in Table 36. Compared with PR48, only SIM12 + PR24-48 RGT and DCV24 + ASU24 significantly improved SVR.

When the individual treatment strategies were compared head-to-head, the only marginally significant difference was improvement with DCV24 + ASU24 compared to SOF24 + RBV24.

Table 36: SVR Genotype 1 Patients With Viral Load < 800,000 or 1,000,000 IU/mL Treatment-Naive: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF24 + RBV24	PR48	1.01 (0.71,1.19)
SOF12 + LDV12		1.01 (0.49,1.23)
SOF24 + LDV24		1.00 (0.30,1.27)
SOF8 + LDV8		1.10 (0.44,1.29)
SOF8 + LDV8 + RBV8		1.02 (0.36,1.27)
SOF12 + LDV12 + RBV12		1.17 (0.67,1.33)
SOF24 + LDV24 + RBV24		1.00 (0.24,1.27)
SIM12 + PR24-48 RGT		1.16 (1.05,1.30)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.15 (0.50,1.33)
DCV24 + ASU24		1.19 (1.08,1.34)
SOF12 + PR12		0.97 (0.14,1.28)
SOF12 + LDV12	SOF24 + RBV24	0.99 (0.53,1.39)
SOF24 + LDV24		0.99 (0.32,1.49)
SOF8 + LDV8		1.07 (0.47,1.58)
SOF8 + LDV8 + RBV8		1.01 (0.39,1.49)
SOF12 + LDV12 + RBV12		1.14 (0.68,1.68)
SOF24 + LDV24 + RBV24		1.00 (0.25,1.51)
SIM12 + PR24-48 RGT		1.15 (0.97,1.69)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.12 (0.52,1.66)
DCV24 + ASU24		1.18 (1.00,1.74)
SOF12 + PR12		0.97 (0.14,1.48)
SOF24 + LDV24	SOF12 + LDV12	0.99 (0.36,1.77)
SOF8 + LDV8		1.07 (0.61,1.84)
SOF8 + LDV8 + RBV8		1.02 (0.47,1.58)

Table 36: SVR Genotype 1 Patients With Viral Load < 800,000 or 1,000,000 IU/mL Treatment-Naive: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF12 + LDV12 + RBV12		1.14 (0.78,2.09)
SOF24 + LDV24 + RBV24		1.00 (0.29,1.68)
SIM12 + PR24-48 RGT		1.15 (0.95,2.38)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.11 (0.62,2.07)
DCV24 + ASU24		1.18 (0.97,2.45)
SOF12 + PR12		0.97 (0.15,1.79)
SOF8 + LDV8	SOF24 + LDV24	1.08 (0.49,3.46)
SOF8 + LDV8 + RBV8		1.02 (0.38,3.22)
SOF12 + LDV12 + RBV12		1.14 (0.77,3.53)
SOF24 + LDV24 + RBV24		1.00 (0.37,2.43)
SIM12 + PR24-48 RGT		1.16 (0.92,3.95)
SOF24 + RBV(low-dose)24		1.04 (0.40,3.41)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.12 (0.52,3.76)
DCV24 + ASU24		1.19 (0.95,4.05)
SOF12 + PR12		0.98 (0.26,1.68)
SOF8 + LDV8 + RBV8	SOF8 + LDV8	0.96 (0.45,1.52)
SOF12 + LDV12 + RBV12		1.05 (0.66,2.37)
SOF24 + LDV24 + RBV24		0.93 (0.25,1.92)
SIM12 + PR24-48 RGT		1.05 (0.91,2.65)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.03 (0.64,1.81)
DCV24 + ASU24		1.08 (0.94,2.75)
SOF12 + PR12		0.91 (0.13,1.99)
SOF12 + LDV12 + RBV12	SOF8 + LDV8 + RBV8	1.12 (0.71,3.03)
SOF24 + LDV24 + RBV24		0.98 (0.28,2.41)
SIM12 + PR24-48 RGT		1.13 (0.92,3.21)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.10 (0.60,2.64)
DCV24 + ASU24		1.16 (0.95,3.29)
SOF12 + PR12		0.96 (0.14,2.50)
SOF24 + LDV24 + RBV24	SOF12 + LDV12 + RBV12	0.88 (0.25,1.28)
SIM12 + PR24-48 RGT		0.99 (0.88,1.75)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.99 (0.47,1.56)
DCV24 + ASU24		1.01 (0.91,1.82)
SOF12 + PR12		0.85 (0.13,1.30)
SIM12 + PR24-48 RGT	SOF24 + LDV24 + RBV24	1.16 (0.93,4.85)

Table 36: SVR Genotype 1 Patients With Viral Load < 800,000 or 1,000,000 IU/mL Treatment-Naive: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.12 (0.57,4.30)
DCV24 + ASU24		1.19 (0.95,4.98)
SOF12 + PR12		0.98 (0.18,2.82)
PAR/RIT12 + OMB12 + DAS12 + RBV12	SIM12 + PR24-48 RGT	1.00 (0.43,1.13)
DCV24 + ASU24		1.03 (0.93,1.14)
SOF12 + PR12		0.83 (0.12,1.09)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	1.03 (0.91,2.41)
SOF12 + PR12		0.87 (0.13,1.90)
SOF12 + PR12	DCV24 + ASU24	0.82 (0.11,1.06)
Random-Effect Model	Residual Deviance	24.72 vs. 29 data points
	Deviance Information Criteria	117.779
Fixed-Effect Model	Residual Deviance	23.87 vs. 29 data points
	Deviance Information Criteria	114.047

c) HIV-Coinfected Patients

Seven studies of treatment-naive genotype 1 patients with CHC infection reported data for HIV-coinfected patients.(75, 83, 88, 90, 91, 94, 95) No studies reported treatment-experienced genotype 1 patients with HIV coinfection.

In treatment-naive patients, the treatments studied were SOF24 + RBV24 (2 studies, SVR rate 76 to 85% in 226 patients), SOF12 + PR12 (1 study, SVR rate 91% in 23 patients of mixed genotype 1 to 4), SOF12 + LDV12 (1 study, SVR rate 98% in 50 patients) and PR48 (3 studies, SVR rate 29 to 50% in 48 patients), teleprevir (2 studies, SVR rate 71 to 80% in 22 patients) and boceprevir (1 study, SVR rate 63% in 64 patients). The evidence network for SVR12 in patients with an HIV coinfection included 410 patients from six studies.(75, 83, 88, 91, 94, 95) Overall, the five treatment regimens considered, provided for 3 direct treatment comparisons (based on three 2-arm studies), and three treatment estimates (based on three single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.39 (95% CrI 0.25 to 0.53).

The results of the random effects NMA model of treatments compared to PR48 are presented in Table 37. Compared with PR48, all treatments (in particular, SOF12 + LDV12 and SOF24 + RBV24) significantly improved SVR.

Table 37: SVR Genotype 1 Patients With HIV Coinfection Treatment-Naive: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	PR48	2.08 (1.39,3.36)
SOF12 + LDV12		2.46 (1.72,3.78)
SOF12 + LDV12	SOF24 + RBV24	1.17 (0.92,1.56)
Random-Effect Model	Residual Deviance	10.15 vs. 12 data points
	Deviance Information Criteria	56.046
Fixed-Effect Model	Residual Deviance	10.02 vs. 12 data points
	Deviance Information Criteria	55.736

Emerging Treatments

One study (C-WORTHY)(90) reported use of the emerging treatments GRA12 + ELB12 ± RBV in this patient population (87% in 30 patients, or 97% with RBV12 in 29 patients).(90)

4.1.7 Subgroup Analyses — Treatment-Experienced Patients

a) Viral Load at Baseline > 800,000 or 1,000,000 IU/mL

The network for treatment-experienced patients with genotype 1 infection and viral load over 800,000 or 1,000,000 IU/mL involved 1,489 patients in 8 studies (43, 46, 57, 61, 73, 74, 85, 102). Overall, the eight treatment regimens considered provided for 7 direct treatment comparisons (based on one four-arm study and one two-arm study), and six treatment estimates (based on six single-arm studies). PR48 was not one of the direct treatment comparisons in this network, therefore it could not be considered as the reference treatment. SOF12 + LDV12 was selected as the reference. The rate of SVR12 for the reference treatment SOF12 + LDV12 was 0.94 (95% CrI 0.89 to 0.98).

The results of the random effects NMA model of treatments compared to PR48 are presented in Table 43.

In particular, when the individual treatment strategies were compared head-to-head:

- SOF24 + LDV24 was significantly better than DCV24 + ASU24 and SOF12 + PR12
- PAR/RIT12 + OMB12 + DAS12 + RBV12 was significantly better than DCV24 + ASU24

Table 38: SVR Genotype 1 Patients with Viral Load > 800,000 or 1,000,000 IU/mL Treatment-Experienced: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + LDV24	SOF12 + LDV12	1.04 (0.98,1.10)
SOF12 + LDV12 + RBV12		1.03 (0.98,1.10)
SOF24 + LDV24 + RBV24		1.05 (1.00,1.11)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.03 (0.91,1.10)
DCV24 + ASU24		0.92 (0.67,1.04)
DCV24 + ASU24 + PR24		0.99 (0.58,1.08)
SOF12 + PR12		0.91 (0.56,1.04)

Table 38: SVR Genotype 1 Patients with Viral Load > 800,000 or 1,000,000 IU/mL Treatment-Experienced: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF12 + LDV12 + RBV12	SOF24 + LDV24	1.00 (0.96,1.03)
SOF24 + LDV24 + RBV24		1.01 (0.97,1.06)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.99 (0.89,1.03)
DCV24 + ASU24		0.89 (0.65,0.98)
DCV24 + ASU24 + PR24		0.96 (0.56,1.03)
SOF12 + PR12		0.88 (0.55,0.99)
SOF24 + LDV24 + RBV24	SOF12 + LDV12 + RBV12	1.02 (0.98,1.06)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.00 (0.91,1.03)
DCV24 + ASU24		0.89 (0.67,0.98)
DCV24 + ASU24 + PR24		0.96 (0.56,1.04)
SOF12 + PR12		0.88 (0.56,0.98)
PAR/RIT12 + OMB12 + DAS12 + RBV12	SOF24 + LDV24 + RBV24	0.98 (0.88,1.02)
DCV24 + ASU24		0.88 (0.64,0.98)
DCV24 + ASU24 + PR24		0.95 (0.56,1.00)
SOF12 + PR12		0.87 (0.53,0.98)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.90 (0.67,0.99)
DCV24 + ASU24 + PR24		0.97 (0.57,1.09)
SOF12 + PR12		0.89 (0.56,1.00)
DCV24 + ASU24 + PR24	DCV24 + ASU24	1.06 (0.64,1.46)
SOF12 + PR12		0.99 (0.66,1.27)
SOF12 + PR12	DCV24 + ASU24 + PR24	0.93 (0.58,1.53)
Random-Effect Model	Residual Deviance	16.3 vs. 18 data points
	Deviance Information Criteria	89.512
Fixed-Effect Model	Residual Deviance	16.03 vs. 18 data points
	Deviance Information Criteria	88.713

b) Viral Load at Baseline < 800,000 or 1,000,000 IU/mL

The network for treatment-experienced patients with genotype 1 infection and viral load less than 800,000 or 1,000,000 IU/mL involved 215 patients in 8 studies (43, 46, 57, 61, 73, 74, 85, 102). Overall, the eight treatment regimens considered provided for 7 direct treatment comparisons (based on one study with four arms and one study with two arms), and six treatment estimates (based on 6 studies with 1 arm). PR48 was not one of the direct comparisons in the network, therefore it could not be considered as the reference treatment. SOF12 + LDV12 was selected as the reference. The rate of SVR12 for the reference treatment SOF12 + LDV12 was 0.91 (95% CrI 0.65 to 0.99).

The results of the random effects NMA model of treatments compared to PR48 are presented in Table 44. When the individual treatment strategies were compared head-to-head (in particular, SOF12 + LDV12, SOF24 + LDV24, PAR/RIT12 + OMB12 + DAS12 + RBV12, DCV24 + ASU24 ± PR24 and SOF12 + PR12) no significant differences for SVR were identified.

Table 39: SVR Genotype 1 Patients with Viral Load < 1,000,000 IU/mL I Treatment-Experienced: Relative Risk for All Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF24 + LDV24	SOF12 + LDV12	1.01 (0.81,1.40)
SOF12 + LDV12 + RBV12		1.02 (0.84,1.40)
SOF24 + LDV24 + RBV24		1.03 (0.82,1.41)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.06 (0.75,1.46)
DCV24 + ASU24		1.01 (0.59,1.39)
DCV24 + ASU24 + PR24		1.06 (0.82,1.47)
SOF12 + PR12		1.00 (0.37,1.34)
SOF12 + LDV12 + RBV12	SOF24 + LDV24	1.01 (0.86,1.22)
SOF24 + LDV24 + RBV24		1.02 (0.79,1.28)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.04 (0.73,1.30)
DCV24 + ASU24		1.00 (0.59,1.22)
DCV24 + ASU24 + PR24		1.05 (0.78,1.32)
SOF12 + PR12		0.99 (0.35,1.23)
SOF24 + LDV24 + RBV24	SOF12 + LDV12 + RBV12	1.01 (0.79,1.24)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.03 (0.74,1.24)
DCV24 + ASU24		0.99 (0.61,1.12)
DCV24 + ASU24 + PR24		1.04 (0.79,1.28)
SOF12 + PR12		0.98 (0.36,1.16)
PAR/RIT12 + OMB12 + DAS12 + RBV12	SOF24 + LDV24 + RBV24	1.03 (0.71,1.32)
DCV24 + ASU24		0.99 (0.56,1.25)
DCV24 + ASU24 + PR24		1.03 (0.83,1.27)
SOF12 + PR12		0.97 (0.34,1.25)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.96 (0.56,1.31)
DCV24 + ASU24 + PR24		1.00 (0.75,1.47)
SOF12 + PR12		0.95 (0.34,1.31)
DCV24 + ASU24 + PR24	DCV24 + ASU24	1.05 (0.79,1.86)
SOF12 + PR12		0.99 (0.38,1.58)
SOF12 + PR12	DCV24 + ASU24 + PR24	0.94 (0.33,1.25)
Random-Effect Model	Residual Deviance	13.36 vs. 18 data points
	Deviance Information Criteria	60.174
Fixed-Effect Model	Residual Deviance	13.41 vs. 18 data points
	Deviance Information Criteria	60.257

4.2 Genotype 2

Network meta-analyses were conducted for a single efficacy outcome, SVR at 12 weeks. The choice of this outcome for NMA was based on clinical relevance, and the sufficiency of the data available to derive robust and consistent network models. Patient populations were analyzed according to treatment experience (naive or experienced) and then by subgroups within each of the two experience categories (e.g., cirrhotic, non-cirrhotic). For each patient group, the relative risks based on the odds ratios from the NMA are provided comparing each DAA treatment to a reference treatment. Results for select head-to-head comparisons of the DAA treatment regimens are also presented. A full listing of the random effects model results, as well as model diagnostics for the fixed and random effects models, is available in Appendix I along with estimated relative risks and absolute risks. Results from additional sensitivity analyses are also discussed in context with the relevant patient populations. Full NMA results for the sensitivity analyses are available in Appendix K.

For genotype 2, 5 involved treatment-naive patients (54, 66, 75, 80, 94) and four studies (33, 67, 80, 100) involved treatment-experienced patients; the number included in the NMA varied by outcome. Of the studies involving experienced patients, only 1 was an RCT. Of the studies involving treatment-naive patients, two were RCTs. The remaining studies reported data for single, uncontrolled intervention arms or comparisons with a historical control. PR24 was used as the reference treatment for genotype 2 treatment-naive patients. As there were no comparative trials of DAA-based regimens with PR24, a supplemental literature search was conducted to identify the necessary data for PR24 in treatment-naive patients with genotype 2 infection that could be incorporated in the NMA. The search yielded one study (FUSION) that could be used for this purpose. The reference treatment used for treatment-experienced patients was SOF12 + RBV12 as PR of any duration was not deemed to be a relevant treatment option in this patient group based on expert clinical input.(33) While DCV + SOF regimens were of interest for the treatment of genotype 2 infection, no data specific to genotype 2 infection were identified.The full tables showing RRs and RDs for all treatments are provided in Appendix I.

A single study (49) reported data for HIV-coinfected patients who were treatment-experienced (prior relapse, partial response and null responders) and given SIM12 + PR12 (extended to 48 weeks for partial, null and patients with cirrhosis). SVR12 rates ranged from 57% to 87%.

4.2.1 Treatment-Naive Patients

a) All Patients

The evidence network for SVR12 in treatment-naive genotype 2 patients included 5 studies (53, 66, 75, 80, 94) and a total of 116 participants (Figure 12). Overall, 3 different treatment regimens were considered, providing for two direct treatment comparisons (based on two 2-arm studies), and three treatment estimates (based on three single-arm studies). The rate of SVR12 for the reference treatment PR24 was 0.78 (95% CrI 0.72 to 0.83).

Figure 12: SVR Genotype 2 Patients Treatment-Naive: Evidence Network

The results of the random effects NMA model of treatments compared to PR48 are presented in Table 40. Compared with PR24, SOF12 + RBV12 significantly improved SVR in genotype 2 treatment-naive patients, whereas SOF12 + PR12 was not significantly different from PR24. When the individual treatment strategies were compared head-to-head, no significant difference was identified.

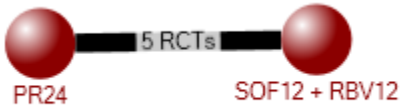
Table 40: SVR Genotype 2 Patients Treatment-Naive: Relative Risk for All Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF12 + RBV12	PR24	1.20 (1.08,1.32)
SOF12 + PR12		1.13 (0.45,1.33)
SOF12 + PR12	SOF12 + RBV12	0.94 (0.39,1.08)
Random-Effect Model	Residual Deviance	9.337 vs. 10 data points
	Deviance Information Criteria	43.641
Fixed-Effect Model	Residual Deviance	9.669 vs. 10 data points
	Deviance Information Criteria	43.536

b) Patients With Cirrhosis

The evidence network for SVR12 in treatment-naive genotype 2 patients with cirrhosis included five studies (66, 75, 80, 94, 100) and a total of 37 participants (Figure 13). Overall, two different treatment regimens were considered, providing for a single direct comparison (based on a single two-arm study), and four treatment estimates (based on four single-arm studies). The rate of SVR12 for the reference treatment PR24 was 0.62 (95% CrI 0.50 to 0.73).

Figure 13: SVR Genotype 2 Patients With Cirrhosis Treatment-Naive: Evidence Network



The results of the random effects NMA model are presented in Table 41. Compared with PR24, SOF12 + RBV12 significantly improved SVR in genotype 2 treatment-naive patients (RR 1.38, 95% CrI 1.03 to 1.79).

Table 41: SVR Genotype 2 Patients With Cirrhosis Treatment-Naive: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF12 + RBV12	PR24	1.38 (1.03,1.79)
Random-Effect Model	Residual Deviance	6.875 vs. 8 data points
	Deviance Information Criteria	31.534
Fixed-Effect Model	Residual Deviance	6.92 vs. 8 data points
	Deviance Information Criteria	31.468

c) Patients Without Cirrhosis

The evidence network for SVR12 in treatment-naive genotype 2 patients without cirrhosis included six studies (53, 66, 75, 80, 94, 100) and a total of 278 participants (Figure 14). Overall, 3 different treatment regimens were considered, providing for two direct treatment comparisons (based on two 2-arm studies), and four treatment estimates (based on four single-arm studies). The rate of SVR12 for the reference treatment PR24 was 0.81 (95% CrI 0.77 to 0.86).

Figure 14: SVR Genotype 2 Patients Without Cirrhosis Treatment-Naive: Evidence Network

The results of the random effects NMA model of all treatments compared to PR24 and each other are presented in Table 42. Compared with PR24, only SOF12 + RBV12 significantly improved SVR in genotype 2 treatment-naive patients without cirrhosis (RR 1.16, 95% CrI 1.08 to 1.24). When the treatment strategies SOF12 + RBV12 and SOF12 + PR12 were compared, there was no significant improvement in SVR.

Table 42: SVR Genotype 2 Patients Without Cirrhosis Treatment-Naive: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF12 + RBV12	PR24	1.16 (1.08,1.24)
SOF12 + PR12		1.15 (0.48,1.27)
SOF12 + PR12	SOF12 + RBV12	0.99 (0.41,1.07)
Random-Effect Model	Residual Deviance	3.912 vs. 6 data points
	Deviance Information Criteria	18.761
Fixed-Effect Model	Residual Deviance	3.841 vs. 6 data points
	Deviance Information Criteria	18.66

4.2.2 Treatment-Experienced Patients

a) All Patients

The evidence network for SVR12 in treatment-experienced genotype 2 patients included four studies (33, 67, 80, 100) and a total of 172 participants (Figure 15). Overall, 3 different treatment regimens were considered, providing for a single direct treatment comparison (based on a single 2-arm study), and three treatment estimates (based on three single-arm studies). The rate of SVR12 for the reference treatment SOF12 + RBV12 therapy was 0.90 (95% CrI 0.85 to 0.94).

Figure 15: SVR Genotype 2 Patients Treatment-Experienced: Evidence Network

The results of the random effects NMA model of all treatments compared to SOF12 + RBV12 and each other are presented in Table 43. Neither SOF16 + RBV16 nor SOF12 + PR12 significantly improved SVR compared with SOF12 + RBV12. SOF12 + PR12 significantly improved SVR when compared to SOF16 + RBV16.

Table 43 SVR Genotype 2 Patients Treatment-Experienced: Relative Risk for All Treatment Comparisons

Treatment	Reference	OR (95% CrI)
SOF16 + RBV16	SOF12 + RBV12	0.86 (0.63,1.02)
SOF12 + PR12		1.07 (0.93,1.15)
SOF12 + PR12	SOF16 + RBV16	1.23 (1.00,1.70)
Random-Effect Model	Residual Deviance	6.58 vs. 8 data points
	Deviance Information Criteria	34.221
Fixed-Effect Model	Residual Deviance	6.609 vs. 8 data points
	Deviance Information Criteria	34.152

b) Patients With Cirrhosis

The evidence network for SVR12 in treatment-experienced genotype 2 patients with cirrhosis included four studies (33, 67, 80, 100) and a total of 172 participants (Figure 16). All had compensated cirrhosis. Overall, 3 different treatment regimens were considered, providing for a single direct treatment comparison (based on a single 2-arm study), and 3 treatment estimates (based on 3 single-arm studies). The rate of SVR12 for the reference treatment SOF12 + RBV12 therapy was 0.73 (95% CrI 0.58 to 0.86).

Figure 16: SVR Genotype 2 Patients With Cirrhosis Treatment-Experienced: Evidence Network

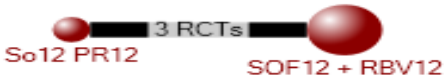
There were no statistically significant differences in SVR rates between any of the three regimens: SOF12 + RBV12, SOF16+ RBV16 and SOF12 +PR12 (Table 44).

Table 44: SVR Genotype 2 Patients With Cirrhosis Treatment-Experienced: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF16 + RBV16	SOF12 + RBV12	1.05 (0.71,1.41)
SOF12 + PR12		1.29 (0.99,1.64)
SOF12 + PR12	SOF16 + RBV16	1.23 (0.89,1.79)
Random-Effect Model	Residual Deviance	6.875 vs. 8 data points
	Deviance Information Criteria	31.534
Fixed-Effect Model	Residual Deviance	6.92 vs. 8 data points
	Deviance Information Criteria	31.468

c) Patients Without Cirrhosis

The evidence network for SVR12 in treatment-experienced genotype 2 patients without cirrhosis included three studies (67, 80, 100) and a total of 95 participants (Figure 17). Overall, two different treatment regimens were considered, providing for no direct treatment comparisons, and three treatment estimates (based on three single-arm studies). The rate of SVR12 for the reference treatment SOF12 + RBV12 therapy was 0.95 (95% CrI 0.91 to 0.98).

Figure 17: SVR Genotype 2 Patients Without Cirrhosis Treatment-Experienced: Evidence Network



SOF12 + PR12 did not significantly improve SVR in the random effects NMA model when compared to SOF12 + RBV12 (Table 45).

Table 45: SVR Genotype 2 Patients Without Cirrhosis Treatment-Experienced: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF12 + PR12	SOF12 + RBV12	1.01 (0.89,1.07)
Random-Effect Model	Residual Deviance	3.912 vs. 6 data points
	Deviance Information Criteria	18.761
Fixed-Effect Model	Residual Deviance	3.841 vs. 6 data points
	Deviance Information Criteria	18.66

4.2.3 Subgroups — Treatment-Naive Patients

a) Viral Load at Baseline > 800,000 or 1,000,000 IU/mL

A subgroup analysis was conducted for genotype 2 treatment-naive patients with a baseline viral load of > 800,000 or 1,000,000 IU/mL. The evidence network for SVR12 in this subgroup included four studies (66, 75, 80, 94) and a total of 193 participants. Overall, two different treatment regimens (SOF12 + RBV12 and PR24) were considered, providing for one direct treatment comparison (based on one two-arm study), and three treatment estimates (based on

three single-arm studies). The rate of SVR12 for the reference treatment PR24 was 0.80 (95% CrI 0.74 to 0.85).

Compared to PR24, SOF12 + RBV12 significantly improved SVR12 in the random effects NMA model (RR 1.25, 95% CrI 1.08 to 1.45).

b) Viral Load at Baseline < 800,000 or 1,000,000 IU/mL

A subgroup analysis was conducted for genotype 2 treatment-naive patients with a baseline viral load of < 800,000 or 1,000,000 IU/mL. The evidence network for SVR12 in this subgroup included four studies (66, 75, 80, 94) and a total of 82 participants. Overall, two different treatment regimens (SOF12 + RBV12 and PR24) were considered, providing for one direct treatment comparison (based on one two-arm study), and three treatment estimates (based on three single-arm studies). The rate of SVR12 for the reference treatment PR24 was 0.75 (95% CrI 0.65 to 0.83).

Compared to PR24, SOF12 + RBV12 significantly improved SVR12 in the random effects NMA model (RR 1.17, 95% CrI 1.07 to 1.28).

4.2.4 Subgroups — HIV Coinfection

Two studies (75, 94) reported on the use of SOF12 + RBV12 (SVR rate 88 to 89% in 45 patients) in genotype 2 treatment-naive patients with HIV coinfection. No studies reported on genotype 2 treatment-experienced patients with HIV coinfection. Data were insufficient for subgroup analyses.

4.3 Genotype 3

Five single-arm studies reported data for genotype 3 patients with CHC infection.(94, 113-118) Since all studies in this NMA were single-arm, there was no natural reference treatment. Clinical experts agreed that PR48 it could be used as a reference treatment so that the single-arm studies could be analyzed in the NMA, although it was not considered a clinically relevant option for treatment-experienced patients. Supplemental literature searches were conducted to identify the best available evidence for SVR rates associated with PR48 in patients with genotype 3 infection. We extracted the PR48 rate of patients who attained for SVR for genotype 3 patients who were naive to treatment from a meta-analysis by Andruilli 2008 (34). For treatment-experienced patients, tThe PR48 data for genotype 3 patients were incorporated into the analysis from Poynard 2009 (35), an observational study. This was a prospective, international, multi-centre, open-label study that evaluated the efficacy and safety of peginterferon-alfa-2b (1.5 mcg/kg/wk) plus weight-based ribavirin (800 to 1,400 mg/day) in 2,333 CHC-infected patients with significant fibrosis/cirrhosis whose previous interferon alfa/ribavirin therapy failed.

During the project, a protocol amendment was made to the eligible regimens for patients with and without cirrhosis. The eligible regimen for inclusion was changed from DAC + SOF for 12 or 24 weeks into 12 weeks for patients without cirrhosis and 24 weeks for patients with compensated cirrhosis. One study (94) reported results on DAC + SOF for 24 weeks in patients with genotype 3 infection and HIV coinfection; however results were reported for a combined group of G2 and G3. The ALLY-3 study (118) reported results on 12 weeks of treatment with DAC + SOF in patients with genotype 3 infection.

4.3.1 Treatment-Naive Patients

a) All Patients

The evidence network for SVR12 in treatment-naive genotype 3 patients included three studies (75, 78, 100) and a total of 237 participants (Figure 18). Overall, three different treatment regimens were considered, providing for no direct treatment comparisons, and three treatment estimates (based on three single-arm studies) (114, 117, 118). Evidence was available for all regimens of interest except SOF12 + PR12 and SOF12 + LDV12 + RBV12, both of which are guideline-recommended as alternative regimens for treatment-naive patients with genotype 3 infection.(1) As well, data specific to genotype 3 were not available for DCV24 + SOF24 ± RBV24, therefore these regimens could not be included in the NMAs. The rate of SVR12 for the reference treatment PR48 was 0.71 (95% CrI 0.69 to 0.73).

Figure 18: SVR Genotype 3 Patients Treatment-Naive — Evidence Network

The results of the random effects NMA model of all treatments compared to PR48 and each other are presented in Table 46. Compared to PR48, both SOF24 + RBV24 and DCV12 + SOF12 significantly improved SVR. There was no significant difference in SVR when DCV12 + SOF12 was compared to SOF24 + RBV24.

Table 46: SVR Genotype 3 Patients Treatment-Naive: Relative Risk for All Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF24 + RBV24	PR48	1.31 (1.21,1.37)
DCV12 + SOF12		1.37 (1.26,1.42)
DCV12 + SOF12	SOF24 + RBV24	1.05 (0.96,1.13)
Random-Effect Model	Residual Deviance	10.56 vs. 10 data points
	Deviance Information Criteria	66.132
Fixed-Effect Model	Residual Deviance	11.32 vs. 10 data points
	Deviance Information Criteria	66.119

b) Sensitivity Analysis – BOSON Study

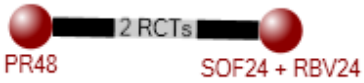
In the absence of evidence in the peer-reviewed literature for use of SOF12 + PR12 in treatment-naive patients with genotype 3 infection, and upon consideration of input from clinical experts indicating the potential clinical utility and cost-effectiveness of this regimen, sensitivity analyses were conducted to include data from the BOSON study in the analysis.(27) This is a relatively large RCT comparing SOF24 + RBV24 to SOF12 + PR12, the results of which have been presented at major conferences. Compared with PR48, all treatments (including SOF12 + PR12) significantly improved SVR. No significant improvements in SVR were found when the DAA regimens were compared to each other.

c) Patients With Cirrhosis

The evidence network for SVR12 in treatment-naive genotype 3 patients with cirrhosis included two studies (75, 100) and a total of 16 participants (Figure 19). Overall, two different treatment regimens were considered, providing for no direct treatment comparisons, and two treatment

estimates (based on two single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.60 (95% CrI 0.56 to 0.64).

Figure 19: SVR Genotype 3 Patients With Cirrhosis Treatment-Naive: Evidence Network



The results of the random effects NMA model of SOF24 + RBV24 compared to PR48 are presented in Table 47. Compared to PR48, SOF24 + RBV24 significantly improved SVR.

Table 47: SVR Genotype 3 Patients With Cirrhosis Treatment-Naive: Relative Risk for All Treatment Comparisons

Treatment	Reference	OR (95% CrI)
SOF24 + RBV24	PR48	1.51(1.14,1.70)
Random-Effect Model	Residual Deviance	7.854 vs. 8 data points
	Deviance Information Criteria	48.042
Fixed-Effect Model	Residual Deviance	8.366 vs. 8 data points
	Deviance Information Criteria	48.013

d) Sensitivity Analysis – BOSON Study

Sensitivity analyses were conducted to include the BOSON study (27) of SOF24 + RBV24 compared to SOF12 + PR12. Compared with PR48, all treatments (including SOF12 + PR12) significantly improved SVR. No significant improvements in SVR were found when the DAA regimens were compared to each other.

e) Patients Without Cirrhosis

The evidence network for SVR12 in treatment-naive genotype 3 patients without cirrhosis included three studies (75, 78, 100) and a total of 221 participants (Figure 20). Overall, three different treatment regimens were considered, providing for no direct treatment comparisons, and three treatment estimates (based on three single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.71 (95% CrI 0.64 to 0.77).

Figure 20: SVR Genotype 3 Patients Without Cirrhosis Treatment-Naive: Evidence Network

The results of the random effects NMA model of SOF24 + RBV24 and DCV12 + SOF12 compared to PR48 and each other are presented in Table 48. Compared to PR48, both SOF24 + RBV24 and DCV12 + SOF12 significantly improved SVR. When compared head-to-head, SOF24 + RBV24 and DCV12 + SOF12 were not significantly different.

Table 48: SVR Genotype 3 Patients Without Cirrhosis Treatment-Naive: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	PR48	1.32 (1.18,1.47)
DCV12 + SOF12		1.38 (1.23,1.53)
DCV12 + SOF12	SOF24 + RBV24	1.04 (0.95,1.14)
Random-Effect Model	Residual Deviance	9.206 vs. 10 data points
	Deviance Information Criteria	59.551
Fixed-Effect Model	Residual Deviance	9.193 vs. 10 data points
	Deviance Information Criteria	59.126

f) Sensitivity Analysis – BOSON Study

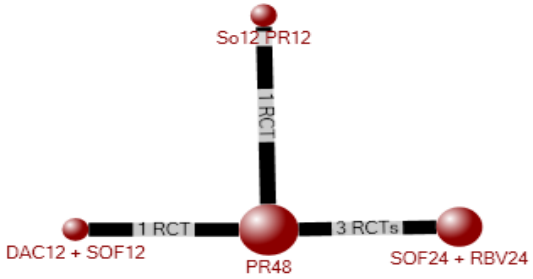
Sensitivity analyses were conducted to include the BOSON study (27) comparing SOF24 + RBV24 to SOF12 + PR12. Compared with PR48, all treatments (including SOF12 + PR12) significantly improved SVR. No significant improvements in SVR were found when the DAA regimens were compared to each other.

4.3.2 Treatment-Experienced Patients

a) All Patients

The evidence network for SVR12 in treatment-experienced genotype 3 patients included five studies (67, 75, 78, 94, 100) and a total of 269 participants (Figure 21). Overall, 4 different treatment regimens were considered, providing for no direct comparisons, and five treatment estimates (based on five single-arm studies). Evidence was available for all regimens of interest except SOF12 + LDV12 + RBV12, which is guideline-recommended as an alternative regimen for treatment-experienced patients with genotype 3 infection.(1) As well, data specific to genotype 3 were not available for DCV24 + SOF24 ± RBV24, therefore these regimens could not be included in the NMAs.The rate of SVR12 for the reference treatment PR48 was 0.55 (95% CrI 0.52 to 0.57).

Figure 21: SVR Genotype 3 Patients Treatment-Experienced: Evidence Network



The results of the random effects NMA model of all treatments compared to PR48 and each other are presented in Table 49. Compared with PR48, SOF24 + RBV24, DCV12 + SOF12 and SOF12 + PR12 significantly improved SVR.

When the individual treatment strategies were compared head-to-head, there were no statistically significant differences in SVR rates between any of the three regimens.

Table 49: SVR Genotype 3 Patients Treatment-Experienced: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	PR48	1.52 (1.35,1.69)
DCV12 + SOF12		1.72 (1.44,1.86)
SOF12 + PR12		1.53 (1.09,1.77)
DCV12 + SOF12	SOF24 + RBV24	1.13 (0.93,1.28)
SOF12 + PR12		1.00 (0.70,1.20)
SOF12 + PR12	DCV12 + SOF12	0.89 (0.63,1.11)
Random-Effect Model	Residual Deviance	10.56 vs. 10 data points
	Deviance Information Criteria	66.132
Fixed-Effect Model	Residual Deviance	11.32 vs. 10 data points
	Deviance Information Criteria	66.119

Sensitivity Analysis

Sensitivity analyses were conducted to include the BOSON study (27) comparing SOF24 + RBV24 to SOF12 + PR12. Compared with PR48, all treatments (including SOF12 + PR12) significantly improved SVR. No significant improvements in SVR were found when the DAA regimens were compared to each other.

b) Patients With Cirrhosis

The evidence network for SVR12 in treatment-experienced genotype 3 patients with cirrhosis included four studies (67, 75, 94, 100) and a total of 88 participants (Figure 22). Overall, three different treatment regimens were considered, providing for no direct comparisons, and four treatment estimates (based on four single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.48 (95% CrI 0.44 to 0.42).

One study reporting data (ALLY-3, Nelson 2015) for genotype 3 cirrhotic patients was not included as the treatment under consideration (DCV12 + SOF12) is not indicated in genotype 3 patients with cirrhosis.

Figure 22: SVR Genotype 3 Patients With Cirrhosis Treatment-Experienced: Evidence Network

The results of the random effects NMA model of all treatments compared to PR48 and each other are presented in Table 50. Compared with PR48, SOF24 + RBV24 and SOF12 + PR12 significantly improved SVR. When the individual treatment strategies were compared head-to-head, SOF24 + RBV24 and SOF12 + PR12 were not significantly different from one another.

Table 50: SVR Genotype 3 Patients With Cirrhosis Treatment-Experienced: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	PR48	1.47 (1.14,1.79)
SOF12 + PR12		1.73 (1.09,2.09)
SOF12 + PR12	SOF24 + RBV24	1.17 (0.73,1.59)
Random-Effect Model	Residual Deviance	7.854 vs. 8 data points
	Deviance Information Criteria	48.042
Fixed-Effect Model	Residual Deviance	8.366 vs. 8 data points
	Deviance Information Criteria	48.013

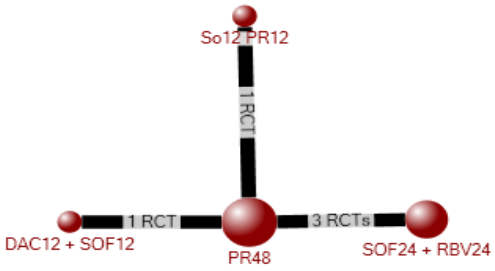
Sensitivity Analysis

Sensitivity analyses were conducted to include the BOSON study (27) comparing SOF24 + RBV24 to SOF12 + PR12. Compared with PR48, all treatments (including SOF12 + PR12) significantly improved SVR. No significant improvements in SVR were found when the DAA regimens were compared to each other.

c) Patients Without Cirrhosis

The evidence network for SVR12 in treatment-experienced genotype three patients without cirrhosis included five studies (67, 75, 78, 94, 100) and a total of 181 participants (Figure 23). Overall, 4 different treatment regimens were considered, providing for no direct comparisons, and five treatment estimates (based on five single-arm studies). The rate of SVR12 for the reference treatment PR48 was 0.61 (95% CrI 0.58 to 0.64).

Figure 23: SVR Genotype 3 Patients Without Cirrhosis Treatment-Experienced: Evidence Network



The results of the random effects NMA model of all treatments compared to PR48 and each other are presented in Table 51. Compared with PR48, SOF24 + RBV24 and DCV12 + SOF12 significantly improved SVR. There was no statistically significant improvement in SVR when SOF12 + PR12 was compared to PR48. When the individual treatment strategies were compared head-to-head, no significant differences for improving SVR were identified.

Table 51: SVR Genotype 3 Patients Without Cirrhosis Treatment-Experienced: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	PR48	1.47 (1.32,1.59)
DCV12 + SOF12		1.54 (1.31,1.67)
SOF12 + PR12		1.38 (0.88,1.62)
DCV12 + SOF12	SOF24 + RBV24	1.05 (0.88,1.18)
SOF12 + PR12		0.94 (0.60,1.13)
SOF12 + PR12	DCV12 + SOF12	0.90 (0.57,1.12)
Random-Effect Model	Residual Deviance	9.206 vs. 10 data points
	Deviance Information Criteria	59.551
Fixed-Effect Model	Residual Deviance	9.193 vs. 10 data points
	Deviance Information Criteria	59.126

Sensitivity Analysis

Sensitivity analyses were conducted to include the BOSON study (27) comparing SOF24 + RBV24 to SOF12 + PR12. Compared with PR48, all treatments (including SOF12 + PR12) significantly improved SVR. No significant improvements in SVR were found when the DAA regimens were compared to each other.

4.3.3 Subgroups – Baseline HCV RNA Level

No data were available for genotype 3 treatment-experienced patients based on their baseline HCV RNA level.

4.3.4 HIV-Coinfected Patients

Data were insufficient to perform network meta-ananlyses for patients with genotype 3 infection coinfected with HIV. A single study reported data on SOF24 +RBV24 (SVR rate 91% in 51 patients). Two studies reported SOF24 + RBV24 in treatment-experienced patients with CHC genotype 3 infection and HIV coinfection (SVR rate 86 to 94% in 66 patients).

4.4 Genotype 4

Four studies (113-116) reported data for patients with genotype 4 CHC infection. One of the four included studies was an RCT.(113) The remaining three studies (114-116) reported data for single, uncontrolled treatment arms. In the absence of trials comparing PR48 with DAA-containing regimens, the PR48 reference data for genotype 4 patients was incorporated into the analysis for treatment-naive patients (all patients, and patients with cirrhosis or patients without cirrhosis) from a meta-analysis by Yee 2014 (36) located using a supplemental literature search. The study aimed to evaluate treatment outcome and host/viral factors on SVR in genotype 4 patients treated with PR in a systematic and quantitative manner. Due to the lack of specific data on patients with cirrhosis, the PR control rate for treatment-naive patients with cirrhosis is based on the data from Yee et al. for patients with METAVIR score of F3/F4.

For treatment-experienced patients, SOF12 + RBV12 was considered the reference treatment based on clinical considerations.

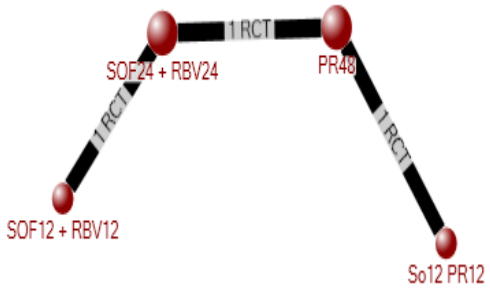
4.4.1 Treatment-Naive Patients

a) All Patients

Three studies (113-115) reported SVR12 (114, 115) and SVR24 (113) rates in treatment-naive patients with genotype 4 infection. One of the studies (113) was a 2-arm RCT comparing SOF24 + RBV24 directly to SOF12 + RBV12. Two of the studies (114, 115) were single-arm studies of SOF24 + RBV24 (114) and SOF12 + PR12 (115). Regimens of interest in this review for genotype 4 infection for which no evidence was identified for treatment-naive patients were SOF12 + LDV12 (which is not currently indicated for genotype 4 but is guideline-recommended(1)) and DCV12 + ASU12 + PR12. The rate of SVR12 for the reference treatment PR48 was 0.52 (95% CrI 0.50 to 0.53).

All three studies, involving a total of 87 treatment-naive patients, were included in the NMA. Overall, 4 different treatment strategies were considered, providing for one direct treatment comparion (based on one 2-arm study) and two treatment estimates (based on two single-srm studies). The evidence network for this outcome is displayed in Figure 24.

Figure 24: SVR Genotype 4 Patients Treatment-Naive: Evidence Network



The results of the random effects NMA model of all treatments compared to PR48 and each other are presented in Table 52. Compared with PR48, SOF24 + RBV24 and SOF12 + PR12 significantly improved SVR, whereas SOF12 + RBV12 was not significantly different from PR48 for improving SVR.

When the individual treatment strategies were compared head-to-head, SOF12 + PR12 was significantly better than SOF12 + RBV12 for improving SVR.

Table 52: SVR Genotype 4 Patients Treatment-Naive Patients: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF12 + RBV12	PR48	0.99 (0.10,1.82)
SOF24 + RBV24		1.63 (1.18,1.84)
SOF12 + PR12		1.85 (1.57,1.95)
SOF24 + RBV24	SOF12 + RBV12	1.60 (0.91,15.18)
SOF12 + PR12		1.85 (1.00,18.78)
SOF12 + PR12	SOF24 + RBV24	1.13 (0.93,1.55)
Random-Effect Model	Residual Deviance	3.976 vs. 4 data points
	Deviance Information Criteria	19.486
Fixed-Effect Model	Residual Deviance	3.899 vs. 4 data points
	Deviance Information Criteria	19.339

Emerging Treatments

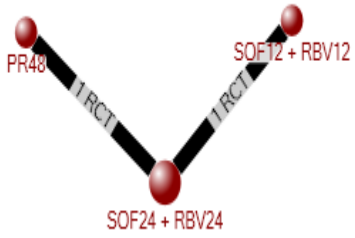
When emerging treatments were added to the network of genotype 4 treatment- naive patients, a total of 37 additional patients reported in two additional studies (55, 101) were included in the NMA. Three new treatments were added to the evidence network. No significant differences were found when the emerging treatments were added to the network (GRA12 + ELB12, DCV12 + ASU12 + BEC12 (75mg BID), DCV12 + ASU12 + BEC12 (150mg BID)).

b) Patients With Cirrhosis

Two studies (113, 114) reported SVR12 (114) and 24 (113) rates in genotype 4 treatment-naive patients with cirrhosis. One of the studies (113) was a 2-arm RCT comparing SOF24 + RBV24 directly to SOF12 + RBV12 and one was a single-arm study (114) of SOF24 + RBV24 with no comparator. The rate of SVR12 for the reference treatment PR48 was 0.38 (95% CrI 0.36 to 0.41).

Both studies of treatment-naive genotype 4 patients (n = 14) with cirrhosis were included in the NMA. Overall, three different treatment strategies were considered, providing for one direct treatment comparison (based on one 2-arm study) and one treatment estimate (based on one single-arm study). The evidence network for this outcome is displayed in Figure 25.

Figure 25: SVR Genotype 4 Patients With Cirrhosis Treatment-Naive: Evidence Network



The results of the random effects NMA model of all treatments compared to PR48 and each other are presented in Table 53. Compared with PR48, SOF24 + RBV24 significantly improved

SVR in genotype 4 treatment-naive cirrhotic patients, whereas SOF12 + RBV12 was not significantly different from PR48 for improving SVR.

When the individual treatment strategies were compared head-to-head, SOF24 + RBV24 and SOF12 + RBV12 were not significantly different from one another.

Table 53: SVR Genotype 4 Patients With Cirrhosis Treatment-Naive: Relative Risk for All Treatment Comparsions

Treatment	Reference	RR (95% CrI)
SOF12 + RBV12	PR 48	0.75 (0.02,2.46)
SOF24 + RBV24		2.27 (1.36,2.65)
SOF24 + RBV24	SOF12 + RBV12	2.88 (0.95,107.80)
Random-Effect Model	Residual Deviance	3.692 vs. 4 data points
	Deviance Information Criteria	14.418
Fixed-Effect Model	Residual Deviance	3.603 vs. 4 data points
	Deviance Information Criteria	14.252

c) Patients Without Cirrhosis

Two studies (113, 114) reported SVR12 (114) and SVR24 (113) rates in genotype 4 treatment-naive patients without cirrhosis. One of the studies (113) was a 2-arm RCT comparing SOF24 + RBV24 directly to SOF12 + RBV12 and one was a single-group study (114) of SOF24 + RBV24 with no comparator. The rate of SVR12 for the reference treatment PR48 was 0.65 (95% CrI 0.63 to 0.67).

Both studies of treatment-naive genotype 4 patients without cirrhosis were included in the NMA. Overall, three different treatment strategies were considered, providing for one direct treatment comparison (based on one 2-arm study) and one treatment estimate (based on one single-arm study). The evidence network for this outcome is displayed in Figure 26.

The results of the NMA between different treatment strategies are provided in Table 54. There were no statistically significant differences between any of the treatment strategies considered (i.e., SOF12 + RBV12 and SOF24 + RBV24) when compared to PR48 or to one another.

Figure 26: SVR Genotype 4 Patients Without Cirrhosis Treatment-Naive: Evidence Network

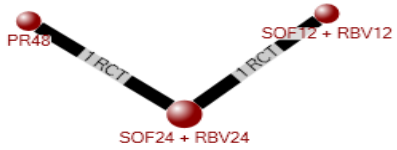


Table 54: SVR Genotype 4 Patients Without Cirrhosis Treatment-Naive: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF12 + RBV12	PR48	1.17 (0.16,1.52)
SOF24 + RBV24		1.28 (0.87,1.47)
SOF24 + RBV24	SOF12 + RBV12	1.08 (0.75,7.34)
Random-Effect Model	Residual Deviance	3.781 vs. 4 data points
	Deviance Information Criteria	17.861
Fixed-Effect Model	Residual Deviance	3.818 vs. 4 data points
	Deviance Information Criteria	17.935

4.4.2 Subgroups – Treatment-Naive

a) Viral Load at Baseline > 1,000,000 IU/mL

The evidence network for SVR12 in treatment-naive genotype 4 patients with viral load at baseline >1,000,000 IU/mL, included two studies (37, 75) and a total of 32 patients. Overall, two treatment regimens were considered, providing for one direct treatment comparison (based on one 2-arm study) and one treatment estimate (based on one single-arm study). The rate of SVR12 for the reference treatment SOF12 + RBV12 was 0.72 (95% CrI 0.47 to 0.90).

The results of the random effects NMA model of the treatment strategies are provided in Table 55. Only two treatment strategies were under consideration, SOF24 + RBV24 and SOF12 + RBV12. There was no significant difference between these treatments in SVR.

Table 55: SVR Genotype 4 Patients With Viral Load > 1,000,000 IU/mL Treatment-Naive Patients: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	SOF12 + RBV12	1.13 (0.79,1.77)
Random-Effect Model	Residual Deviance	3.409 vs. 4 data points
	Deviance Information Criteria	15.435
Fixed-Effect Model	Residual Deviance	3.446 vs. 4 data points
	Deviance Information Criteria	15.427

b) Viral Load At Baseline < 1,000,000 IU/mL

The evidence network for SVR12 in treatment-naive genotype 4 patients with viral load at baseline < 1,000,000 IU/mL, included two studies (37, 75) and a total of 27 patients. Overall, two treatment regimens were considered, providing for one direct treatment comparison (based on one 2-arm study) and one treatment estimate (based on one single-arm study). The rate of SVR12 for the reference treatment SOF12 + RBV12 was 0.86 (95% CrI 0.64 to 0.97).

The results of the random effects NMA model of the treatment strategies are provided in Table 56. Only two treatment strategies were under consideration, SOF24 + RBV24 and SOF12 + RBV12. There was no significant differences between these treatments in SVR.

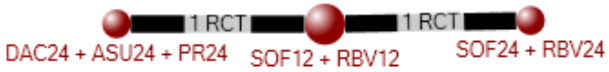
Table 56: SVR Genotype 4 Patients With Viral Load < 1,000,000 IU/mL Treatment-Naive Patients: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	SOF12 + RBV12	1.09 (0.88,1.46)
Random-Effect Model	Residual Deviance	2.824 vs. 4 data points
	Deviance Information Criteria	12.44
Fixed-Effect Model	Residual Deviance	2.777 vs. 4 data points
	Deviance Information Criteria	12.375

4.4.3 Treatment-Experienced Patients

a) All Patients

The evidence network for SVR12 in treatment-experienced genotype 4 patients included two studies (37, 57) and a total of 76 patients (Figure 27). Overall, three different treatment regimens were considered, providing for one direct treatment comparison (based on one 2-arm study), and one treatment estimate (based on one single-arm study). Regimens of interest in this review for genotype 4 infection for which no evidence was identified for treatment-experienced patients were SOF12 + PR12 and SOF12 + LDV12 (which is not currently indicated for genotype 4 but is guideline-recommended(1)).

Figure 27: SVR Genotype 4 Patients Treatment-Experienced Evidence Network



The results of the random effects NMA model of the treatment strategies are provided in Table 57. Compared with SOF12 + RBV12, the DCV24 + ASU24 + PR24 regimen significantly improved SVR in genotype 4 treatment-experienced patient. There was no statistically significant difference between SOF12 + RBV12 and SOF24 + RBV24 or between DCV24 + ASU24 + PR24 and SOF24 + RBV24.

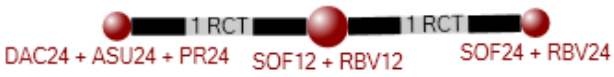
Table 57: SVR Genotype 4 Patients Treatment-Experienced: Relative Risks for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	SOF12 + RBV12	1.41 (0.85,2.04)
DCV24 + ASU24 + PR24		1.55 (1.18,2.18)
DCV24 + ASU24 + PR24	SOF24 + RBV24	1.09 (0.87,1.77)
Random-Effect Model	Residual Deviance	3.976 vs. 4 data points
	Deviance Information Criteria	19.486
Fixed-Effect Model	Residual Deviance	3.899 vs. 4 data points
	Deviance Information Criteria	19.339

b) Patients With Cirrhosis

The evidence network for SVR12 in treatment-experienced genotype 4 patients with cirrhosis included two studies (37, 57) and a total of 28 participants (Figure 28). Overall, three different

treatment regimens were considered, providing for a single direct treatment comparison (based on one 2-arm study), and one treatment estimate (based on one single-arm study).

Figure 28: SVR Genotype 4 Patients With Cirrhosis Treatment-Experienced: Evidence Network



The results of the random effects NMA model of the treatment strategies are provided in Table 58. Compared with SOF12 + RBV12, the DCV24 + ASU24 + PR24 regimen significantly improved SVR in genotype 4 treatment-experienced patients. There was no statistically significant difference between SOF12+ RBV12 and SOF24 + RBV24 or between DCV24 + ASU24 + PR24 and SOF24+RBV24.

Table 58: SVR Genotype 4 Patients With Cirrhosis Treatment-Experienced: Relative Risks for All Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF24 + RBV24	SOF12 + RBV12	1.47 (0.57,3.51)
DCV24 + ASU24 + PR24		1.63 (1.00,3.81)
DCV24 + ASU24 + PR24	SOF24 + RBV24	1.06 (0.71,2.99)
Random-Effect Model	Residual Deviance	3.692 vs. 4 data points
	Deviance Information Criteria	14.418
Fixed-Effect Model	Residual Deviance	3.603 vs. 4 data points
	Deviance Information Criteria	14.252

c) Patients Without Cirrhosis

The evidence network for SVR12 in treatment-experienced genotype 4 patients without cirrhosis included two studies (37, 57) and a total of 48 participants (Figure 29). Overall, three different treatment regimens were considered, providing for a single direct treatment comparison (based on one 2-arm study), and one treatment estimate (based on one single-arm study).

Figure 29: SVR Genotype 4 Patients Without Cirrhosis Treatment-Experienced: Evidence Network

The results of the random effects NMA model of the treatment strategies are provided in Table 59. Compared with SOF12 + RBV12, the DCV24 + ASU24 + PR24 regimen significantly improved SVR in genotype 4 treatment-experienced patients. There was no statistically significant difference between SOF12 + RBV12 and SOF24 + RBV24 or between DCV24 + ASU24 + PR24 and SOF24 + RBV24.

Table 59: SVR Genotype 4 Patients Without Cirrhosis Treatment-Experienced: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	SOF12 + RBV12	1.28 (0.68,1.91)
DCV24 + ASU24 + PR24		1.49 (1.12,2.12)
DCV24 + ASU24 + PR24	SOF24 + RBV24	1.15 (0.87,2.13)
Random-Effect Model	Residual Deviance	3.781 vs. 4 data points
	Deviance Information Criteria	17.861
Fixed-Effect Model	Residual Deviance	3.818 vs. 4 data points
	Deviance Information Criteria	17.935

4.4.4 Subgroups – Treatment-Experienced

a) Viral Load at Baseline > 800,000 or 1,000,000 IU/mL

The evidence network for SVR12 in treatment-experienced genotype 4 patients with viral load at baseline > 800,000 or 1,000,000 IU/mL, included two studies (37, 57) and a total of 50 patients from one 2-arm study and one single-arm study. Overall, three treatment regimens were considered, providing for one direct treatment comparison (based on one two-arm study) and one treatment estimate (based on one single-arm study). The rate of SVR12 for the reference treatment SOF12 + RBV12 was 0.48 (95% CrI 0.30 to 0.67).

The results of the random effects NMA model of the treatment strategies are provided in Table 60. Compared with SOF12 + RBV12 therapy, DCV24 + ASU24 + PR24 significantly improved SVR, whereas SOF24 + RBV24 was not significantly different from SOF12 + RBV12 for improved SVR.

When the individual treatment strategies were compared head-to-head, DCV24 + ASU24 + PR24 and SOF24 + RBV24 were not significantly different.

Table 60: SVR Genotype 4 Patients With Viral Load > 800,000 or 1,000,000 IU/mL Treatment-Experienced: Relative Risk for All Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	SOF12 + RBV12	1.76 (0.93,2.93)
DCV24 + ASU24 + PR24		1.96 (1.37,3.18)
DCV24 + ASU24 + PR24	SOF24 + RBV24	1.09 (0.86,2.02)
Random-Effect Model	Residual Deviance	3.684 vs. 4 data points
	Deviance Information Criteria	17.244
Fixed-Effect Model	Residual Deviance	3.747 vs. 4 data points
	Deviance Information Criteria	17.37

b) Viral Load at Baseline < 800,000 or 1,000,000 IU/mL

The evidence network for SVR12 in treatment-experienced genotype 4 patients with viral load at baseline < 800,000 or 1,000,000 IU/mL, included two studies (37, 57) and a total of 26 patients from one 2-arm study and one single-arm study. Overall, three treatment regimens were

considered, providing for one direct treatment comparison (based on one 2-arm study) and one treatment estimate (based on one single-arm study). The rate of SVR12 for the reference treatment SOF12 + RBV12 was 0.88 (95% CrI 0.60 to 0.98).

The results of the random effects NMA model of the treatment strategies are provided in Table 60. Compared with SOF12 + RBV12 therapy, SOF24 + RBV24 and DCV24 + ASU24 + PR24 were not significantly different for improved SVR.

When the individual treatment strategies were compared head-to-head, DCV24 + ASU24 + PR24 and SOF24 + RBV24 were not significantly different.

Table 61: SVR Genotype 4 Patients With Viral Load < 800,000 or 1,000,000 IU/mL Treatment-Experienced: Relative Risk for All Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF24 + RBV24	SOF12 + RBV12	1.02 (0.46,1.48)
DCV24 + ASU24 + PR24		1.05 (0.61,1.55)
DCV24 + ASU24 + PR24	SOF24 + RBV24	1.03 (0.58,2.40)
Random-Effect Model	Residual Deviance	3.341 vs. 4 data points
	Deviance Information Criteria	12.853
Fixed-Effect Model	Residual Deviance	3.262 vs. 4 data points
	Deviance Information Criteria	12.716

4.4.5 Subgroups – HIV Coinfected

Two studies reported results for SOF24 + RBV24 (1 study, SVR rate 84% in 31 patients)(88) and SOF12 + PR12 (SVR rate 91% in 23 patients mixed genotype 1 to 4)(75) in genotype 4 treatment-naive patients with HIV coinfection. No studies reported on genotype 4 treatment-experienced patients with HIV coinfection. Data were insufficient for subgroup analyses.

4.5 Genotypes 5 and 6

The NEUTRINO study (115) was a single-arm interventional trial evaluating SOF12 + PR12 in treatment-naive patients with CHC genotypes 1, 4, 5, and 6 infection. Only one patient with genotype 5 and 6 patients with genotype 6 infection were included in NEUTRINO. The C-EDGE study(101) was a blinded, randomized, placebo-controlled trial evaluating a fixed-dose combination of grazoprevir 100mg/elbasvir 50 mg for 12 weeks in patients with genotypes 1, 4, and 6 infection. Only 10 patients with genotype 6 were included in this study. It is not clear if any of the patients with genotype 5 or 6 included in these studies had cirrhosis.

Two studies in patients with CHC genotype 6 infection met the inclusion criteria for the systematic review. These trials evaluated SOF12 + PR12 or grazoprevir/elbasvir for 12 weeks in patients who had never received treatment for CHC infection. One of these studies also included treatment-naive patients with CHC genotype 5 infection.

All six patients with genotype 6 and the one patient with genotype 5 who received SOF + PR in the NEUTRINO study achieved SVR12. Eight out of the 10 (80%) patients with genotype 6 who received grazoprevir/elbasvir in C-EDGE study achieved SVR12, while two patients experienced virologic relapse.

4.6 Liver Transplant Recipients – All Genotypes

Two studies reported SVR rates for liver transplant recipients with CHC infection. One study (47) reported SVR in a group of mixed genotype 1 (83%), 2 (0%),3 (15%), 4 (3%) and mixed treatment experience (88% experienced) HCV patients (n = 40) (47). Patients were treated with SOF24 + RBV24 (n = 40) and 70% (90% confidence interval: 56% to 82%) achieved SVR at 12 weeks. Results were additionally presented by genotype and METAVIR score for those who achieved SVR12. Fifty-seven percent of patients with genotype 1a, 21% of patients with genotype 1b or 3, and 0% of patients with genotype 4 achieved SVR12. Of the patients with METAVIR score = F4 (considered cirrhotic), 36% achieved SVR12. Outcomes were not presented according to previous treatment status (47).

A second study (62) reported SVR in adult liver transplant recipients with genotype 1 (85% genotype 1a) and mild or no fibrosis. Thirty-four participants received a once-daily dose of PAR/RIT24 + OMB24 + DAS24 ± RBV (RBV dose was at the discretion of the investigator). Of the 34 study participants, 33 had a sustained virologic response at post-treatment weeks 12 and 24, for a rate of 97% (95% confidence interval, 85 to 100).

5 RESULTS: HARMS – ADVERSE EVENTS

Network meta-analyses were conducted for three harms outcomes: rash, anemia and depression. Patient populations across all genotypes were analyzed according to treatment experience (naive or experienced). For each patient group, the relative risks based on the odds ratios from the NMA comparing each DAA treatment to PR48 are provided. Results for select head-to-head comparisons of the DAA treatment regimens are also presented. A full summary of random effects model results for each outcome is available in Appendix J along with estimated relative risks and absolute risks. Results from additional sensitivity analyses involving emerging treatment regimens are also discussed in context with the relevant patient population. Full NMA results for the sensitivity analyses are available in Appendix K.

5.1 Rash

5.1.1 Treatment-Naive Patients

The evidence network for rash in treatment-naive patients included 31 studies (44, 50, 51, 53, 54, 58-60, 62, 63, 65, 66, 72, 73, 82, 91, 93-95, 104, 106-109) and a total of 6,678 patients. Overall, 21 different treatment regimens were considered, providing for 21 direct comparisons (based on one 4-arm study and 15 2-arm studies), and 15 treatment estimates (based on 15 single-arm studies). The NMA based on this evidence network was consistent (Appendix J). The rate of rash for the reference treatment PR48 was 0.18 (95% CrI 0.15 to 0.22).

The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in Table 62. Compared with PR48 dual therapy, SOF12 + LDV12, DCV24 + ASU24 and PAR/RIT12 + OMB12 + DAS12 were significantly associated with less rash in treatment-naive patients.

When the individual DAA treatment strategies were compared head-to-head:

- SOF12 + LDV12, PAR/RIT12 + OMB12 + DAS12 and DCV24 + ASU24 were significantly associated with less rash compared SOF12 + PR12, SIM12 + PR24-48 RGT and PAR/RIT12 + OMB12 + DAS12 + RBV12

Table 62: Rash — All Genotype Patients Treatment-Naive: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF24 + RBV24	PR48	0.77 (0.08,2.72)
SOF12 + LDV12		0.26 (0.14,0.48)
SOF12 + PR12		0.80 (0.37,1.77)
SIM12 + PR24-48 RGT		1.12 (0.81,1.52)
PAR/RIT12 + OMB12 + DAS12		0.22 (0.09,0.53)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.72 (0.38,1.30)
DCV24 + ASU24		0.13 (0.05,0.32)
DCV12 + SOF12		0.37 (0.05,1.61)
SOF12 + LDV12	SOF24 + RBV24	0.34 (0.10,3.38)
SOF12 + PR12		1.08 (0.28,10.51)
SIM12 + PR24-48 RGT		1.45 (0.39,14.60)

Table 62: Rash — All Genotype Patients Treatment-Naive: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% Crl)**
PAR/RIT12 + OMB12 + DAS12		0.29 (0.06,2.99)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.95 (0.23,9.36)
DCV24 + ASU24		0.17 (0.03,2.01)
DCV12 + SOF12		0.51 (0.05,6.45)
SOF12 + PR12	SOF12 + LDV12	3.08 (1.82,5.37)
SIM12 + PR24-48 RGT		4.27 (2.13,8.55)
PAR/RIT12 + OMB12 + DAS12		0.85 (0.28,2.39)
PAR/RIT12 + OMB12 + DAS12 + RBV12		2.74 (1.42,5.22)
DCV24 + ASU24		0.49 (0.15,1.55)
DCV12 + SOF12		1.41 (0.18,6.40)
SIM12 + PR24-48 RGT	SOF12 + PR12	1.39 (0.59,3.19)
PAR/RIT12 + OMB12 + DAS12		0.27 (0.08,0.84)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.89 (0.39,2.03)
DCV24 + ASU24		0.16 (0.04,0.55)
DCV12 + SOF12		0.45 (0.05,2.30)
PAR/RIT12 + OMB12 + DAS12	SIM12 + PR24-48 RGT	0.20 (0.07,0.50)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.65 (0.31,1.25)
DCV24 + ASU24		0.12 (0.05,0.27)
DCV12 + SOF12		0.33 (0.05,1.52)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PAR/RIT12 + OMB12 + DAS12	3.26 (1.12,9.73)
DCV24 + ASU24		0.59 (0.15,2.21)
DCV12 + SOF12		1.69 (0.19,9.73)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.18 (0.06,0.55)
DCV12 + SOF12		0.52 (0.07,2.32)
DCV12 + SOF12	DCV24 + ASU24	2.82 (0.34,17.84)
Random-Effect Model	Residual Deviance	62.47 vs. 64 data points
	Deviance Information Criteria	371.62
Fixed-Effect Model	Residual Deviance	63.66 vs. 64 data points
	Deviance Information Criteria	371.027

Emerging Treatments

When emerging treatments were added to the network of treatment-naive patients, a total of 341 additional patients reported in three studies (64, 90) were included in the NMA. Six new treatments were added to the evidence network. GRA + ELB (+ RBV for 8 weeks, or ± RBV for 12 weeks) were the only emerging regimens included. The rate of SVR12 for the reference

treatment PR48 dual therapy was 0.18 (95% CrI 0.15 to 0.22).The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix K.

Compared with PR48, none of the emerging treatments was associated with a significantly decreased risk of rash. When the emerging DAA strategies were compared head-to-head with the existing DAA treatments, GRA18 + ELB18 (50 mg QD) + RBV18 was significantly associated with more rash than SOF12 + LDV12, PAR/RIT12 + OMB12 + DAS12, DCV24 + ASU24, and SOF24 + RBV (low-dose)24. None of the GRA + ELB treatment durations (± RBV) were significantly associated with more or less rash when compared to the rest of the treatments in the network.

5.1.2 Treatment-Experienced Patients

The evidence network for rash in treatment-experienced patients included 22 studies (33, 43, 45, 53, 54, 57, 67, 69, 70, 73, 81, 85, 87, 94, 96, 102, 103, 105, 111, 112) and a total of 3,833 patients. Overall, 17 different treatment regimens were considered, providing for 12 direct comparisons (based on one 4-arm study and six 2-arm studies), and 15 treatment estimates (based on 15 single-arm studies). The NMA based on this evidence network was consistent (Appendix J). The rate of rash for the reference treatment PR48 was 0.13 (95% CrI 0.11 to 0.16).

The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in Table 63. Compared with PR48 dual therapy, SOF12 + LDV12, and PAR/RIT12 + OMB12 + DAS12 ± RBV12 were significantly associated with less rash in treatment-experienced patients.

When the individual DAA treatment strategies were compared head-to-head:

- SOF 12+ LDV12 was significantly associated with less rash compared with SOF12 + PR12, SIM12 + PR24-48 RGT, SOF24 + RBV24 and DCV24 + ASU24 +PR24
- PAR/RIT12 + OMB12 + DAS12 was significantly associated with less rash compared with SOF12 + PR12, SIM12 + PR24-48 RGT, DCV24 + ASU24 + PR24 and PAR/RIT12 + OMB12 + DAS12 + RBV12
- PAR/RIT12 + OMB12 + DAS12 + RBV12 and DCV24 + ASU24 was significantly associated with less rash compared with DCV24 + ASU24 + PR24
- DCV24 + ASU24 was significantly associated with less rash compared with SOF12 + PR12 and DCV24 + ASU24 +PR24

Table 63: Rash – All Genotype Patients Treatment-Experienced: Relative Risk for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SIM12 + SOF12	PR48	0.58 (0.04,3.80)
SOF12 + LDV12		0.17 (0.04,0.56)
SIM12 + PR24-48 RGT		1.02 (0.44,2.12)
SOF24 + RBV24		1.26 (0.27,3.66)
PAR/RIT12 + OMB12 + DAS12		0.06 (0.00,0.36)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.61 (0.24,1.81)
DCV24 + ASU24		0.27 (0.07,0.88)
DCV24 + ASU24 + PR24		2.62 (0.99,4.94)

Table 63: Rash – All Genotype Patients Treatment-Experienced: Relative Risk for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF12 + PR12		1.39 (0.64,2.81)
SOF12 + LDV12	SIM12 + SOF12	0.28 (0.03,5.20)
SIM12 + PR24-48 RGT		1.76 (0.23,27.34)
SOF24 + RBV24		2.08 (0.21,35.67)
PAR/RIT12 + OMB12 + DAS12		0.09 (0.00,2.75)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.08 (0.13,18.41)
DCV24 + ASU24		0.46 (0.05,7.36)
DCV24 + ASU24 + PR24		4.36 (0.70,56.71)
SOF12 + PR12		2.39 (0.32,37.63)
SIM12 + PR24-48 RGT	SOF12 + LDV12	6.20 (1.39,28.60)
SOF24 + RBV24		7.46 (1.18,39.57)
PAR/RIT12 + OMB12 + DAS12		0.34 (0.02,3.14)
PAR/RIT12 + OMB12 + DAS12 + RBV12		3.72 (0.82,20.06)
DCV24 + ASU24		1.58 (0.28,9.21)
DCV24 + ASU24 + PR24		15.60 (3.44,64.06)
SOF12 + PR12		8.50 (1.94,37.97)
SOF24 + RBV24	SIM12 + PR24-48 RGT	1.23 (0.23,4.71)
PAR/RIT12 + OMB12 + DAS12		0.05 (0.00,0.43)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.60 (0.18,2.42)
DCV24 + ASU24		0.26 (0.05,1.11)
DCV24 + ASU24 + PR24		2.54 (0.76,7.29)
SOF12 + PR12		1.36 (0.48,3.96)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PAR/RIT12 + OMB12 + DAS12	11.19(1.72,174.90)
DCV24 + ASU24		4.77 (0.49,91.28)
DCV24 + ASU24 + PR24		45.32 (5.66,810.90)
SOF12 + PR12		24.92 (3.35,469.80)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.43 (0.08,1.85)
DCV24 + ASU24 + PR24		4.21 (1.00,12.84)
SOF12 + PR12		2.29 (0.61,7.39)
DCV24 + ASU24 + PR24	DCV24 + ASU24	9.49 (2.81,35.25)
SOF12 + PR12		5.22 (1.26,24.91)
SOF12 + PR12	DCV24 + ASU24 + PR24	0.54 (0.20,1.76)
Random-Effect Model	Residual Deviance	49.87 vs. data points
	Deviance Information Criteria	278.127
Fixed-Effect Model	Residual Deviance	52.35 vs. data points
	Deviance Information Criteria	278.13

Emerging Treatments

When emerging treatments were added to the network of treatment-experienced patients, a total of 130 patients reported in one 4-arm study (67)were included in the NMA. Four new treatments were added to the evidence network (GRA + ELB 50mg QD for 12 or 18 weeks ± RBV). The rate of SVR12 for the reference treatment PR48 was 0.14 (95% CrI 0.11 to 0.16).

The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix K.

Compared with PR48, GRA18 + ELB18(50mg QD) was significantly associated with less rash. When the GRA+ ELB (50mg QD) treatment strategies were compared head-to-head with the existing DAA treatments, GRA18 + ELB18 (50mg QD) was significantly associated with less rash when compared to SOF12 + LDV12 ± RBV12, SOF24 + LDV24 + RBV24, SOF12+ SIM12+RBV12, SOF24 + RBV24, DCV24 + ASU24 + PR24, and SOF12 + PR12.

5.2 Anemia

5.2.1 Treatment-Naive Patients

The evidence network for anemia in treatment-naive patients included 31 studies (44, 50, 51, 53, 54, 56, 59, 60, 63, 65, 66, 68, 72, 82, 88, 91, 93-95, 104, 106-109) and a total of 6,517 patients. Overall, 20 different treatment regimens were considered, providing for 22 direct comparisons (based on one 4-arm study and 16 2-arm studies), and 14 treatment estimates (based on 14 single-arm studies). The NMA based on this evidence network was consistent (Appendix J). The rate of anemia for the reference treatment PR48 was 0.21 (95% CrI 0.18 to 0.25).

The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in Table 64. Compared with PR48, SOF12 + LDV12, PAR/RIT12 + OMB12 + DAS12 ± RBV12 and DCV12 + SOF12 were significantly associated with less anemia in treatment-naive patients.

When the individual DAA treatment strategies were compared head-to-head:

- SOF12+ LDV12, PAR/RIT12 + OMB12 + DAS12 ± RBV12 and DCV12 + SOF12 were significantly associated with less anemia compared to SOF12 + PR12
- SOF12+ LDV12, PAR/RIT12 + OMB12 + DAS12 and DCV12 + SOF12 were significantly associated with less anemia compared to SOF24 + RBV24 and SIM12 + PR24-48 RGT
- SOF12+ LDV12 was significantly associated with less anemia compared to PAR/RIT12 + OMB12 + DAS12 ± RBV12

Table 64: Anemia — All Genotype PatientsTreatment-Naive: Relative Risks for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF24 + RBV24	PR48	1.26(0.48,2.53)
SOF12 + LDV12		0.06(0.02,0.13)
SOF12 + PR12		1.49(0.80,2.45)
SIM12 + PR24-48 RGT		0.82(0.59,1.12)
PAR/RIT12 + OMB12 + DAS12		0.35(0.14,0.75)
PAR/RIT12 + OMB12 + DAS12 +		0.38(0.15,0.84)

Table 64: Anemia — All Genotype PatientsTreatment-Naive: Relative Risks for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
RBV12		
DCV12 + SOF12		0.09(0.01,0.70)
SOF12 + LDV12	SOF24 + RBV24	0.04(0.01,0.16)
SOF12 + PR12		1.19(0.48,3.35)
SIM12 + PR24-48 RGT		0.65(0.31,1.79)
PAR/RIT12 + OMB12 + DAS12		0.27(0.09,0.94)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.31(0.10,1.01)
DCV12 + SOF12		0.07(0.00,0.71)
SOF12 + PR12	SOF12 + LDV12	26.17(11.76,65.24)
SIM12 + PR24-48 RGT		14.89(6.03,37.43)
PAR/RIT12 + OMB12 + DAS12		6.24(1.82,20.88)
PAR/RIT12 + OMB12 + DAS12 + RBV12		6.78(2.62,18.20)
DCV12 + SOF12		1.53(0.08,14.99)
SIM12 + PR24-48 RGT	SOF12 + PR12	0.56(0.33,1.01)
PAR/RIT12 + OMB12 + DAS12		0.23(0.08,0.63)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.26(0.10,0.63)
DCV12 + SOF12		0.06(0.00,0.51)
PAR/RIT12 + OMB12 + DAS12	SIM12 + PR24-48 RGT	0.42(0.17,0.98)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.47(0.19,1.08)
DCV12 + SOF12		0.10(0.01,0.88)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PAR/RIT12 + OMB12 + DAS12	1.11(0.33,3.72)
DCV12 + SOF12		0.25(0.01,2.54)
DCV12 + SOF12	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.23(0.01,1.91)
Random-Effect Model	Residual Deviance	62.48 vs. 64 data points
	Deviance Information Criteria	367.889
Fixed-Effect Model	Residual Deviance	63.13 vs. 64 data points
	Deviance Information Criteria	366.667

Emerging Treatments

When emerging treatments were added to the network of treatment-naive patients, a total of 657 additional patients reported in 4 studies (64, 90, 101) were included in the NMA. Six new GRA + ELB treatments were added to the evidence network. The rate of anemia for the reference treatment PR48 was 0.21 (95% CrI 0.18 to 0.24).

The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix K.

Compared with PR48, GRA12 + ELB12 and GRA12 + ELB12 (50mg QD) were significantly associated with less anemia than PR48 in treatment-naive patients. When the individual DAA treatment strategies were compared head-to-head:

- GRA12 + ELB12 was significantly associated with less anemia compared to SOF12 + RBV12, SOF24 + RBV24, SOF12 + PR12, SOF12 PR24-48 RGT and SIM12 + PR24-48 RGT
- GRA12 + ELB12 (50 mg QD) was significantly associated with less anemia compared to SOF24 + RBV24, SOF12 + PR12 and SIM12 + PR24-48 RGT
- GRA18 + ELB18 (50mg QD) was significantly associated with less anemia compared to GRA12 + ELB12 + RBV12
- GRA12 + ELB12 + RBV12 was significantly associated with more anemia compared to SOF12 + LDV12
- GRA18 + ELB18 (50mg QD) + RBV18 was significantly associated with more anemia compared to GRA12 + ELB12 (50mg QD), GRA18 + ELB18 (50mg QD) and SOF12 + LDV12

5.2.2 Treatment-Experienced Patients

The evidence network for anemia in treatment-experienced patients included 18 studies (33, 43, 45, 53, 54, 57, 67, 68, 85, 87, 94, 96, 102, 103, 105, 111, 112) and a total of 3,572 patients. Overall, 14 different treatment regimens were considered, providing for 12 direct comparisons (based on one 4-arm study and six 2-arm studies), and 11 treatment estimates (based on11 single-arm studies). The NMA based on this evidence network was consistent (Appendix J). The rate of anemia for the reference treatment PR48 was 0.19 (95% CrI 0.16 to 0.22).

The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in Table 65. Compared with PR48, SOF12 + LDV12, PAR/RIT12 + OMB12 + DAS12 ± RBV12 and DCV24 + ASU24 + PR24 were significantly associated with less anemia in treatment-experienced patients.

When the individual DAA treatment strategies were compared head-to-head:

- SOF 12+ LDV12 and PAR/RIT12 + OMB12 + DAS12 were significantly associated with less anemia compared to SOF12 + PR12, SIM12 + PR24-48 RGT, SOF24 + RBV24, PAR/RIT12 + OMB12 + DAS12 + RBV12 and DCV24 + ASU24 + PR24
- PAR/RIT12 + OMB12 + DAS12 + RBV12 and DCV24 + ASU24 + PR24 were significantly associated with less anemia compared to SOF12 + PR12

Table 65: Anemia – All Genotype Patients Treatment-Experienced: Relative Risks for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF12 + LDV12	PR48	0.02 (0.00,0.11)
SIM12 + PR24-48 RGT		0.83 (0.45,1.48)
SOF24 + RBV24		0.41 (0.08,1.35)
PAR/RIT12 + OMB12 + DAS12		0.01 (0.00,0.07)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.27 (0.11,0.66)
DCV24 + ASU24 + PR24		0.28 (0.10,0.79)
SOF12 + PR12		1.02 (0.56,1.69)
SIM12 + PR24-48 RGT	SOF12 + LDV12	33.92 (6.74,314.90)
SOF24 + RBV24		16.58 (1.77,180.50)

Table 65: Anemia – All Genotype Patients Treatment-Experienced: Relative Risks for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
PAR/RIT12 + OMB12 + DAS12		0.37 (0.03,7.00)
PAR/RIT12 + OMB12 + DAS12 + RBV12		11.29 (1.98,111.90)
DCV24 + ASU24 + PR24		11.36 (1.85,120.10)
SOF12 + PR12		40.96 (8.35,384.60)
SOF24 + RBV24	SIM12 + PR24-48 RGT	0.48 (0.09,1.94)
PAR/RIT12 + OMB12 + DAS12		0.01 (0.00,0.10)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.33 (0.12,1.00)
DCV24 + ASU24 + PR24		0.33 (0.10,1.12)
SOF12 + PR12		1.22 (0.53,2.72)
PAR/RIT12 + OMB12 + DAS12	SOF24 + RBV24	0.02 (0.00,0.30)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.68 (0.16,4.16)
DCV24 + ASU24 + PR24		0.69 (0.14,4.83)
SOF12 + PR12		2.48 (0.64,14.00)
PAR/RIT12 + OMB12 + DAS12 + RBV12	PAR/RIT12 + OMB12 + DAS12	29.04 (3.23,418.50)
DCV24 + ASU24 + PR24		29.55 (2.94,458.60)
SOF12 + PR12		107.60 (13.04,1289.00)
DCV24 + ASU24 + PR24	PAR/RIT12 + OMB12 + DAS12 + RBV12	1.00 (0.30,3.45)
SOF12 + PR12		3.68 (1.27,10.29)
SOF12 + PR12	DCV24 + ASU24 + PR24	3.63 (1.10,11.84)
Random-Effect Model	Residual Deviance	37.06 vs. 38 data points
	Deviance Information Criteria	223.003
Fixed-Effect Model	Residual Deviance	37.64 vs. 38 data points
	Deviance Information Criteria	222.563

Emerging Treatments

When emerging treatments were added to the network of treatment- experienced patients, a total of 407 additional patients reported in two studies (52, 64) were included in the NMA. Five new treatments were added to the evidence network. The rate of anemia for the reference treatment PR48 was 0.19 (95% CrI 0.16 to 0.21).

The results of the random effects NMA model of the emerging treatments compared to PR48 and each other are presented in Appendix K.

Compared with PR48, GRA + ELB (50mg QD) 12 and 18 weeks were significantly associated with less anemia in treatment-experienced patients. When the individual DAA treatment strategies were compared head-to-head with the emerging treatment strategies:

- GRA12 + ELB12 (50mg QD) was significantly associated with less anemia compared to SOF24 + LDV24 + RBV24

- GRA12 + ELB12 (50mg QD) and GRA18 + ELB18 (50mg QD) were significantly associated with less anemia compared to SIM12 + PR24-48 RGT and SOF12 + PR12
- GRA12 + ELB12 + RBV12, GRA12 + ELB12 (50mg QD) + RBV12 and GRA18 + ELB18 (50mg QD) + RBV18 were significantly associated with more anemia compared to SOF12 + LDV12 and PAR/RIT12 + OMB12 + DAS12

5.3 Depression

5.3.1 Treatment- Naive Patients

The evidence network for depression in treatment-naive patients included 23 studies (44, 53, 54, 56, 60, 63, 65, 66, 72, 73, 88, 91, 93-95, 106-109)and a total of 785 patients. Overall, 21 different treatment regimens were considered, providing for 17 direct comparisons (based on one 4-arm study and 11 2-arm studies), and 11 treatment estimates (based on 11 single-arm studies). The NMA based on this evidence network was consistent (Appendix J). The rate of rash for the reference treatment PR48 was 0.14 (95% CrI 0.11 to 0.17).

The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in **Table 66**. Compared with PR48, SOF12 + LDV12 and DCV24 + ASU24 were significantly associated with less depression in treatment-naive patients.

When the individual DAA treatment strategies were compared head-to-head:
- SOF 12 + LDV12 were significantly associated with less depression compared SOF12 + PR12, SIM12 + PR24-48 RGT, SOF24 + RBV24, DCV24 + ASU24, DCV12 + SOF12 and PAR/RIT12 + OMB12 + DAS12 + RBV12

Table 66: Depression – All Genotype Patients Treatment-Naive: Relative Risks for Selected Treatment Comparisons

Treatment	Reference	RR (95% CrI)
SOF12 + LDV12	PR48	0.02 (0.00,0.10)
SOF12 + PR12		0.57 (0.21,1.53)
SIM12 + PR24-48 RGT		0.72 (0.42,1.28)
SOF24 + RBV24		0.78 (0.17,3.18)
DCV24 + ASU24		0.25 (0.07,0.92)
DCV12 + SOF12		0.51 (0.04,3.15)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.42 (0.08,1.53)
SOF12 + PR12	SOF12 + LDV12	29.89 (6.36,219.60)
SIM12 + PR24-48 RGT		39.33 (7.04,345.10)
SOF24 + RBV24		41.46 (4.06,513.70)
DCV24 + ASU24		13.69 (1.67,147.00)
DCV12 + SOF12		25.70 (1.14,445.30)
PAR/RIT12 + OMB12 + DAS12 + RBV12		21.54 (2.09,261.00)
SIM12 + PR24-48 RGT	SOF12 + PR12	1.27 (0.46,3.63)
SOF24 + RBV24		1.34 (0.22,7.69)
DCV24 + ASU24		0.45 (0.09,2.02)
DCV12 + SOF12		0.86 (0.06,7.46)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.74 (0.11,3.42)

Table 66: Depression – All Genotype Patients Treatment-Naive: Relative Risks for Selected Treatment Comparisons		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	SIM12 + PR24-48 RGT	1.07 (0.20,4.90)
DCV24 + ASU24		0.35 (0.11,1.08)
DCV12 + SOF12		0.69 (0.05,4.71)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.57 (0.10,2.33)
DCV24 + ASU24	SOF24 + RBV24	0.33 (0.05,2.45)
DCV12 + SOF12		0.65 (0.03,7.20)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.53 (0.06,4.07)
DCV12 + SOF12	DCV24 + ASU24	1.97 (0.11,18.81)
PAR/RIT12 + OMB12 + DAS12 + RBV12		1.63 (0.20,9.74)
PAR/RIT12 + OMB12 + DAS12 + RBV12	DCV12 + SOF12	0.82 (0.07,15.11)
Random-Effect Model	Residual Deviance	53.05 vs. 48 data points
	Deviance Information Criteria	267.581
Fixed-Effect Model	Residual Deviance	56.27 vs. 48 data points
	Deviance Information Criteria	268.659

Emerging Treatments

No studies reported depression outcomes in treatment-naive patients for the emerging treatments of interest in this review.

5.3.2 Treatment-Experienced Patients

The evidence network for depression in treatment-experienced patients included 12 studies (33, 53, 54, 87, 94, 96, 102, 103, 111, 112) and a total of 2,260 patients. Overall, nine different treatment regimens were considered, providing for four direct comparisons (based on four two-arm studies), and eight treatment estimates (based on eight single-arm studies). The NMA based on this evidence network was consistent (Appendix J). The rate of rash for the reference treatment PR48 was 0.13 (95% CrI 0.10 to 0.17).

The results of the random effects NMA model of selected treatment compared to PR48 and each other are presented in Table 67. Compared with PR48, SOF24 + RBV24, PAR/RIT12 + OMB12 + DAS12 + RBV12 and DCV24 + ASU24 were significantly associated with less depression in treatment-experienced patients.

When the individual DAA treatment strategies were compared head-to-head, there were no siginificant differences in depression.

Table 67: Depression – All Genotype Patients Treatment-Experienced: Relative		
Treatment	**Reference**	**RR (95% CrI)**
SOF24 + RBV24	PR48	0.17 (0.01,0.99)
PAR/RIT12 + OMB12 + DAS12 + RBV12		0.27 (0.07,0.93)
DCV24 + ASU24		0.11 (0.02,0.50)

Table 67: Depression – All Genotype Patients Treatment-Experienced: Relative		
Treatment	**Reference**	**RR (95% CrI)**
PAR/RIT12 + OMB12 + DAS12 + RBV12	SOF24 + RBV24	1.63 (0.16,26.24)
DCV24 + ASU24		0.67 (0.08,9.59)
DCV24 + ASU24	PAR/RIT12 + OMB12 + DAS12 + RBV12	0.41 (0.05,3.19)
Random-Effect Model	Residual Deviance	23.48 vs. 24 data points
	Deviance Information Criteria	135.299
Fixed-Effect Model	Residual Deviance	23.98 vs. 24 data points
	Deviance Information Criteria	135.244

Emerging Treatments

No studies reported depression outcomes in treatment-experienced patients for the emerging treatments of interest in this review.

5.4 Other Safety Events

In addition to rash, anemia and depression, other safety events were considered. The data available and/or the frequency of these safety events were not sufficient for NMA.

5.4.1 Treatment-Naive Patients

The occurrence of other safety events, as reported in the studies included in the review, is reported in Table 68 for treatment-naive paients. In particular:

- Withdrawals due to adverse events, mortality (all cause), mortality (liver-related), suicidal ideation, hepatocellular carcinoma and liver transplants were infrequently reported across all treatments
- Adverse events, fatigue and pruritus were frequently reported across all treatments
- PR48 was often associated with harms, and
- SOF12 + PR12, SOF12 + RBV12, SOF24 + RBV24, SIM12 + PR24-48 RGT were associated with several harms.

Table 68: Other Safety Events – All Genotype Patients Treatment-Naive: Frequency of Reporting			
Safety	**Range**	**Exceeds 10%**	**Exceeds 35%**
Withdrawals – all causes	0 to 46%	PR48 (5) SOF12 + PR12 (2) SOF12 + RBV12 (2) SOF24 + RBV24 (3)	PR48 (3)
Withdrawals due to adverse events	0 to 1% Except 3% for PAR/RIP + OMB12 + DAS12 + RBV12 (1); 2% for SOF12 + PR12 (1)		

Table 68: Other Safety Events – All Genotype Patients Treatment-Naive: Frequency of Reporting			
Safety	**Range**	**Exceeds 10%**	**Exceeds 35%**
Discontinuations – all causes	0 to 68%	PR48 (2) SOF12 + PR12 (1) SOF12 + RBV12 (1) SOF24 + RBV24 (3) SIM12 + PR24-48 RGT (2) DCV24 + ASU24 (1)	PR48 (6)
Discontinuations due to adverse events	0 to 20%	PR48 (2)	
Relapse	0 to 40%	PR48 (5) SOF12 + RBV12 (3) SOF24 + RBV24 (4) SIM12 + PR24-48 RGT (1)	SOF24 + RBV24 (1)
Mortality – all causes	0 to 1% Except 2% for PR48 (1)		
Mortality – liver-related	0% or NR		
Serious adverse events	0 to 21%	PR48 (2) SOF12 + RBV12 (1)	
Adverse events	42 to 100%		All
Fatigue	0 to 68%		All
Pruritus	0 to 57%	All	
Neutropenia	0 to 30%	PR48 (7) SOF12 + PR12 (4) SIM12 + PR24-48 RGT (3)	
Thrombocytopenia	0 to 17%	SOF12 + PR12 (2)	
Flu-like symptoms	0 to 30%	PR48 (7) SOF12 + PR12 (1) SIM12 + PR24-48 RGT (3)	
Suicidal ideation	0 to 3% 2% for SIM12 + PR24-48 RGT		
Epoetin alfa use	0 to 43%	PR48 (2)	
Blood transfusion	0 to 9%		
Hepatocellular carcinoma	Rare		
Liver transplants	Rare		

5.4.2 Treatment-Experienced Patients

The occurrence of other safety events, as reported in the studies included in the review, is reported in Table 69 for treatment-experienced paients. Similar to treatment-naive patients:

- Withdrawals due to adverse events, mortality (all cause), mortality (liver-related), suicidal ideation, hepatocellular carcinoma and liver transplants were infrequently reported across all treatments:
  - Adverse events, fatigue and pruritus were frequently reported across all treatments
  - PR48 was often associated with harms, and
  - SOF12 + PR12, SOF12 + RBV12, SOF24 + RBV24, SIM12 + PR24-48 RGT were associated with several harms.

Table 69: Other Safety Events – All Genotype Patients Treatment-Experienced: Frequency of Reporting			
Safety	**Range**	**Exceeds 10%**	**Exceeds 35%**
Withdrawals – all causes	0 to 48%	PR48 (3) SOF24 + RBV24 (1)	SOF12 + RBV12 (1)
Withdrawals due to adverse events	0 to 2% 2% for SIM12 PR48 (2), PR48 (1)		
Discontinuations – all causes	0 to 71%	PR48 (1) SIM12 PR48 (3) DCV24 + ASU24 (3)	PR48 (2)
Discontinuations due to adverse events	0 to 10%		
Relapse	0 to 90%	PR48 (4) SOF24 + RBV24 (1) SIM12 PR24-48 (1) SIM12 PR48 (1) SOF12 + PR12 (2) DCV24 + ASU24 + BEC12 (1)	SOF12 + RBV12 (2)
Mortality – all causes	0 to 3%		
Mortality – liver-related	0 to 3%		
Serious adverse events	0 to 12%	SOF24 + LDV24 (1) SIM12 PR48 (1) DCV24 + ASU24 (1)	
Adverse events	37 to 100%		All
Fatigue	0 to 78%		All
Pruritus	0 to 52%	All	
Neutropenia	0 to 27%	PR48 (4) SOF12 + PR12 (2) SIM12 PR48 (2) SIM12 PR24-48 (1) DCV24 + ASU24 + PR24 (1)	
Thrombocytopenia	0 to 15%	SOF12 + PR12 (1)	
Flu-like symptoms	0 to 55%	PR48 (4) SOF12 + PR12 (2) SIM12 + PR24-48 RGT (1) SIM12 PR48 (2) DCV24 + ASU24 + PR24 (1)	
Suicidal ideation	0 to 5% 5% for SOF12 + LDV12 + RBV12 (1)		
Epoetin alfa use	0 to 41%	PR48 (1)	
Blood transfusion	0 to 9%		
Hepatocellular carcinoma	0 to 6% 6% for SIM12 + PR24-48 RGT		
Liver transplants	Rare		

6 DISCUSSION

Patients with CHC infection have expressed the need for new treatments that have higher cure rates, better side effect profiles and reduced treatment burden compared with existing PR-based therapies, and that are accessible and affordable. The introduction of new DAAs may address some unmet needs in patients with CHC infection, but the comparative benefit and harms of the new DAA-based regimens needs to be evaluated, especially in light of their high cost. The objective of this Therapeutic Review was to evaluate the comparative benefits, harms, and cost-effectiveness of the DAA regimens for CHC infection. It was undertaken to help inform formulary listing decisions for the approved and emerging DAA therapies by identifying the most cost-effective strategies based on patient characteristics and prior treatment history.

6.1 Summary of Evidence

A total of 77 studies (26, 33, 37, 43-112) in adults with CHC infection met the inclusion criteria for this systematic review, 6 of which were of regimens considered to be emerging according to our research protocol. Of these studies, 27 were in patients who were treatment-naive (44, 50, 51, 55, 56, 58-60, 65-67, 72, 82, 83, 88, 91, 95, 101, 104, 106-110), 16 were in patients who were treatment-experienced (43, 45, 46, 52, 57, 67, 70, 81, 85, 87, 102, 103, 105, 111, 112), 28 were in patients with combined treatment experience (26, 33, 37, 47, 49, 53, 54, 61-64, 68, 69, 73-76, 78, 80, 84, 86, 90, 92-94, 100), 7 were in patients who had HIV coinfection (75, 83, 88, 90, 91, 94, 95) and two were in patients who were liver transplant recipients (47, 62). No studies in populations of special interest, i.e., patients with hepatitis B or tuberculosis coinfection, or in patients who had failed treatment with a DAA-only regimen, met the inclusion criteria.

Separate analyses were conducted for populations based on genotype and prior treatment history due to anticipated differences in treatment efficacy, and because these parameters are used in clinical practice to determine optimal management. Safety analyses were conducted across genotypes while addressing populations separately based on prior treatment history.

A number of treatment regimens were evaluated, including those approved by Health Canada or for which CADTH had received pre-NOC submissions to the CDR regimens not currently approved but considered of clinical relevance based on Canadian or US clinical practice guidelines(2, 28), or those considered as emerging treatments having a high likelihood of regulatory approval in Canada in the near future (i.e., within approximately 12 months) based upon information available to CADTH as of February 2015. Treatment regimens included DAA regimens with and without PR or RBV, and interferon-free DAA treatment regimens. Due to their diminished clinical relevance or removal from the market, boceprevir, telaprevir and PR alone were included only as comparators to the other regimens for treatment of genotype 1 infection, and to enhance the robustness of the treatment network geometry for the NMAs. Treatment regimens considered to be emerging were included only in supplemental analyses.

In studies of patients with CHC infection, 49 studies included patients with genotype 1 (26, 43-46, 49-53, 56-66, 68-70, 72-77, 81-97, 101, 102), 11 studies included patients with genotype 2 (33, 54, 65-67, 75, 80, 88, 93, 94, 100), 11 studies included patients with genotype 3 (33, 54, 65-67, 75, 78, 88, 93, 94, 100), 8 studies included patients with genotype 4 (37, 55, 57, 60, 66, 75, 88, 101), two studies included patients with genotype 5 (60, 66), and three studies included patients with genotype 6 (60, 66, 101). Thirty-one randomized and comparative studies (26, 33, 37, 43-46, 50, 51, 53-56, 64, 65, 69, 70, 72-74, 76, 82, 84, 87, 90-93, 101, 102), including 10 RCTs carried forward from the previous review.(103-112).

Given the lack of RCTs directly comparing the new and emerging DAA treatment regimens, we conducted an indirect treatment comparison using Bayesian NMA methods for the outcomes of SVR at 12 weeks, anemia, rash, and depression. The data available varied for each NMA analysis.

6.2 Interpretation of Results

6.2.1 Efficacy – Sustained Virologic Response At 12 Weeks

This review focuses on newer treatment regimens for CHC infection, in particular, Harvoni, Holkira Pak and daclatasvir-based regimens. A summary of the NMA results for CHC patients with genotype 1 infection with particular reference to these regimens is provided in Table 70. This table provides a summary, by patient subgroup and treatment history, of when these regimens significantly improved SVR compared to the treatments listed in the table.

In particular:

- For treatment-naive patients, all three regimens were superior to PR-based treatments, with Harvoni and Holkira Pak demonstrating this more often. In some cases, Harvoni and Holkira Pak were better than daclatasvir-based regimens. There was less evidence for treatment-naive patients with cirrhosis.
- For treatment-experienced patients, all three regimens were superior to PR-based treatments, in particular Harvoni and Holkira Pak. There was limited evidence for patients with cirrhosis. In some cases, Harvoni and Holkira Pak were better than daclatasvir-based regimens (in particular, Holkira Pak was better for genotype 1b and for patients without cirrhosis).
- For treatment-experienced patients with prior relapse, prior partial response, or null response, Holkira Pak demonstrated increased SVR rates compared to PR-based treatments, and compared to Harvoni and daclatasvir-based regimens.
- In sensitivity analyses incorporating the Harvoni 8-week regimen for treatment-naive patients without cirrhosis, this regimen was superior to PR and there were no significant differences compared with Holkira Pak, the Harvoni 12-week regimen, or daclatasvir-based regimens). Harvoni 8 for 8 weeks is only approved in Canada for treatment-naive, non-cirrhotic patients with genotype 1 infection with a baseline HCV RNA < 6 million IU/mL. According to clinical experts, the majority of treatment-naive patients have a baseline viral load below this threshold, and should therefore be candidates for the 8-week regimen.

Table 70: Genotype 1 Patients: Summary of the Results for SVR With Reference to Harvoni, Holkira Pak and Daclatasvir			
Patient Population	**Harvoni (SOF12 + LDV12) Significantly Improved SVR Compared With**	**Holkira Pak (PAR/RIT12 + OMB12 + DAS12) Significantly Improved SVR Compared With**	**Daclatasvir (DCV24 + ASU24) Significantly Improved SVR Compared With**
Treatment-Naive Patients			
All	PR48 SOF24 + RBV24 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24	PR48 SOF24 + RBV24 SIM12 + PR24-48 RGT (with RBV12) PR48 SOF24 + RBV24 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24	PR48 SIM12 + PR24-48 RGT (for DCV12 + SOF12) PR48
Genotype 1a	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT	(with RBV12) PR48 SOF12 + PR12	
Genotype 1b	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24	PR48	PR48 SIM12 + PR24-48 RGT
Cirrhotic	PR48 SOF24 + RBV24 SIM12 + PR24-48 RGT		PR48
Non-Cirrhotic	PR48 SOF24 + RBV24 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24	PR48 (with RBV12) PR48 SOF24 + RBV24 SIM12 + PR24-48 RGT	PR48 SIM12 + PR24-48 RGT (for DCV12 + SOF12) PR48
Treatment-Experienced Patients			
All	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SIM12 + PR48 DCV24 + ASU24 (24 weeks) PR48	PR48 (with RBV12) PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SIM12 + PR48 DCV24 + ASU24	PR48 SIM12 + PR48 (with PR24) PR48 SIM12 + PR48 SIM12 + PR24-48 RGT
Genotype 1a	PR48 SIM12 + PR24-48 RGT SIM12 + PR48 (24 weeks) PR48	(with RBV12) PR48 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12	(with PR24) PR48

Table 70: Genotype 1 Patients: Summary of the Results for SVR With Reference to Harvoni, Holkira Pak and Daclatasvir			
Patient Population	**Harvoni (SOF12 + LDV12) Significantly Improved SVR Compared With**	**Holkira Pak (PAR/RIT12 + OMB12 + DAS12) Significantly Improved SVR Compared With**	**Daclatasvir (DCV24 + ASU24) Significantly Improved SVR Compared With**
Genotype 1b	PR48 (24 weeks) PR48	PR48 SIM12 + PR24-48 RGT (with RBV12) PR48 SOF12 + LDV12 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12 DCV24 + ASU24	PR48 (with PR24) PR48 SOF12 + LDV12 SOF24 + LDV24 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12 DCV24 + ASU24
Cirrhotic	PR48 (24 weeks) PR48		PR48 (with PR24) PR48 SIM12 + PR48
Non-Cirrhotic	PR48 SIM12 + PR24-48 RGT	PR48 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12 DCV24 + ASU24 SIM12 + SOF12 (with RBV12) PR48 SOF12 + LDV12 SIM12 + PR24-48 RGT SIM12 + PR48 SOF12 + PR12 DCV24 + ASU24 DCV24 + ASU24 + PR24 SIM12 + SOF12	PR48 (with PR24) PR48 SIM12 + PR24-48 RGT
Treatment-Experienced Patients With Prior Relapse			
All	PR48	PR48 SIM12 + PR24-48 RGT (with RBV12) PR48 SIM12 + PR24-48 RGT	
Genotype 1a		(with RBV12) PR48	
Genotype 1b		(with RBV12) PR48	

Table 70: Genotype 1 Patients: Summary of the Results for SVR With Reference to Harvoni, Holkira Pak and Daclatasvir			
Patient Population	**Harvoni (SOF12 + LDV12) Significantly Improved SVR Compared With**	**Holkira Pak (PAR/RIT12 + OMB12 + DAS12) Significantly Improved SVR Compared With**	**Daclatasvir (DCV24 + ASU24) Significantly Improved SVR Compared With**
Cirrhotic			
Non-Cirrhotic		PR48 SIM12 + PR24-48 RGT (with RBV12) PR48 SIM12 + PR24-48 RGT	
Treatment-Experienced Patients With Prior Partial Response			
All		PR48 (with RBV12) PR48 SIM12 + PR48	PR48 (with PR24) PR48
Genotype 1a		(with RBV12) PR48 SIM12 + PR48	
Genotype 1b		(with RBV12) PR48	
Cirrhotic			
Non-Cirrhotic		PR48 (with RBV12) PR48	
TREATMENT-EXPERIENCED PATIENTS WITH PRIOR NULL			
All		PR48 (with RBV12) PR48 SOF12 + PR12 SIM12 + PR48	PR48 SOF12 + PR12 (with PR24) PR48 SOF12 + PR12
Genotype 1a		(with RBV12) PR48 SIM12 + PR48 (24 weeks with RBV24) PR48 SIM12 + PR48	
Genotype 1b		(with RBV12) PR48 SIM12 + PR48 DCV24 + ASU24	

Table 70: Genotype 1 Patients: Summary of the Results for SVR With Reference to Harvoni, Holkira Pak and Daclatasvir			
Patient Population	**Harvoni (SOF12 + LDV12) Significantly Improved SVR Compared With**	**Holkira Pak (PAR/RIT12 + OMB12 + DAS12) Significantly Improved SVR Compared With**	**Daclatasvir (DCV24 + ASU24) Significantly Improved SVR Compared With**
Cirrhotic			
Non-Cirrhotic		PR48 SIM12 + PR48 (with RBV12) PR48 SIM12 + PR48	(with PR24) SIM12 + PR48

NMA analysis was also conducted in patients with genotype 2, 3 or 4 CHC infection. The data available were more limited compared with genotype 1 and, with fewer treatment strategies being evaluated, the networks were simpler and there were a limited number of treatment comparisons resulting from the analysis.

In Table 71, the SVR results for specific treatments that have been compared and reported in this review are summarized.

In particular:

- For patients with genotype 2 infection, SOF12 + RBV12 significantly improved SVR rates over PR24 in treatment-naive patients, but SOF12 + PR12 did not. In treatment-experienced patients, neither SOF16 + RBV16 nor SOF12+PR12 were significantly different from SOF12+ RBV12.
- For patients with genotype 3 infection and regardless of treatment experience, SOF24 + RBV24, DCV12 + SOF12, and SOF12 + PR12 significantly improved SVR compared with PR48, and there were no significant differences between these regimens.
- For patients with genotype 4 infection, DCV24 + ASU24 + PR24 significantly improved SVR compared to SOF12 + RBV12 in treatment-experienced patients overall, and for patients with and without cirrhosis. SOF12 + PR12 significantly improved SVR compared to SOF12 + RBV12 in treatment-naive patients overall.

Table 71: Genotype 2 to 4 Patients: Summary of the Results for SVR With Reference to Reported Treatment Regimens										
Patient Population	**Genotype 2**			**Genotype 3**			**Genotype 4**			
	SOF12 + RBV12	**SOF12 + PR12**	**SOF16 + RBV16**	**SOF24 + RBV24**	**DCV12 + SOF 12**	**SOF12 + PR12**	**SOF12 + RBV12**	**SOF24 + RBV24**	**SOF12 + PR12**	**DCV24 + ASU24 + PR24**
Treatment-Naive Patients (PR24 Reference for Genotype 2) (PR48 Reference for Genotypes 3/4)										
All	PR24	NS[a]	[c]	PR48	PR48		NS	PR48	PR48 SOF12+ RBV12	
Cirrhotic	PR24			PR48			NS	PR48		
Non-Cirrhotic	PR24	NS		PR48	PR48		NS	NS		
Treatment-Experienced Patients (SOF12 + RBV12 Reference for Genotypes 2/4) (PR48 Reference for Genotype 3)										
All	---[b]	NS SOF16+ RBV16	NS	PR48	PR48	PR48	---	NS		SOF12+ RBV12
Cirrhotic	---	NS	NS	PR48		PR48	---	NS		SOF12+ RBV12
Non-Cirrhotic	---	NS		PR48	PR48	NS	---	NS		SOF12+ RBV12

[a] NS indicates that no significant difference was found.
[b] Dashes (---) indicates that the treatment was the reference standard.
[c] Blank cell indicates that the treatment was not considered for this patient population.

The data for CHC genotype 5 and 6 infections were insufficient for analysis. All six patients with genotype 6 and the one patient with genotype 5 who received SOF + PR in the NEUTRINO study achieved SVR12. Eight out of the 10 (80%) patients with genotype 6 who received grazoprevir/elbasvir in C-EDGE study achieved SVR12, while two patients experienced virologic relapse.

6.2.2 Safety

Three key adverse events were identified – rash, anemia and depression — based on their impact on patients' quality of life and health care resources. These events were analyzed using NMA methods with all genotypes (1 through 4) combined in the analysis, and separate analyses by treatment-naive and treatment-experienced patients.

A summary of the NMA results with particular reference to Harvoni, Holkira, and daclatasvir-based regimens is provided in Table 72. This table provides a summary, by treatment history, of when these three regimens were significantly associated with fewer adverse events (i.e., rash, anemia and depression) compared to the treatments listed in the table.

In particular:

For treatment-naive patients:

- All three regimens were associated with significantly lower risks for rash and anemia than PR-based treatments, but only Harvoni and daclatasvir-based regimens were significantly associated with less depression compared to PR-based treatments.
- For rash, Holkira Pak with RBV was less favourable than Harvoni, Holkira Pak without RBV and daclatasvir-based regimens.
- For anemia, Holkira Pak with or without RBV was less favourable than Harvoni.
- For depression, Holkira Pak with RBV and daclatasvir were less favourable than Harvoni.

For treatment-experienced patients:

- All three regimens were associated with significantly less rash and anemia than PR-based treatments, but evidence was sparse for depression.
- For rash, daclatasvir with PR was less favourable than Harvoni, Holkira Pak and daclatasvir without PR.
- For anemia, Holkira Pak with RBV was less favourable than Harvoni and Holkira Pak without RBV.

Table 72: All Patients: Summary of the Results for Rash, Anemia and Depression With Reference to Harvoni, Holkira Pak and Daclatasvir

Safety Event	Harvoni (SOF12 + LDV12) Significantly Associated With Less Events Compared With	Holkira Pak (PAR/RIT12 + OMB12 + DAS12) Significantly Associated With Less Events Compared With	Daclatasvir (DCV24 + ASU24) Significantly Associated With Less Events Compared With
Treatment-Naive Patients – All Genotypes			
Rash	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT PAR/RIT12 + OMB12 + DAS12 + RBV12	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT PAR/RIT12 + OMB12 + DAS12 + RBV12	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT PAR/RIT12 + OMB12 + DAS12 + RBV12
Anemia	PR48 SOF12 + PR12 SOF24 + RBV24 SIM12 + PR24-48 RGT PAR/RIT12 + OMB12 + DAS12 ± RBV12	PR48 SOF12 + PR12 SOF24 + RBV24 SIM12 + PR24-48 RGT (with RBV12) PR48 SOF12 + PR12	(with DCV12 + SOF12) PR48 SOF12 + PR12 SOF24 + RBV24 SIM12 + PR24-48 RGT
Depression	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SOF24 + RBV24 DCV24 + ASU24 DCV12 + SOF12 PAR/RIT12 + OMB12 + DAS12 + RBV12		PR48

Table 72: All Patients: Summary of the Results for Rash, Anemia and Depression With Reference to Harvoni, Holkira Pak and Daclatasvir			
Safety Event	**Harvoni (SOF12 + LDV12) Significantly Associated With Less Events Compared With**	**Holkira Pak (PAR/RIT12 + OMB12 + DAS12) Significantly Associated With Less Events Compared With**	**Daclatasvir (DCV24 + ASU24) Significantly Associated With Less Events Compared With**
Treatment-Experienced Patients – All Genotypes			
Rash	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SOF24 + RBV24 DCV24 + ASU24 + PR24	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT DCV24 + ASU24 +PR24 PAR/RIT12 + OMB12 + DAS12 + RBV12 (with RBV12) PR48 DCV24 + ASU24 + PR24	PR48 DCV24 + ASU24 + PR24 SOF12 + PR12
Anemia	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SOF214 + RBV24 DCV24 + ASU24 +PR24 PAR/RIT12 + OMB12 + DAS12 + RBV12	PR48 SOF12 + PR12 SIM12 + PR24-48 RGT SOF24 + RBV24 DCV24 + ASU24 +PR24 PAR/RIT12 + OMB12 + DAS12 + RBV12 (with RBV12) PR48 SOF12 + PR12	(with PR24) PR48 SOF12 + PR12
Depression		(with RBV12) PR48	PR48

In addition to rash, anemia and depression, other safety events were considered. The data available and/or the frequency of these safety events were not sufficient for NMA.

In particular:

For treatment-naive patients:

- Withdrawals due to adverse events, mortality (all cause), mortality (liver-related), suicidal ideation, hepatocellular carcinoma and liver transplants were infrequently reported across all treatments:
- Adverse events, fatigue and pruritus were frequently reported across all treatments
- PR48 was often associated with harms, and
- SOF12 + PR12, SOF12 + RBV12, SOF24 + RBV24, SIM12 + PR24-48 RGT were associated with several harms.

For treatment-experienced patients:

- Withdrawals due to adverse events, mortality (all cause), mortality (liver-related), suicidal ideation, hepatocellular carcinoma and liver transplants were infrequently reported across all treatments:
- Adverse events, fatigue and pruritus were frequently reported across all treatments

- PR48 was often associated with harms, and
- SOF12 + PR12, SOF12 + RBV12, SOF24 + RBV24, SIM12 + PR24-48 RGT were associated with several harms.

6.2.3 Subgroups and Supplemental Analyses

Several additional analyses were conducted to explore potential sources of heterogeneity. These included NMAs stratified by:

- Patients with HIV coinfection
- Patients with a viral load at baseline of greater or less than 800,000 IU/ML or 6 $\log_{10}$ (genotype 1, 2 and 4 only, by previous treatment experience).

In Tables 73 and 74, a summary of the subgroups based on viral load and HIV coinfection is provided for patients with genotype 1 and 4 infection respectively. Since the treatments of greatest interest were Harvoni, Holkira Pak and daclatasvir-based regimens, a summary of the NMA results with particular reference to these three regimens is provided in Table 73. This table provides a summary, by patient treatment history, of when these three regimens significantly improved SVR compared to the treatments listed in the table, for the three subgroups: low viral load (i.e., less than 800,000 or 1,000,000 IU/mL), high viral load and HIV coinfection.

In particular, for subgroups of treatment-naive patients:

- For patients with higher viral load, all three regimens significantly improved SVR compared to PR-based treatment (PR48 and SOF12 + PR12), including Harvoni for 8 weeks.
- For patients with lower viral load, daclatasvir significantly improved SVR compared to PR48 and SOF24 + RBV24.
- Data were limited to evaluate patients with HIV coinfection, however Harvoni significantly improved SVR in this population compared to PR48.

It should be noted that the approved indication for Harvoni 8 weeks is for treatment-naive patients with genotype 1 infection and no cirrhosis, a threshold that is much higher that the thresholds used to define low and high viral load in the included trials. The approved indication was based on a post-hoc analysis of relapse rates for patients with baseline HCV RNA above and below the 6 million IU/mL threshold.

For subgroups of treatment-experienced patients:

- Both Harvoni and Holkira Pak significantly improved SVR compared to daclatasvir in groups with a higher viral load.
- Data were insufficient to evaluate lower viral load and HIV coinfection.

Table 73: Genotype 1 Patients: Summary of the Results for SVR in Subgroups of Viral Load and HIV Coinfection with Reference to Harvoni, Holkira Pak and Daclatasvir			
Patient Population	**Harvoni (SOF12 + LDV12) Significantly Improved SVR Compared With**	**Holkira Pak (PAR/RIT12 + OMB12 + DAS12) Significantly Improved SVR Compared With**	**Daclatasvir (DCV24 + ASU24) Significantly Improved SVR Compared With**
Treatment-Naive Patients			
Higher Viral Load[a]	PR48 SOF12 + PR12 (8 weeks) PR48 SOF12 + PR12	(with RBV12) PR48 SOF12 + PR12	PR48 SOF12 + PR12
Lower Viral Load[b]			PR48 SOF24 + RBV24
HIV Coinfection	PR48		
Treatment-Experienced Patients			
Higher Viral Load[a]	(with RBV) DCV24 + ASU24 SOF12 PR12	(with RBV12) DCV24 + ASU24	
Lower Viral Load[b]	No significant differences identified		
HIV Coinfection	Insufficient data		

[a]Lower viral load = pre-treatment HCV RNA of < 1,000,000 IU/mL
[b]Higher viral load = pre-treatment HCV RNA of >1,000,000 IU/mL.

The NMA analysis was also conducted in patients with genotype 4 CHC infection. As before, the data available were limited compared with genotype 1 infection and, with fewer treatment strategies being evaluated, the networks were simple and the number of treatment comparisons resulting from the analysis were limited.

In Table 74, the specific treatments that have been evaluated and reported are identified and their significance in improving SVR compared to the other treatments provided.

In particular, compared to SOF12 + RBV12, DAC24 + ASU24 + PR24 significantly improved SVR in treatment-experienced patients with high viral load. Otherwise, the results were non-significant.

Table 74: Genotype 4 Patients: Summary of the Results for SVR in Subgroups of Viral Load and HIV Coinfection With Reference to Reported Treatment Regimens			
Patient Population	**SOF12 + RBV12 Significantly Improved SVR Compared With**	**SOF24 + RBV24 Significantly Improved SVR Compared With**	**Daclatasvir (DCV24 + ASU24) Significantly Improved SVR Compared With**
Treatment-Naive Patients			
Higher Viral Load	NS[a]	NS	[c]
Lower Viral Load	NS	NS	
Treatment-Experienced Patients (Reference SOF12 + RBV12)			
Higher Viral Load	---[b]	NS	(with PR24) SOF12 + RBV12
Lower Viral Load	---	NS	NS

[a] NS indicates that no significant difference was found.
[b] Dashes (---) indicates that the treatment was the reference standard.
[c] Blank cell indicates that the treatment was not considered for this patient population.

Data were insufficient to conduct analyses for compensated cirrhosis, advanced compensated cirrhosis, and decompensated cirrhosis or for HBV or TB coinfection in patients with CHC within or across all genotypes.

Supplemental analyses were also conducted incorporated for:

- Treatment regimens identified as emerging in the protocol
- SOF8 + LDV8 (Harvoni 8 weeks) treatment regimen into the base-case analyses in genotype 1
- TURQUOISE II study incorporated into the network for SVR genotype 1 cirrhotic
- BOSON abstract/PPT only into genotype 3 relevant analyses.

The TURQUOISE II study (26), along with nine other studies included in the systematic review, reported combined baseline characteristics for treatment-naive and -experienced patients. Separate baseline data stratified by previous treatment experience was a requirement to conduct the matching exercise with the “virtual” study arms hence studies not reporting required data were excluded from the NMA. Experts believed the inclusion of TURQUOISE II in the NMA was important as it was the only study to report SVR results for PAR/RIT12 + OMB12 + DAS12 + RBV12 in the genotype 1 population with cirrhosisHence, the TURQUOISE II study was incorporated into the treatment network as part of a sensitivity analysis for SVR for genotype 1 cirrhotic patients using the assumption that the baseline characteristics for the naive and experienced patients were the same. Although the clinical experts acknowledged that the assumption of similar baseline characteristics between naive and experienced patients could bias the treatment effect towards PAR/RIT12 + OMB12 + DAS12 + RBV12 for experienced patients, the value of having this treatment in the network was felt to outweigh this risk. Unlike TURQUOISE II, the nine other studies reporting combined baseline characteristics were not included in the NMA as part of sensitivity analyses since their exclusion was not felt to be as impactful to the results of the NMA.

The systematic review included information available in the public domain only and excluded abstracts reporting primary study results. The only exception was made for the BOSON trial comparing SOF12 + PR12 to SOF24 + RBV24 in genotype 3 patients, as clinical experts considered that omission of this large, randomized trial would limit the value of the analysis for this genotype. Inclusion of the BOSON data presented at a recent conference in sensitivity analyses allowed for SOF12 + PR12 to be brought into the treatment-naive network for

genotype 3, revealing that SOF12 + PR12 was significantly superior to PR48, and not significantly different from SOF24 + RBV24 or DCV12 + SOF12. For treatment-experienced patients with genotype 3 infection, SOF12 + PR12 was already included in the NMA based on a trial published in the peer-reviewed literature; inclusion of the BOSON data for this population did not change the results, i.e., SOF12 + PR12 remained superior to PR4, and was not significantly different from DCV12 + SOF12 or SOF24 + RBV24. The conference data available from BOSON indicated that SOF12+ PR12 was associated with higher SVR rates than SOF24 + PR24 across both treatment-naive and -experienced, and cirrhotic and non-cirrhotic subgroups, however statistical significance was not presented and sample sizes with each subgroup were small. While BOSON also enrolled patients with genotype 2 infection, data on SVR rates were not available according to treatment experience or cirrhosis status, which prevented inclusion of the BOSON results as a sensitivity analysis for the genotype 2 NMA.

Of the regimens currently approved in Canada for the treatment of CHC infection, the combination of sofosbuvir with simeprevir is unique in that it has a Notice of Compliance with Conditions (NOC/c) (for the treatment of patients with genotype 1 infection and compensated liver disease) pending the results of studies confirming its clinical benefit. At the time of this review, interim data for the two phase III single-arm studies of SIM + SOF in genotype 1 treatment-naive or -experienced patients with and without cirrhosis, OPTIMIST-1 (119) and OPTIMIST-2 (120), had been presented at conferences but had not yet been published. In OPTIMIST-1, 97% of patients treated with SIM12 + SOF12 (n = 150/155) achieved SVR12 which was superior to the SVR 12 rate of 87% in the historical control group. Patients treated with SIM8 + SOF8 achieved an SVR12 rate of 83% (n = 128/155) which was not superior to the SVR12 rate of 83% in the historical control group. Certain subgroups of patients achieved SVR12 rates of 100%. In the OPTIMIST-2 trial, treatment with SIM12 + SOF12 resulted in SVR12 rates of 84% (n = 86/103), which was superior to the SVR12 rate of 70% in the historical control group.(119, 120) These data were not considered for inclusion in sensitivity analyses for the genotype 1 NMAs as SIM12 + SOF12 was already included in the base-case analyses on the basis of trial evidence published in the peer-reviewed literature.

6.3 Strengths and Limitations

6.3.1 Strengths

This systematic review was conducted according to a pre-specified protocol. In addition, the list of included studies was vetted by clinical and methodological experts, and posted for external stakeholder comment. Standard approaches for collecting evidence and performing data extraction, and evaluating study quality were utilized. Heterogeneity across trials in terms of patient characteristics, trial methodologies, and treatment protocols was carefully assessed. Subgroup and sensitivity analyses were conducted, where data allowed, to explore and control for potential sources of heterogeneity. These included patients with or without cirrhosis, prior treatment experience, genotype subtype, and DAA dosage regimens.

We separated analyses for patients with and without cirrhosis as patients with cirrhosis achieve lower rates of SVR with PR and are at higher risk of treatment-related complications. Pooling data for METAVIR F3 and F4 subgroups may inflate the treatment effects for those with cirrhosis, and so we limited our analyses of cirrhosis to those with a fibrosis score of 4 or who were explicitly reported in the publication to be cirrhotic.

6.3.2 Key Limitations

The systematic review was limited by the quality of the included studies. Of the 67 studies included in the systematic review, overall quality was adequate; however, all but two studies had one or more methodological domains with an unclear or high risk of bias. Moreover, data for some DAAs in specific populations were limited to open-label, uncontrolled (or historically controlled) studies, thus limiting our ability to assess comparative efficacy and safety using standard Bayesian indirect comparison methodologies. No individual patient data were available for analyses, so it was not possible to use comparative effectiveness methods, such as propensity scores weighting, for matching studies and identifying a comparator arm or conducting an adjusted analysis. Instead, single-arm studies were incorporated into the NMA by creating a "virtual" study where a comparator arm matched for baseline patient characteristics was identified for the single arm.

NMAs were not conducted for all outcomes of interest in the systematic review. The outcomes analyzed were selected based on their clinical importance to the research questions and the economic model. The adverse events analyzed were limited to those specific events deemed to have the greatest impact on patients' quality of life or ability to complete treatment regimens, or those that required additional interventions or incurred substantial costs to manage.

Limited data were available for severity of fibrosis by METAVIR score for the interferon-free DAA treatment regimens; instead, the more recent studies define patients according to whether they have cirrhosis or not. In order to maintain the most robust network possible for SVR12, analyses were stratified by non-cirrhosis (i.e., METAVIR score 1 to 3) and cirrhosis (i.e., METAVIR score of 4). This classification method resulted in 6 studies reporting fibrosis scores of 3 and 4 combined, being excluded from the NMA for SVR12. In addition, due to sparse data, our subgroup analyses for patients with cirrhosis may lack power, and the uncertainty in the findings are reflected in the wide CrIs.

A large majority of included studies excluded patients with TB, hepatitis B coinfection, decompensated cirrhosis, or other significant illnesses; as such, we were unable to perform NMA for these special patient populations. The primary outcome for most studies was SVR12, but some of the earlier studies reported SVR24, and some studies reported both. No studies reported long- term outcomes.

In the NMAs, the estimate generated for the assessment of outcomes is RR, and the calculation of relative risk was based on the ORs and the "control" event rate (i.e., PR event rate) as a representative of the "real" population event rate. Additionally, in genotypes 2 to 4, a reference comparison was sometimes not available, or the studies in the NMA were all single arm, and a reference treatment was required to statistically connect the treatments for analysis. In these cases, additional studies (meta-analyses [MA], followed by primary observational studies if no MA data available) were identified by clinical experts to be used to provide the required estimates. Since real-world SVR rates for the reference treatments of interest may be lower than those observed in controlled clinical trials, the use of observational study data to bring reference treatments into NMAs may bias efficacy results in favour of the DAA-containing regimens.

The number of trials that contributed to some of the NMAs was limited which may have yielded less precise estimates than if we were able to create more robust evidence networks. Data were insufficient to conduct an NMA for some subpopulations of interest and in genotypes 5 and 6. Specifically, small numbers of patients with cirrhosis, patients previously treated (with PR, DAA+PR or DAA alone, and patients coinfected with HIV were included. Limited data was

especially an issue in the analysis of genotype 1 patients with cirrhosis and all analyses for genotypes 2 to 4; thus, the results showed wide CrIs. Results should be interpreted with caution.

We were unable to perform regression analyses to determine whether the proportion of patients with specific baseline characteristics or epidemiological factors in the trials had an impact on our findings.

Consistency was assessed whenever a closed loop was available by comparing consistency and inconsistency models. However, in many of the analyses, there was no closed loop available. There were no closed loops in genotype 2 to 4 analyses. We were unable to compare direct and indirect evidence between DAAs due to the absence of head-to-head trials and due to the large number of single-arm studies with historical control. Hence, our ability to assess consistency was limited. In the base-case analysis, similar treatment effects were assumed for peginterferon 2a and 2b, but there is evidence that patients who receive peginterferon 2a as part of their treatment regimen show better efficacy than those who receive peginterferon 2b. We were unable to conduct a sensitivity analysis in which peginterferon 2a and 2b regimens were considered to have different efficacy and safety. Additionally, we did not conduct direct pairwise comparisons for outcomes included in the NMA due to the high proportion of single-arm studies.

We were unable to analyze adverse events according to their severity, as data on severity were not consistently reported. In addition, different definitions of adverse events may have been used across studies, but due to the lack of detailed descriptions and study protocols, we were unable to assess potential differences.

A strength of this review was its comprehensiveness in identifying and assessing clinically relevant regimens for the treatment of CHC infection that are currently approved in Canada, recommended by major guidelines, or likely to be available in the near future. However, evidence that could be included in NMA was not available for some regimens of interest, namely: DCV24 + SOF24 for genotype 1 infection; DCV + ASU + PR for treatment-naive patients with genotype 1 infection; DCV12 + SOF12 for treatment-experienced patients with genotype 1 infection; DCV + SOF for genotype 2 infection; SOF12 + PR 12 for treatment-naive patients with genotype 3 infection (although the sensitivity analysis incorporating results from BOSON mitigated this evidence gap); SOF12 + LDV12 + RBV12 and DCV24 + SOF24 ± RBV24 for genotype 3 infection regardless of treatment experience; SOF12 + LDV12 and DCV12 + ASU12 + PR12 for patients with genotype 4 infection and SOF12 + PR12 for treatment-experienced patients with genotype 4 infection. Trial data for some of these regimens may be available in conference abstracts, which were not included in the systematic review. Furthermore, given the rapid and ongoing developments in the field, and because changes to review scope could only be made up to a certain point (February 2015) without compromising methodological quality and timeliness, it is possible that some regimens currently considered relevant may not have been captured in the review.

In the era when PR-based therapy was the only option for treatment of CHC infection, there were concerns surrounding the impact of therapy on patient quality of life due to the significant adverse effects associated with interferon. The improved adverse effect profile of interferon-free therapies should yield benefits in terms of improved, or at least maintained, quality of life compared with PR-based regimens. While quality of life was originally considered as an outcome of interest for this review, a scan of several trials revealed that quality of life was measured using a variety of instruments, and direct comparisons between interferon-free and interferon-based regimens, or between various interferon-free regimens, on quality of life were rare. Furthermore, interferon-free regimens were generally superior to interferon-based

regimens on SVR and key safety outcomes, therefore any benefits with respect to quality of life would only augment their benefit-risk profile. For these reasons, quality of life was not included as an outcome of interest in the systematic review.

6.3.3 Other Considerations

Results from the systematic review and indirect treatment comparison suggest that interferon-free DAAs are more effective at achieving an SVR than 48 weeks of PR in adults with CHC infection, however, results vary by genotype, subgroup and previous treatment experience. In general, no interferon-free DAA was found to be more effective than another DAA in achieving SVR among treatment-naive or the overall treatment-experienced populations, based on indirect evidence, although Harvoni and Holkira Pak have their advantages in some patient group and treatment history settings.

Three Clinical Practice Guidelines in Canada (Canadian Association for the Study of the Liver (CASL)), the United States (American Association for the Study of Liver Diseases (AASLD)) and Europe (European Association for the Study of the Liver (EASL)) have recently updated their recommendations in 2015 to include the DAA treatment regimens. Although our findings are generally consistent, some discrepancies exist, and we were unable to corroborate recommendations in some subgroups as we did not run analyses within specific subgroups (e.g., genotype 1a treatment-naive cirrhotic patients without Q80K polymorphism). EASL Guidelines pool together naive and experienced patients in their recommendations, which makes detailed comparisons to our findings challenging. We were not able to confirm any of the recommendations for genotype 5 and 6 as data were insufficient to perform NMA for these genotypes.

There are no other technology assessments that have comprehensively assessed the comparative efficacy or cost-effectiveness of the interferon-free DAA treatment regimens across all genotypes. The California Technology Assessment Forum (CTAF) perfomed a frequentist indirect treatment comparison and value assessment of sofosbuvir and simeprevir in April 2014 in patients with genotype 1, 2 or 3 CHC infection. While they note that the lack of head-to-head trials makes it difficult to assess the relative efficacy of the different treatment regimens, they assumed reference group SVR12 rates observed in control groups of other included studies to incorporate single arms studies into the network, and in some cases, pooled SVR12 across multiple study arms. They note, as this study does, that the effect estimates produced from the indirect comparisons through use of the “virtual” or extrapolated control arms should be considered to have greater uncertainty than the confidence interval or credible interval suggests. Although the CTAF review included fewer comparisons and fewer studies, results were generally consistent with our findings across genotypes 1 to 3. They summarize that for most groups, the DAA treatment regimens offer a clear improvement over PR. The study scope was insufficient to elucidate differences among SIM and SOF (combined or with/without RBV alone) given the high rates of SVR (90% or higher in some treatment groups).

Among the populations of special interest, no conclusions can be drawn regarding the efficacy and safety of DAAs in patients who have undergone a liver transplant, were coinfected with HBV or TB or who were re-treated after failing to achieve an SVR with DAA therapy, due to the absence of clinical trials.

Several evidence gaps were identified in the systematic review, particularly for patients with cirrhosis, those who have failed a DAA plus PR or DAA alone treatment regimen, and patients with genotype 5 and 6 infection, which limited our ability to fully examine the comparative

efficacy and safety across populations. Furthermore, all comparisons between DAAs were based on indirect evidence because of the absence of head-to-head RCTs. Data were also limited for some subgroups, and the findings from these analyses were therefore either incomplete because there were no data for the specified regimen, or were uncertain, as reflected by the wide CrIs.

7 CONCLUSIONS AND IMPLICATIONS FOR DECISION-MAKING

For SVR:

- For treatment-naive and -experienced patients with genotype 1 infection, Harvoni, Holkira Pak and daclatasvir were superior to PR-based treatments. Harvoni and Holkira Pak were better than daclatasvir-based regimens in some patient subgroups. There was limited evidence for patients with cirrhosis.
- The data available for genotype 2 to 4 were limited. For patients with genotype 2 infection, SOF12 + RBV12 significantly improved SVR rates over PR24 in treatment-naive patients, but SOF12 + PR12 did not. In treatment-experienced patients, neither SOF16 + RBV16 nor SOF12 + PR12 were significantly different from SOF12+ RBV12.
- For patients with genotype 3 infection and regardless of treatment experience, SOF24 + RBV24, DCV12 + SOF12, and SOF12 + PR12 significantly improved SVR compared with PR48, and there were no significant differences between these regimens.
- For genotype 4 patients, DCV24 + ASU24 + PR24 and SOF12 + PR12 were superior to SOF12 + RBV12 in treatment-experienced and naive patients respectively.
- The data for genotype 5 and 6 infection were insufficient for analysis.
- Data were limited to evaluate patients with HIV coinfection, however Harvoni and SOF24 + RBV24 significantly improved SVR compared to PR48 in treatment-naive patients with genotype 1 infection. NMA could not be performed for patients infected with other genotypes and coinfected with HIV, although the following regimens demonstrated high rates of SVR in treatment-naive patients in individual trials: SOF12 + RBV12 in genotype 2; SOF24 + RBV24 in genotype 3; SOF24 + RBV24 and SOF12 + PR12 in genotype 4. There were no data for treatment-experienced patients with HIV coinfection.
- No evidence was available to allow analysis of efficacy for the following regimens: DCV24 + SOF24 for genotype 1 infection; DCV + ASU + PR for treatment-naive patients with genotype 1 infection; DCV12 + SOF12 for treatment-experienced patients with genotype 1 infection; DCV + SOF for genotype 2 infection; SOF12 + LDV12 + RBV12 and DCV24 + SOF24 ± RBV24 for genotype 3 infection regardless of treatment experience; SOF12 + LDV12 and DCV12 + ASU12 + PR12 for patients with genotype 4 infection; and SOF12 + PR12 for treatment-experienced patients with genotype 4 infection.

For rash, anemia, depression:

- For treatment-naive and -experienced patients, Harvoni, Holkira Pak and daclatasvir-based regimens were associated with lower risks for rash and anemia than PR-based treatments, but only Harvoni and daclatasvir-based regimens were associated with less depression compared to PR-based treatments. In particular, Holkira Pak with RBV was less favourable than Harvoni.
- For treatment-experienced patients, Harvoni, Holkira Pak and daclatasvir-based regimens were associated with less rash and anemia than PR-based treatments, but evidence was sparse for depression. For rash, daclatasvir with PR was less favourable than Harvoni, Holkira Pak and daclatasvir without PR. For anemia, Holkira Pak with RBV was less favourable than Harvoni and Holkira Pak without RBV.

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